STATISTICAL ANALYSIS PLAN

PROTOCOL: REP0122

Phase 2, proof-of-concept, randomized, double-blinded, placebo-controlled, multicenter study to assess efficacy and safety of reparixin as add-on therapy to standard of care in adult patients with Acute Respiratory Distress Syndrome (RESPIRATIO)

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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Prepared for:	Dompé farmaceutici S.p.A
Prepared by:	PPD Principal Biostatistician, PPD

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

Statistician details:	
Name:	PPD
Job Role:	Principal Biostatistician
Company:	PPD
Signature:	PPD
Date of signature:	*(DD Mmm YYYY)*

Sponsor Approver details:	
Name:	PPD
Job Role:	Biostatistician, consultant Dompé
Company:	Dompé farmaceutici S.p.A. [Dompé] Via Santa Lucia 6, 20122 Milan, Italy
Signature:	PPD
Date of signature:	*(DD Mmm YYYY)*
Name:	PPD
Job Role:	Medical Director, consultant Dompé
Company:	Dompé farmaceutici S.p.A. [Dompé] Via Santa Lucia 6, 20122 Milan, Italy
Signature:	PPD
Date of signature:	*(DD Mmm YYYY)*
Name:	PPD
Job Role:	Senior Clinical Project Manager, consultant Dompé
Company:	Dompé farmaceutici S.p.A. [Dompé] Via Santa Lucia 6, 20122 Milan, Italy

Signature:	PPD
Date of signature:	*(DD Mmm YYYY)*

Contents

Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
CSR	Clinical Study Report
eCRF	electronic Case Report Form
DMC	Data Monitoring Committee
ECMO	Extracorporeal Membrane Oxygenation
ENR	Enrolled set
EU	European Union
FAS	Full Analysis set
FIO2	Fractional inspired oxygen
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
LTAC	Long Term Acute Care
MAR	Missing at Random
MedDRA	Medical Dictionary for regulatory activities
MI	Multiple Imputation
MI-RD	Multiple Imputation using retrieve dropouts
MNAR	Missing Not at Random
OI	Oxygenation index
PaO2	Partial pressure of oxygen
PEEP	Positive End Expiratory Pressure
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per protocol set
PT	Preferred Term
RAGE	Receptor for Advanced Glycation End products
RALE	Radiographic Assessment of Lung Edema
RND	Randomized set
SAE	Serious Adverse Event
SAF	Safety set
SaO2	Oxygen saturation of hemoglobin
SAP	Statistical Analysis Plan

SEM	Standard error of the mean
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SpO2	Peripheral Capillary Oxygen Saturation
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TID	Ter in die (three times a day)
US	United States
VFD	Ventilatory-free days

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1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of REP0122 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 (CSR).
This SAP is based on study protocol Version No. 3.0 - 8 February 2024 [2] , Case Report Form Version No. 7.0 – 20 NOV2024 [3].

Pharmacokinetics: Serum PK samples collected during the study were not planned to undergo testing by the lab prior to the planned primary analyses of the study results. The analysis of PK samples in this study may be described and reported in the future under separate cover.

2. Study Objectives

The primary objective of this trial is to characterize the efficacy of reparixin in ameliorating lung injury and systemic inflammation and expediting clinical recovery and liberation from mechanical ventilation in adult patients with moderate to severe ARDS (PaO_2/FIO_2 ratio ≤ 200). Furthermore, the primary objective also includes the assessment of the effect of reparixin on systemic biomarkers linked to a hyper-inflammatory ARDS phenotype.

2.1 Overview of planned statistical analyses

The study plans for the following statistical analyses:

- Analyses for the Data Monitoring Committee (DMC): these analyses will be produced periodically according to the DMC Charter.
- Final analysis: this analysis (final) will be conducted after all enrolled subjects have completed the study, the study database locked and the randomization will be broken (unblinding).

The list of tables, listings, and figures to be provided at each analysis is reported in a separate appendix.

2.2 Primary objective

To characterize the efficacy of reparixin in ameliorating lung injury and systemic inflammation and expediting clinical recovery and liberation from mechanical ventilation in adult patients with moderate to severe ARDS (PaO2/FIO2 ratio ≤ 200).

2.3 Secondary objectives

To assess the effect of reparixin on systemic biomarkers linked to a hyper-inflammatory ARDS phenotype.

2.4 Safety objectives

To evaluate the safety of reparixin versus placebo in the specific clinical setting, including the effect on the incidence of secondary infections.

3. Study Design

3.1 General design and plan

This is an international, multicenter, 1:1 randomized, double-blind, placebo-controlled, phase II proof-of-concept trial. It will enroll approximately 66 adult patients hospitalized with ARDS that meet the inclusion criteria, randomly assigned at 1:1 ratio to receive either reparixin 1200 mg (treatment group) through a nasogastric tube or matched placebo (control group) TID for 14 days with optional continuation of treatment up to 21 days, if patient is still intubated on Day 14.
All patients must receive standard and supportive care according to their clinical status and local guidelines during the whole study period.
Each patient will be involved in the study for up to 60 days.
The study will consist of 4 study periods:

- Screening
- Randomization and Baseline assessments
- Treatment (14 days, with the option of extension up to 21 days if the patient is still intubated on Day 14)
- Follow-up (up to 28 days and hospital discharge if later than 28 days; and then up to day- 60).

Patients will be assessed daily while hospitalized up to extubation from first IMP administration. The end of this study is defined as the end of follow-up.
If the patient discontinues treatment prematurely without withdrawing his consent and without being discharged from the hospital, subsequent visits will be done according to study Protocol.

If the patient discontinues treatment prematurely without withdrawing his consent but was discharged from the hospital, he will have to complete the hospital discharge visit and the follow-up visit at Day 60.

3.1.1 Date of first and last administration of study drug

The date/time of first administration of study drug is defined as the first date/time of administration of IMP as per "Study Product Administration" eCRF form. This value must be consistent with the date/time of first administration as per "Randomization and IMP assignment" eCRF form. In case of different date/times, the earliest will be used as start of treatment.

The date/time of last administration of study drug is defined as the last date/time of administration of IMP as per "Study Product Administration eCRF form. This value must be consistent with the Last IMP intake Date/Time as per "End of Treatment" eCRF form. In case of different dates, the latest will be used as treatment end.

3.2 Visit Schedule and Visit Windows

3.2.1 Study Day

Study Day (based on Date)

The study day describes the day of the event or assessment date, relative to the reference start date which is the date of Start of IMP (Day 1) or date of Randomization if not treated.
The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date, etc.) – reference start date + 1 if event is on or after the reference start date.
- The date of the event (visit date, onset date of an event, assessment date, etc.) – reference start date if event precedes the reference start date.

If an assessment referring to Day 1 Visit is collected after the IMP intake and on the same calendar day of IMP intake, the measurement will be kept as assessment collected at Day 1.

As a general rule, the following will be applied:
Day X date= Day 1 date + (X-1) days, where Day 1 = day of the 1st IMP intake.

Study Day (based on Date/Time)

For several measurements, the actual date and time of assessment (when available) are recorded in the eCRF.

By protocol section 7.1: ”Hour 1 of day 1 starts when the first dose of the IMP is administered. Subsequent days are measured in 24-hour intervals from hour 1. Therefore, day 2(±8h) signifies 24 hours±8 hours from hour 1 , and so on”.

For these assessments, the Study Day will be measured as time interval on the basis of date/time approach suggested by the study protocol, with some adjustment as follows.

The reference start date/time is the date/time of Start of IMP.

- Day1 = from (1st IMP intake + 1 minute) to (12h – 1 minute from 1st IMP intake)
  - Range for Day 1: from 1 minute after 1st IMP intake to 11h and 59 minutes after 1st IMP intake
- Day2 = 24h from 1st IMP intake +/- 12 h -1 minute
  - Range for Day 2: from 12h after 1st IMP intake to 35h and 59 minutes after 1st IMP intake
- Day3 = 48h from 1st IMP intake +/- 12 h -1 minute
  - Range for Day 3: from 36h after 1st IMP intake to 59h and 59 minutes after 1st IMP intake
- The table below shows the ranges and midpoints for the study days up to day 14. The following study days are derived using the same logic.

	MIN	MAX	MIDPOINT
Day 1	1st IMP intake Date/Time + 1 min	1st IMP intake Date/Time + 11h and 59 min	6h
Day 2	1st IMP intake Date/Time + 12h	1st IMP intake Date/Time + 35h and 59 min	24h
Day 3	1st IMP intake Date/Time + 36h	1st IMP intake Date/Time + 59h and 59 min	48h
Day 4	1st IMP intake Date/Time + 60h	1st IMP intake Date/Time + 83h and 59 min	72h
Day 5	1st IMP intake Date/Time + 84h	1st IMP intake Date/Time + 107h and 59 min	96h
Day 6	1st IMP intake Date/Time + 108h	1st IMP intake Date/Time + 131h and 59 min	120h
Day 7	1st IMP intake Date/Time + 132h	1st IMP intake Date/Time + 155h and 59 min	144h
Day 8	1st IMP intake Date/Time + 156h	1st IMP intake Date/Time + 179h and 59 min	168h
Day 9	1st IMP intake Date/Time + 180h	1st IMP intake Date/Time +203h and 59 min	192h
Day 10	1st IMP intake Date/Time + 204h	1st IMP intake Date/Time + 227h and 59 min	216h
Day 11	1st IMP intake Date/Time + 228h	1st IMP intake Date/Time + 251h and 59 min	240h
Day 12	1st IMP intake Date/Time + 252h	1st IMP intake Date/Time + 275h and 59 min	264h
Day 13	1st IMP intake Date/Time + 276h	1st IMP intake Date/Time + 299h and 59 min	288h

Day 14	1st IMP intake Date/Time + 300h	1st IMP intake Date/Time + 323h and 59 min	312h

Differently from what it was reported in the study protocol, the window used for each day is +/- 12 hours to let each assessment to be unequivocally classified in a given day (not possible by using the time window +/- 8h).

With the exception of Day 1, which covers 12 hours (11 h and 58 minutes), all the other days cover 24 hours (23h and 59 min).

For each endpoint described in section 3.5.1 and 3.5.2, it will be specified whether the study Day will be defined on the basis of Date or Date/time. Section 11.1.1 provides further details with regards to variables derivations based on date or date/time.

Please refer to Table 1: Study Flow Chart for full details on the schedule of suggested assessments.

Notes:

- Study Days will be derived using the algorithms defined above.
- Analysis based on visits (Chest Imaging, labs, ECG …) will use the assessments collected at that visit, regardless of the study days.

3.2.2 Baseline

Given the nature of the study, screening, randomization/baseline and Day 1 Visits (this last corresponding to the date of 1st IMP Intake) may occur on the same calendar day and multiple measurements may be collected in that day.
Regardless of the way Study Day is defined, Baseline is derived as the last measurement collected before the IMP intake (date/time), regardless of the visit at which the measurement refers to.
Section 11.1.1 provides further details with regards to baseline definition based on study endpoint.

Notes:
If a measurement referring to Day 1 Visit is collected before the IMP intake, but in the same calendar day of IMP intake, the measurement will be used only for the derivation of the baseline (i.e., the measure will not be used for both baseline and Day 1).
If, after following the rules described above for the Study Day derivation, no other measurement can be used as Day 1, Day 1 will be set at missing (i.e., assessments collected at nominal visit "Day 1" occurring prior the 1st IMP intake will not be summarized under "Day 1" timepoint).

Table 1: Study Flow Chart

Days (windows)	Screening (day-1 or 1)	Randomization and baseline assessments[1]	Day 1	Day 2 (±8h)	Day 3 (±8h)	Day7 (±1)	Day 14 (±2)	End of Treatment[21]	Extubation to Hospital Discharge (every 48h±8h)	Day 28 (±2) and Hospital Discharge[19]	Day 60
ELIGIBILITY											
Informed consent signed	X										
Demo-graphics, Medical History, Disease-Specific Information, allergies	X										
Pregnancy test[2]	X										
STUDY INTERVENTION											
Randomization		X									
IMP administration[3]			Daily through day 14 with the option to extend to day 21								
STUDY PROCEDURES											
Vital signs (RR, HR, MAP)		Daily through extubation							X		
PaO2 (or SaO2), FIO2	X	Daily through extubation							X	X	
PaCO2		Daily through extubation									
Mechanical ventilation parameters[4]		Daily through extubation									
SOFA score		Daily through extubation									
Neuromuscular blocking agents, inhaled vasodilators[6]		Daily through extubation									
Prone positioning[6]		Daily through extubation									
Vasoactive medications[7]		Daily through extubation									
ECMO[8]		Daily through extubation									
CPAP attempts [9]		Daily through extubation									
Chest imaging[10]	X	X		X	X	X	X				
Biomarkers[11]		X			X	X	X				
Reintubation[12]										X	
Other clinical events[13]										X	
Follow up[14]											X

Days (windows)	Screening (day-1 or 1)	Randomization and baseline assessments[1]	Day 1	Day 2 (±8h)	Day 3 (±8h)	Day7 (±1)	Day 14 (±2)	End of Treatment[21]	Extubation to Hospital Discharge (every 48h±8h)	Day 28 (±2) and Hospital Discharge[19]	Day 60
SAFETY TESTS											
Adverse events	◄	----	----	----	----	----	----	----	----	----	►
Concomitant medications	◄	----	----	----	----	----	----	----	----	----	►
Safety hematology and biochemistry[15]	X				X	X	X	X		X	
eGFR[16]	X				X	X	X	X		X	
Hepatic function[17]	X				X	X	X	X			
ECG	X				X	X	X	X		X[21]	
CCI [redacted]											

1. Baseline and initiation of IMP (day1) may coincide
2. In females of childbearing potential, only date will be required
3. Study product will be administered every 8 hours (q8h) for 14 days, and optionally up to 21 days
4. Mode of ventilation, TV, mean airway pressure, plateau airway pressure, PEEP
5. Use or not of neuromuscular blocking medications and/or inhaled vasodilators
6. Use or not of the modality of prone positioning
7. Type and dose of vasoactive medications measured in norepinephrine equivalents
8. Transition or not to ECMO
9. Defined as use of pressure support ventilation equal to 5 cmH_2O with PEEP equal to 5 cmH_2O for 2 hours
10. Chest imaging at screening will be in the form of CXR or CT scan based on institutional preferences and resources. CXR will be performed at other timepoints. If no more than 24 hours have elapsed from a screening CXR, baseline CXR will be deferred.
11. IL-6, IL-8, PAI-1, TNFr-1, ICAM-1, RAGE
12. Denotes repeat intubation at least 24 hours after a successful extubation
13. Denotes: Duration of IMV, ICU length of stay, need for reintubation (after initial extubation, over length of hospitalization), Hospital length of stay, performance of tracheostomy, transfer to LTAC facility*
14. Verification of vital status and inquiry about AE (phone interview)
15. Includes Hematology (RBB, hematocrit, hemoglobin, WBC, neutrophils and lymphocytes absolute count, platelets count) and Biochemistry (sodium, potassium, chloride, calcium, glucose, creatinine, albumin, AST, ALT, total and direct bilirubin). Results obtained at the hospital in the previous 48 hours can be accepted as screening values.
16. Estimated glomerular filtration rate (eGFR) determined by 2021 CKD-EPI
17. Hepatic function is evaluated based on ALT/AST and total/direct bilirubin levels – day 14 assessment required if treatment is prolonged up to day 21
18. CCI [redacted]

19. If hospital discharge occurs <28d, a 28-d follow-up in-person visit should be performed. If this is not feasible, a phone follow-up will be planned to collect: Duration of IMV, ICU length of stay, need for reintubation, Hospital length of stay, performance of tracheostomy, transfer to LTAC* facility, or mortality.

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21. Only at hospital discharge

*An LTAC is a Long Term Acute Care Hospital, i.e., a facility that specializes in the treatment of patients with serious medical conditions, including patients with ongoing needs for mechanical ventilation, but who no longer require intensive care or extensive diagnostic procedures. The patients in LTAC are transferred there directly from the intensive care unit because they require more care than they can receive in a rehabilitation center, skilled care facility or at home.

3.2.3 Visit re-mapping

For the endpoints that use nominal visit, a visit re-mapping will be implemented.
In case data are missing at Day 2, Day 3, Day 7, Day 14, Day 28, and Day 60 analysis visit, data collected at End of treatment or Hospital discharge will be remapped as follows:

- if the date of collection is within the analysis timepoint window , it will be remapped to the missing scheduled timepoint (example: End of Treatment happens at day 13 of study and there is no data collected at visit Day 14 for that subject, then the data collected in the End of Treatment moment will be remapped to Day 14 and it will be used in the analysis for that timepoint).
- In case both "End of Treatment" and "Hospital Discharge" visits can be remapped to the same missing scheduled timepoint, the record closer to the nominal visit date will be remapped (e.g.: "Day 14" is missing, but "EOT" happened on day 14 and hospital discharge on day 15, both visits fit within the window of "Day 14" but only "EOT" will be remapped, as it's the closest one).
- In case both "End of Treatment" and "Hospital Discharge" visits can be remapped to the same missing scheduled timepoint, and are both at the same distance from the nominal visit, the one that occurs first, e.g. the EOT visit, will be remapped.

End of Treatment and Hospital Discharge will also be analyzed “as such”, irrespective of whether they were also remapped to another study visit.

3.3 Sample size justification

The sample size of the study is calculated based on results from literature [5-8]. Evaluation of the efficacy for this study is being accomplished through estimation of a 95% confidence interval. No hypotheses are specified for this study and no p-values are being calculated but for descriptive purposes, therefore no level of significance is specified.
Considering a randomization ratio 1:1 (reparixin vs. placebo), a sample size of 60 evaluable subjects is considered adequate for assessing the difference between groups in primary endpoints, i.e., change from baseline in OI at day 7 and VFD at day 28.
The given sample size will provide a reasonable precision in the estimation of group differences in primary endpoints to an expected margin of error for a 95% one-sided confidence interval of at most 46.5% the standard deviation, whatever it is:

- Assuming a standard deviation of 11.5 points for OI, the 95% one-sided confidence interval for the difference between groups will have a width of 5.35 points;
- Assuming a standard deviation of 8 days for VFD, the 95% one-sided confidence interval for the difference between groups will have a width of 3.75 days.

If 10% of enrolled patients will not be evaluable for primary analysis, the total number of patients to be enrolled will be approximately 66.

3.4 Randomization and blinding

3.4.1 Randomization

Enrolled patients will be randomized in a 1:1 ratio to either reparixin or placebo according to the stratified randomization list. Dropouts after randomization will not be replaced.
The permuted block randomization list will be generated with a computer procedure by a CRO independent statistician not involved in the conduct of the study and will be provided to Dompé in a sealed envelope to prevent unblinding. The facility responsible of IMP packaging/labelling will also receive appropriate randomization codes for the purpose of IMP preparation.
Randomization will be performed through Interactive Response System (IRS). Each Patient Kit number will be randomly associated with a treatment group. Access to individual patient treatment code will be allowed only in the event of a medical emergency where the knowledge of patient treatment is required to provide the patient with appropriate care. The investigator and Dompé Pharmacovigilance will have access to the randomization code for a specific patient in case of a medical emergency or for safety reasons. Unblinding events will be recorded and reported in the Clinical Study Report (CSR). The treatment assignment information will be kept confidential and will not be disclosed to any other.
Once the study has been completed and the database has been locked, the treatment assignment information will be accessible to the study biostatistician(s) who will perform the statistical analyses and will generate reports.

3.4.1.1 Stratification factors

Randomization list will be stratified by site. Site is also included in the statistical model, as random effect, for the analysis of the primary efficacy endpoints (section 7.1.1.1)
Given the high number of sites and the relatively small number of patients per site, a pooling strategy will be considered as an option to be applied at the time of the Blinded Data Review Meeting.
In case there will be specific groups of Standard Of Care identified across sites, these will be grouped and the new stratification factor to consider for the analysis would become “Standard of Care”. This option will be discussed during the Blind Data Review Meeting.

3.4.2 Unblinding

Appearance, including packaging and labelling, of the IMP (tablets, packaging) will not allow to recognize actual treatment (either reparixin or placebo).

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 Interactive Response System (IRS).
Investigators will be allowed to unblind study medication directly through the Interactive Response Technology (IRT) system; any unblinding must be notified to the CRO's medical monitor. Training is provided to investigators prior to authorization to use the IRT system and the unblinding function is outlined in the study specific user guide.
Dompé Pharmacovigilance, Safety and Surveillance Department shall break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case requires expedited regulatory reporting and fulfils expedited regulatory reporting requirements. Unmasked information will not be disclosed to Investigators and other Sponsor staff.
With the exception of the above-mentioned episodes, the identity of the treatments will remain unknown to the subject, investigator, site staff, CRO and Dompé's personnel until the study completion and formal unmasking. Only the Data Monitoring Committee (DMC) will have access to group-unblinded and/or fully unblinded DMC reports.
For analysis purposes, the randomization codes will be broken when the last enrolled patient has completed therapy, and once the database has been locked.

3.5 Efficacy endpoints

This section lists all study endpoints together with the clarification on the study day to be considered for each endpoint.

3.5.1 Primary endpoint

- Change in oxygenation index (OI) from baseline to day 7 [study day: date/time]
  OI defined as: % mean airway pressure x FIO2/PaO2 (A difference between groups in 7-days OI of 6.6 points was significantly associated with 28-days mortality (Go et al., 2016). Thus, such a difference in the change in 7-days OI, ranked as the most important endpoint, will be valued as a proxy of clinical success)

- Ventilator free days (VFD) at day 28 [study day: date/time]

3.5.2 Secondary efficacy endpoints

The following secondary endpoints will be considered.

- Change in OI from baseline to day 4 [study day: date/time]

- Acute lung injury score [composite of PaO2/FIO2 ratio, PEEP, lung compliance (plateau airway pressure minus PEEP/TV) and extent of pulmonary infiltrates] at 2, 3, 7, 14 days (if still intubated) [by visit and date/time]
- SOFA scores at 2, 3, 7, 14 days (if still intubated) [study day: date/time]
- Ventilatory ratio at 2, 3, 7, 14 days (if still intubated) [study day: date/time]
- Incidence of ECMO at day 14 [study day: date]
- Use of vasoactive medications at day 14 [study day: date/time]
- Change from baseline of CXR assessment of pulmonary edema by "radiographic assessment of lung edema" (RALE) score at 2, 3, 7, 14 days [by visit]
- Percentage of patients achieving pressure support ventilation equal to 5 cmH_2O with PEEP equal to 5 cmH_2O for 2 hours (measure of weaning) by day 28 and hospital discharge [study day: date]
- ICU-free days by day 28 and hospital discharge [study day: date]
- Hospital-free days by day 28 [study day: date]
- Incidence of tracheostomies by day 28 and hospital discharge [by visit]
- Incidence of LTAC facility by day 28 and hospital discharge [by visit]
- All-cause mortality by day 28 [study day: date]
- Hospital discharge by day 28 [study day: date]
- All-cause mortality by day 60 [study day: date]
- Change from baseline to day 3, 7 and 14 in plasma levels of Il-6, IL-8, PAI-1, Plasma TNFr-1, ICAM-1, RAGE [by visit]

3.6 Safety endpoints

- Haematology/biochemistry tests change from screening to day 3±8h, 7±1, 14±2, 21±2 (if still receiving reparixin), 28±2 visits and at hospital discharge [by visit]
- eGFR, absolute value and change from screening to day 3±8h, 7±1, 14±2, 21±2 (if still receiving reparixin), 28±2 visits and hospital discharge [by visit]
- Hepatic Function (ALT/AST, total/direct bilirubin), absolute values and change from screening to day 3±8h, 7±1, 14±2, 21±2 (if still receiving reparixin) visits and at hospital discharge [by visit]

- ECG/rhythm analysis changes from screening to day 3±8h, 7±1, 14±2, 21±2 (if still receiving reparixin), 28±2 visits and hospital discharge. [by visit]
- Incidence of secondary infections defined as new (occurring after the first IMP intake) infection in a previously known to be sterile site, including blood, body fluid or tissue, or new pathogen isolated from cultures of biological samples known to be previously infected by day 28 [study day: see section 11.1.1]
- Incidence of TEAEs and TESAEs from the beginning of study treatment to up to the end of study participation.
- Vital Signs change from baseline to daily assessment through extubation (namely, day 1, day 2, day 3, day 7, day 14, day 21) [study day: date/time]

4. Statistical Analysis

4.1 General

All patient data collected during the study will be listed by patient and site.
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, first (Q1) and third (Q3) quartiles, range (minimum and maximum) will be presented; 95% confidence intervals will be presented, where applicable.
- For categorical data, frequency distributions and percentages will be presented; 95% confidence intervals (Wilson method with continuity correction) per category will be presented, where applicable. Where applicable (and if not otherwise stated), treatments will be compared by means of Fisher's exact test or Chi-squared, depending on data distribution (i.e., deciding for Fisher test if there are cells with expected count less than 5).
- 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 [4]). 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 timepoints. Subjects who are free from event will be censored at the last available date. An additional analysis for time to death will be performed, where specific reasons for discontinuation will be incorporated into the analysis for determining censoring and failure status. Specifically, study discontinuation for Adverse Event or, Death or, Loss to follow-up 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 other statistical testing (for descriptive purposes) will be 0.05 and two-sided tests will be used.

For the two co-primary endpoints, normality assumptions will be checked through visual inspection and statistical tests (Shapiro-Wilk's test). The following scenario can be expected:

- normality assumptions are met with both checks, only data using original scales will be analyzed by the parametric test;
- normality assumptions are not met on at least one of the two checks: data will be presented in the original and also in the transformed scales by using parametric tests (as supplementary analysis). In the table on log-transformed scale, the back-transformed treatment estimate will be provided for interpretation purposes. In case normality is not met on the original scale and it is not met also on the log-transformed scale, the analysis will be performed on the original scale only.

Visual inspection is intended as the visual evaluation of the histogram, and the normal quantile-quantile plot (Q-Q) plot of the observed values of the variable of interest (section 7.1.1.1 and 7.1.1.2 provide more details).

- For the histogram, normality is assessed if the histogram of the data mimics a normal distribution (bell-shaped histogram).
- For the Q-Q plot, it is constructed by plotting the empirical quantiles of the data against corresponding quantiles of the normal distribution. If the empirical distribution of the data is approximately normal, the quantiles of the data will closely match the normal quantiles, and the points on the plot will fall near the line y=x.

Normality checks (based on visual inspection and statistical tests) are to be performed on observed data and – in case normality on observed data is not met - also on logarithmic scale. Normality will be checked at the Blind Data Review Meeting.

Graphs used for the visual inspection and the statistical tests will be saved as SAS outputs in PDF and delivered together with the TLF package as supplementary material.

The visual inspection and the statistical test for the normality assumption of the ANOVA model for the co-primary endpoints are intended for:

- the primary analysis
- supplementary analysis (PP set).

In case normality is not met, log-transformed data will be used for :

- the primary analysis
- supplementary analyses (complete case and PP set)
- Sensitivity analysis (MAR).

For all other analyses (e.g., secondary efficacy endpoints), normality assumptions will only be checked through the statistical test (Shapiro-Wilk's test). If the normality assumption is not fulfilled data will be presented in the original scale and analyzed by both parametric and non-parametric tests.

In case data transformation is needed to meet normality assumptions, a specific focus will be added in CSR for interpreting the fact that the comparison between treatments is based on the transformed scale. A similar approach will be followed in case of use of non-parametric tests. Interpretation of potential discordant results between analyses performed on original and transformed scales (or analysis on original scale tested using parametric and non-parametric methods) will also be provided in the CSR.

Additional post-hoc analysis may be produced according to the results obtained. Any deviations from the original statistical plan (including unplanned analyses) will be documented in the CSR.

4.2 Analysis sets

4.2.1 Screened set

The Screened set will consist of all patients with signed written informed consent.

4.2.2 Enrolled set (ENR)

The ENR set will consist of all patients with signed written informed consent and fulfillment of eligibility criteria (i.e., not reported as screening failure).

4.2.3 Randomized set (RND)

The RND set will consist of all patients in the ENR set who are randomized to the study, regardless of whether they receive the IMP or not. The RND population will be used for the primary analysis of the study (including the Analysis of primary endpoint as described in Section Analysis of primary endpoint7.1 and Table 2).

4.2.4 Full Analysis set (FAS)

The FAS population will consist of all randomized patients who received at least one dose of the investigational product. FAS population will be analyzed according to intention-to-treat (ITT) principle, i.e., by treatment allocation regardless happening of intercurrent events. The FAS population will be used for the supplementary analyses of the primary analysis of the study and to present results on secondary efficacy data.

4.2.5 Safety set (SAF)

The SAF set will consist of all randomized patients who received at least one dose of the investigational product. SAF set will be analyzed according to the actual treatment received. The SAF population will be used to present results on safety data. For the derivation of the actual treatment, the longest exposure to the randomized/actual treatment will be considered: subjects will be analyzed using the actual treatment if they are exposed to it for the longest period of time (in case the exposure to the randomized treatment is equal to the exposure to the actual treatment, the actual treatment will be considered). The following scenarios will be considered:

- For patients with no issue with the randomized treatment, the actual will be equal to the randomized one
- For patients with issues (i.e., misallocation of the randomized treatment) the actual treatment will be derived by considering the longest exposure to the randomized/wrong treatment assigned: subjects will be analyzed using the treatment in the wrong kit assigned if they are exposed to it for the longest period of time (in case the exposure to the randomized treatment is equal to the exposure to the treatment in the wrong kit assigned, the "wrong" treatment will be considered).

Note: by chance, the misallocated kit could contain the treatment the patient had been randomized at.

4.2.6 Per Protocol set (PP)

The PP set will consist of all patients in the FAS population who do not have Protocol Deviations impacting on the analysis of primary endpoints (that lead to exclusion from PP set). The PP population will be used for supplementary analyses.

4.3 Usage of analysis sets

The usage of the analysis sets for the creation of tables and figures is 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 Sets

Analysis	Screened Set	ENR	RND	FAS	SAF	PP
Subject enrolment and disposition	X	X	X			
Protocol deviations			X			
Study discontinuations			X			

Analysis	Screened Set	ENR	RND	FAS	SAF	PP
IMP Discontinuations (for DMC, as described in section 4.9)					X	
Demographics and baseline characteristics			X*			
Medical/Surgical History and Concomitant Diseases			X			
Prior and concomitant medications			X		X	
Other baseline characteristics			X			
Compliance to IMP				X	X	
Exposure to IMP				X	X	
Analysis of primary efficacy endpoint			X			
Sensitivity analyses			X			
Supplementary analyses			X	X		X
Analysis of secondary efficacy endpoints				X		
Adverse events					X	
Clinical laboratory evaluation					X	
Vital signs					X	
ECGs					X	

* as described in section 4.9, additional analyses on demographics were requested by DMC and they were based on the RND set.

4.4 Estimands

4.4.1 Primary estimands

The primary estimand #1 is defined by the following attributes:

- Population: Adult patients hospitalized for Acute Respiratory Distress Syndrome, as defined by the inclusion-exclusion criteria of the study.
- Variables: Oxygenation index (OI) at baseline and at day 7.
- Intercurrent events:
    - Death before Day 7, or at Day 7 if OI is not present, as a terminal event which precludes the observation of the variable, will be handled by the composite strategy. Day 7 value is derived using Study Day based on Date (i.e., Day 7= First IMP Intake + 6), since only date of death is collected. The event will be included in the estimand by imputing for OI at day 7, an extreme unfavorable value characterizing the treatment failure. The 90°

percentile of the distribution of the observed values will be used (the value will be rounded to present only one decimal place only for data presentation, not for imputation).

- For patients that at day 7 are extubated and OI is not evaluable, extubation will be handled by the composite strategy as an event which precludes the observation of the variable of interest. The event will be included in the estimand by imputing for OI at day 7 a sufficiently extreme favorable value characterizing the treatment success. The 10° percentile of the distribution of the observed values will be used (the value will be rounded to present only one decimal place, only for data presentation, not for imputation). A patient is extubated at day 7 if the patient results not intubated in the time range [First IMP Intake Date/Time +132h, First IMP Intake Date/Time +155h and 59 min].
- Treatment discontinuation, which may affect interpretation of the variable, will be handled by the treatment policy strategy. The occurrence of the intercurrent event will be irrelevant. All observed values will be used regardless of occurrence of the intercurrent event. Retrieved dropouts will be used for data imputation of all missing data (not due to death and not due to extubation), whichever is the reason of missingness.

- Population-level summary: Change in oxygenation index (OI) from baseline to day 7

Estimand #1: Difference in means between Reparixin and Placebo in the change in oxygenation index (OI) from baseline to Day 7 in adult patients hospitalized for Acute Respiratory Distress Syndrome, as defined by the inclusion-exclusion criteria of the study, regardless of treatment discontinuation whatever the reason and alive up to day 7, intubated at Day 7.

The primary estimand #2 is defined by the following:

- Population: Adult patients hospitalized for Acute Respiratory Distress Syndrome, as defined by the inclusion-exclusion criteria of the study.
- Variables: Ventilator free days (VFD) at day 28.
- Intercurrent events:
  - Death before or on Day 28, as a terminal event which precludes the complete observation of the variable, will be handled by the composite strategy. The event will be included in the estimand with an extreme unfavorable value (0) characterizing the treatment failure.
  - Treatment discontinuation, which may affect interpretation of the variable, will be handled by the treatment policy strategy. The occurrence of the intercurrent event will be irrelevant. All observed values will be used regardless of occurrence of the

intercurrent event. Retrieved dropouts will be used for data imputation of all missing data (not due to death), whichever is the reason of missingness.

- Population-level summary: Mean VFD at day 28.

Estimand #2: Difference in means between Reparixin and Placebo in Ventilation Free Days (VFD) at Day 28 in adult patients hospitalized for Acute Respiratory Distress Syndrome, as defined by the inclusion-exclusion criteria of the study, regardless of treatment discontinuation whatever the reason and alive at day 28.

4.5 Sub-group analyses

Subgroup analyses will be performed within subgroups defined by the following baseline characteristics:

- Age class (<65 yrs, ≥ 65 yrs),
- Gender,
- Race/ethnicity.

Within each subgroup level, analyses (descriptive summaries and ANOVA models) will be performed on the primary endpoints according to the methods defined for the primary analysis in Section 7.1.1.

In the ANOVA models, when presenting the analysis by subgroup, the covariate related to the subgroup will not be considered.

When performing MI for subgroups, the same MI as created for the main primary analysis will be used, by applying the related filter (i.e., subgroup analysis will not involve additional MI). If a specific level in subgroup analysis doesn't contain any missing, estimates of proc mixed will be considered (without using MI).

At the time of BDRM, categories of the subgroups above can be combined if the number of patients into categories is found to be too small or subgroups variables can be removed if categories are unbalanced.

4.6 Covariates

The list of covariates to be used for analyses is described in section 7.1.1.

4.7 Pooling of sites

As described in section 3.4.1.1, Site is included in the statistical model as random effect, for the analysis of the primary efficacy endpoints (section 7.1.1.1).
Given the high number of sites and the relatively small number of patients per site, a pooling strategy will be considered as an option to be applied at the time of the Blinded Data Review Meeting.

4.8 Interim analyses

No interim analysis is foreseen.

4.9 Data Monitoring Committee

DMC meetings will be performed during the trial 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 DMC meeting:

- Subject enrolment and disposition
- Protocol deviations
- Study discontinuations
- Demographics and baseline characteristics
- Medical history / conc meds
- Compliance to IMP
- Exposure to IMP
- Adverse events
- Clinical laboratory evaluation
- Vital signs
- ECGs

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 to balance patient safety risk against a possible gain in efficacy.
The DMC will consider the appropriateness of trial continuation if there is emerging evidence that reparixin is harmful.
After the 2nd DMC meeting (19Sept2024), the following analyses have been requested by the DMC members as additional analyses of the 2nd DMC meeting and in view of the 3rd DMC meeting:

- Descriptive statistics of Co-Primary endpoints. The purpose was not to monitor primary endpoints for early efficacy termination and no statistical test was to be performed.

CCI

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

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

    CCI [redacted]

[redacted]

4.10 Handling of missing and incomplete data

All reasonable efforts will be made to reduce the rate of missing data. Investigators will be trained about the importance of patient retention and full data capture. Also, any reasonable attempts should be made by the investigators to emphasize continued subject's participation for the full duration of the trial.
Patients who discontinue the treatment will not be withdrawn from the study by default, but will be asked to complete safety and efficacy observations as per the protocol, unless otherwise they withdraw their consent. Patients who discontinue study treatment and decide to remain in the study by following the schedule of assessments and continuing to adhere to protocol requirements are defined as "retrieved dropout" patients (section 11.1.1 provides details on the definition).
For the main analyses of the primary endpoints, missing data will be managed as follows:

- Missing data due to death, preventing the collection of the endpoint, will be imputed with an unfavourable value (see section 4.4.1).
- Missing data in extubated patient, preventing the collection of the endpoint (for Change in OI at Day 7 only), will be imputed with a favourable value (see section 4.4.1).
- Missing data due to treatment discontinuation or any other reason (whichever the reason) will be handled by means of Multiple Imputation (MI) approach as detailed in Section 7.1.1.

Sensitivity analysis of the primary endpoints can be based on different missingness assumptions (section 7.1.2.1)
In the descriptive summaries, the number of subjects with missing data will be presented under the "Missing" category. Missing values will be included in the denominator count when computing percentages. When continuous data will be summarized, only the non-missing values will be evaluated for computing summary statistics. Any exception will be declared.

4.11 Changes in the planned analysis

The following changes have been included compared to the study protocol:

- Section 4.2.3: The Primary Analysis (including sensitivity analysis) is planned on the Randomized Set, as per Regulatory Authority request. Full Analysis set will be used for Supplementary Analysis and for analysis of secondary endpoints.
- Protocol section 9.5 mentions "Subjects who are free from events at the time of DB lock will be censored at the DB lock date. Reasons for discontinuation will be incorporated into the analysis for determining censoring and failure status. Specifically, study discontinuation for Adverse Event, Death, Lost to follow-up or other negative outcomes will be considered as failure events." As per SAP, other negative outcomes will not be considered in the analysis: only study discontinuation for Adverse Event, Death or Loss to follow-up will be considered as

failure events. Also, it has been added in the SAP that subjects free of events are censored at last available date.

- Protocol section 9.5.1.1 mentions "Normal distribution will be assessed graphically.": for the two co-primary endpoints normality assumptions will be checked through visual inspection and statistical tests (Shapiro-Wilk's test) as detailed in section 4.1, while for all other relevant endpoints normality is checked only via statistical test (Shapiro-Wilk's test).
- CCI [redacted]
- Sensitivity and supplementary analysis have been added as described in SAP sections 7.1.2 and 0
- A new analysis has been added to be performed only on the subset of complete cases (i.e., without considering patients with missing endpoint) that reached Day 7 still intubated: details are provided in SAP section 7.1.3.6.
- The study protocol mentions among the secondary endpoints "Hospital-free days by day 28 and hospital discharge": the endpoint will be evaluated only at day 28 ("Hospital-free days by day 28") since at discharge the number of hospital-free days will be 0 by definition.

4.12 Data Review Meeting

BDRM will be held before DB lock. Any other details will be provided in the BDRM Plan or similar document. A BDRM report containing all decisions impacting the analysis will be prepared prior to DB Lock.

4.13 Software

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

5. Evaluation of Demographic and Baseline Characteristics

5.1 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 screened overall (N).

- Subjects enrolled overall (N, 100%).
- Subjects enrolled but not randomized and reasons for non-allocation overall (N, %).
- Subjects randomized by treatment group, and overall (N, %).
- Number of subjects who completed each planned visit.
- Subjects randomized but not treated by treatment group, and overall (N, %).
- Subjects in each analysis set (RND, FAS, SAF, PP) and reasons for exclusion by treatment group, and overall (N, %). Reasons for exclusion from population are defined below:

Population	Reason for Exclusion
RND	Use reasons collected under "specify reason" in "Was the patient randomized=No" in "Randomization and IMP assignment" CRF form
FAS	Randomized but not treated
SAF	Randomized but not treated
PP	Randomized but not treated / protocol deviation leading to exclusion

With regards to percentage calculation:

- For the second and third bullet points the percentage denominator will be the number of ENR subjects,
- For the fourth bullet point, percentage overall denominator will be the number of ENR subjects, while percentage denominator within each treatment group will be the number of RND subjects;
- For the fifth and sixth bullet points, the percentage denominator will be the number of randomized subjects
- For the last bullet point, percentage will be based on RND set..

Listings will be provided based on ENR set.

5.2 Protocol violations

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, minor, and protocol deviation impacting on the analysis of primary endpoints that lead to exclusion from PP set will be summarized for each treatment and overall. Further details on PD management and classification are provided in the Protocol Deviation Management Plan and relevant documentation.
As an example, a non-exhaustive list of Protocol Deviations leading to exclusion from the PP set can be the following:

- Inclusion of the patient in the study in violation of inclusion/exclusion criteria
- Intake of prohibited medications

- Poor compliance with IMP
- Missing of assessments for the primary endpoint

Protocol deviations will be listed as well using the randomized set.

5.3 Study discontinuations

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

- Study completers,
- Total length of study from randomization,
- Subjects who discontinued the study prematurely (and reasons),
- Subject who completed the IMP
- Subjects who discontinued the IMP (and reasons),
- Subjects who discontinued the IMP but completed the study,
- Subjects who discontinued the IMP and discontinued the study prematurely,
- Broken randomization code (and reasons).

If more than 30% of randomized subjects overall discontinue the study prematurely, the distribution of the time from randomization to discontinuation will be summarized using time-to-event method.

5.4 Demographics and baseline characteristics

The baseline demographic characteristics will be summarized by treatment and overall, by means of descriptive statistics on the RND set. In the case the RND set is not the same as FAS set, the summary of baseline characteristics will be replicated on FAS set. No statistical testing will be carried out for demographic or other baseline characteristics.
The following demographic information will be reported:

- Geographic region of the site (Europe, US), country within region, and sites within country.
- Age (years).
- Age class (<40 yrs, 40 – 64 yrs, ≥ 65 yrs).
- Sex (Male, Female).
- If female,
    - Potential childbearing (Childbearing potential, Postmenopausal with no menstrual bleeding for at least one year prior to study start, surgically sterilized).
    - Contraception method (s).
    - Was the pregnancy test performed? (Yes, No)
    - If yes,
        - Result of urine dipstick (Negative, Positive)

- If positive,
  - confirmed by performing the serum pregnancy test? (Yes, No)
  - If yes,
    - Result of serum pregnancy test
- Race/Ethnicity (White, Black or African American, Asian, Hispanic or Latino, Other);
- Height (cm),
- Weight (Kg)
- BMI (kg/m2)
- BMI (BMI≤25kg/m2, 25kg/m2<BMI≤30kg/m2, BMI>30kg/m2).

The following information on use of substances will be reported:

- Has the patient ever consumed alcohol? (Never, Former, Current)
- If former or current
  - Amount of alcohol consumed daily (< 1 Liter of wine (or equivalent), >= 1 Liter of wine (or equivalent))
  - Approximate duration of alcohol consumption (years)
- Has the patient ever used tobacco? (Never, Former or Current);
- If former or current
  - Amount of cigarettes consumed daily (<10 cigarettes (or equivalent), ≥10 cigarettes (or equivalent))
  - Approximate duration of tobacco consumption (years)

The following information on influenza virology will be reported:

- Has the patient been recently tested for influenza? (Yes, No)
- If yes,
  - Influenza test result (Positive or Negative);

The following specific information on COVID-19 will be reported:

- Did the patient receive vaccination for COVID-19? (Yes, No).
- If yes:
  - Received vaccine(s)
  - Last vaccine received
  - Time from Date of last COVID-19 vaccination to randomization
  - Total number of doses received
- Time from Date of diagnosis of moderate to severe ARDS as defined in inclusion criterion 3 to randomization
- Time from hospital/ED admission to randomization

5.5 Medical and surgical history

A disease is classified as:

- "Medical/Surgical history" if it is not ongoing at screening visit.
- "Concomitant disease" if it is ongoing at screening visit.

Medical/Surgical history and/or concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA, Version 25.0 or later) dictionary and reported in separate tabulations. Frequency distributions and percentages will be summarized by treatment, by System Organ Class (SOC) and Preferred Term (PT), sorted in decreasing order of total frequency on the RND set. In the case the RND set is not the same as FAS set, the summary of baseline characteristics will be replicated on FAS set. Counts will be given for both SOC and PT by subject. Subjects experiencing more than one previous/concomitant disease event will be counted only once within each SOC and PT.

5.6 Prior and concomitant medications

Based on the start/end medication date(s) reported in the eCRF (see Table 5 for derivation rules), a medication will be defined as:

- "Prior medication" if stopped in the 7 days before the screening or, however, prior to administration of the first dose of study treatment.
- Other Prior medication" if stopped prior to 7 days before the screening.
- "Concomitant medication" if taken on or after the administration of the first dose of study treatment. In particular, all medications which start prior to, on or after the first administration of study treatment and start no later than date of study completion or discontinuation and end on or after the first administration of study treatment or are ongoing at the study completion or discontinuation are considered.

In case of missing information not directly allowing allocation to either of the three above categories of medications, the medication will be considered as concomitant.
Prior and/or concomitant medications will be coded using World Health Organization Drug Dictionary (Version March 2022, or later) and reported in separate tabulations.
Frequency distributions and percentages will be summarized by treatment, by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name, sorted in decreasing order of total frequency on the RND set and SAF set. In the case the RND set is not the same as FAS set, the summary of baseline characteristics will be replicated on FAS set. Subjects taking more than one medication classified in the same category will be counted only once. Other Prior medication category will only be listed.

5.7 Other baseline characteristics

Other baseline characteristics will be summarized by treatment and overall, by means of descriptive statistics on the RND population. In the case the RND set is not the same as FAS set, the summary of baseline characteristics will be replicated on FAS set.

5.7.1 Lung function

Baseline lung function parameters:

- SpO_2 (%),
- SaO_2 (%),
- PaO_2 (mmHg),
- $PaCO_2$ (mmHg),
- FiO_2 (0.21 to 1),
- PaO_2/FiO_2 ratio (mmHg) ,
- SpO_2/FiO_2 (derived)

will be descriptively summarized by treatment and overall as a continuous variable. Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS, No Result) for SpO_2 (%), SaO_2 (%), PaO_2 (mmHg) and $PaCO_2$ (mmHg) will be reported as well. Information on the lung function assessment (performed/not performed) will be reported, with reasons in case of not execution.

5.7.2 Chest imaging

Information on chest imaging baseline assessment will be summarized by treatment and overall, by means of descriptive statistics. Information on the assessment (performed/not performed) will be reported, with reasons in case of not execution. The following information will be reported:

- Method (X-rays, CT scan)
- Confirmation of lung involvement and inflammation (Yes, No)
- Clinical evaluation(s)
- Number of quadrants with alveolar infiltrates

5.7.3 SOFA Score

Information on SOFA score baseline assessment will be summarized by treatment and overall, by means of descriptive statistics. Information on the assessment (performed/not performed) will be reported, with reasons in case of not execution. Up to CRF V6.0, sites entered in eCRF the single items and the SOFA score was automatically calculated. Starting from CRF V7.0 sites have either
1) the possibility to complete the single items (if they are all available) and get the SOFA Score automatically calculated

OR
2) they can enter the total SOFA score manually, without completing the single items.
Summaries will not differentiate between these two methods of collecting the total SOFA score (i.e. will report the total score regardless if it is manually entered or automatically calculated from single items).
If both scores (manually and automatically calculated) are present, the value automatically calculated will be used in the analysis.

5.7.4 Child Pugh Score and Class

Baseline Child Pugh Score, when applicable, will be descriptively summarized by treatment and overall as categorical variable with the classes A: 5-6, B: 7-9, C: 10–15. Information on the Child Pugh Score assessment (performed/not applicable/ not performed) will be reported, with reason in case of not execution.

5.7.5 Mechanical ventilation parameters

Information on Mechanical ventilation assessment will be summarized by treatment and overall, by means of descriptive statistics. Information on the assessment (performed/not performed) will be reported, with reasons in case of not execution. The following baseline information will be reported:

- Ventilator mode,
- Tidal volume (mL),
- Ventilator Rate,
- PEEP (cmH_2O),
- Mean airway pressure (cmH_2O),
- Plateau airway pressure (cmH_2O)
- Dynamic Compliance (mL/cmH2O)

With regards to ventilator mode, the classes will be grouped together as follows. Any further data collected not falling in the classification below will be discussed with the clinical team and classified accordingly.

Ventilator mode	
Classes (UPPERCASE)	**Grouped Classes**
AC AC/VC ASSIST CONTROL FULL MECHANICAL VENT SUPPORT A/C ASSIST CONTROL A/C A/C PC AC VC AC, Volume Control AC/Pressure Control (S)CMV CMV VOLUME AC/S VOLUME A/CS CMV ASSIST CONTROL VOLUME AC/S CMV	CMV, volume control
BIBAP BIPAP PC-BIPAP	BIPAP
APRV APV APV CMV AIRWAY PRESSURE RELEASE VALVE APRV BIVENT APRV BIVENT_AP RV BIVENT AP RV	APRV
SIMV PC	SIMV PC
PRESSURE SUPPORT PS CPAP-PS	Pressure support

5.7.6 Ventilation - specific information

Ventilation - specific information baseline assessment will be summarized by treatment and overall. Information on the assessment (performed/not performed) will be reported, with reasons in case of not execution. The following information will be reported:

- Use of neuromuscular blocking agents (Yes, No)
- Use of inhaled vasodilators (Yes, No)
- Use of the modality of prone positioning (Yes, No)
- Vasoactive medications (Yes, No)
- Sedation (Yes, No)

6. Evaluation of Treatment Compliance and Exposure

6.1 Compliance to study drug and treatment

The assessment of patients' compliance to the IMP will be made by determining the number of tablets administered. On a per patient basis, the evaluation of the compliance 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 tablets 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 early treatment discontinuation/completion. A fourth daily administration may also be possible for subjects having the drug intakes 6h apart.
The determination of the total number of tablets scheduled during the treatment period starts with the date and time of the 1st IMP intake, and ends with the date and time of the last IMP intake. Details for derivation are reported in section 11.1.1 .

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

Compliance will be presented on FAS and SAF sets.

6.2 Exposure to study drug

The extent of exposure to IMP in days will be summarized with descriptive statistics by treatment group. The extent of exposure (days) will be calculated using:
Extent of exposure (days) = Date of last administration of IMP – Date of first administration of IMP + 1.
Exposure will be tabulated on the FAS and SAF set.
A listing will be provided as well including all data on the study drug administrations.

7. Evaluation of Efficacy

7.1 Analysis of primary endpoint

7.1.1 Analysis details

7.1.1.1 Change in OI from baseline to day 7 of treatment

Summary statistics will be provided for the variable and by subgroups defined in section 4.5.
For the estimand definition, please refer to section 4.4.1, while for the derivation of the endpoint please refer to section 11.1.1.
Summary statistics will include imputed values at Day 7 for patients who die or are extubated, as defined in section 11.1.1.

The change in OI from baseline will be analyzed by means of an ANOVA adjusting by pre-defined factors (treatment, baseline value of the variable, gender, age class (<65, >=65 years) as fixed effect and site as random effect). In the case baseline value for OI is missing, data will be imputed as described below.

If convergence is not reached or the Estimated G-matrix is not positive definite in at least one of the models after imputation, the random effect will be dropped.

Check of the normality assumption will be performed on change from baseline data, before applying imputation process. As per section 4.1, Normality checks (based on visual inspection and statistical tests) are to be performed on observed data and – in case normality on observed data is not met - also on logarithmic scale. When performing normality checks on logarithmic scale, the checks will be performed on the logarithm of the change from baseline, derived as log (OI at day 7) - log (OI at baseline).
If assumption of normality is not confirmed (see section 4.1) analysis on original scale will be kept. An additional supplementary analysis on log-transformed data (on observed data i.e., not on change from baseline) will also be performed (see section 7.1.3.4).

In case of missing baseline OI, a MI approach will be implemented to impute it.
A MI regression model based on Markov Chain Monte Carlo (MCMC) will be created by including treatment, gender, age class (<65, >=65 years), baseline OI and Day 1 OI as covariates. A thousand data sets will be generated. The random seed number will be CCI . Details are provided below.

For the imputation of Day 7 missing data, rules described in section 0 will be applied, and following the estimand definition, for missingness due to treatment discontinuation or any other reason (whichever the reason), MI-RD regression model will be created by including treatment, OI baseline value (imputed as described in this section), gender and age class (<65, >=65 years) as covariates (further details about the MI process are described below).

If there are not enough retrieved dropouts for convergence of MI-RD regression model, the Copy Reference approach will be used using OI baseline value, gender and age class (<65, >=65 years) as

covariates. Imputation of values in the two treatment arms will be done using the non-missing values from all the patients in the control group. The final decision on the use of the MI-RD vs Copy-Reference will be done at the time of the analysis and reported in the CSR.

Whether for MI-RD or Copy-Reference approach, the adjusted estimated changes from baseline for each treatment arm together with the corresponding 95% confidence intervals will be shown. The difference between Reparixin and placebo in the change from baseline at Day 7 will be displayed together with the corresponding two-sided 90% confidence interval (in order to reflect the one-sided 95% confidence intervals). One-sided p-value (alpha=0.05 one-sided) will also be displayed for descriptive purpose.

MI process will be implemented as follows:

STEP1: Run MI for OI baseline missing data on 1000 imputations using:

CCI [redacted]

Use numeric variable in the MCMC model.

At the blinded DRM, a discussion on the pattern of missingness will be held and it will be evaluated if data show a monotone pattern. If it will be evaluated that no monotone pattern is there, the statement “impute=monotone” will be deleted from the SAS code.

STEP 2: A MI-RD for Day 7 missing data will be performed on the output datasets created in step 1 (with “nimpute=1”). A thousand datasets will be generated. The random seed number will be CCI [redacted]. Missing OI data at Day 7 will be imputed using the specified MI regression model. MI regression model will include treatment, OI baseline value (as described in step 1), gender and age class (<65, >=65 years) as covariates. According to MI-RD approach, only non-missing values from retrieve dropouts will be used to inform the MI regression model.

STEP 3: Derive change from baseline (using imputed/non imputed data).

STEP 4: Each of the 1000 datasets with observed and imputed data will be analyzed using the ANOVA model.

STEP 5: Rubin’s rule will be used for combining results to draw inference.

7.1.1.2 VFD at day 28

Summary statistics will be provided for the variable and by subgroups defined in section 4.5. For the estimand definition, please refer to section 4.4.1, while for the derivation of the endpoint please refer to section 11.1.1.

VFD at day 28 will be analysed using an ANOVA model as described in section 7.1.1.1 (considering as covariates: treatment, gender and age class (<65, >=65 years)).
If convergence is not reached or the Estimated G-matrix is not positive definite in at least one of the models after imputation, the random effect will be dropped.

Check of the normality assumption will be performed on the observed data, before applying imputation process.
If assumption of normality is not confirmed (see section 4.1) analysis on original scale will be kept. An additional supplementary analysis on log-transformed data will also be performed (see section 7.1.3.4).

For the imputation of ventilatory free days missing data at day 28, rules described in section 0 will be applied, and following the estimand definition, for missingness due to treatment discontinuation or any other reason (whichever the reason), MI regression model will include treatment, gender and age class (<65, >=65 years) as covariates. A thousand data sets will be generated. The random seed number will be CCI . MI will be implemented in the following steps:

1. Missing data at Day 28 will be imputed using the specified MI regression model. According to MI-RD approach, only non-missing values from retrieve dropouts will be used to inform the MI regression model. A total of 1000 datasets will be created. These datasets will be utilized in Step #2.
2. Each of the 1000 dataset with observed and imputed data will be analyzed using the ANOVA model. Rubin's rule will be used for combining results to draw inference.

If there are not enough retrieved dropouts for convergence of MI-RD regression model, the Copy Reference approach will be used using gender and age class (<65, >=65 years) as covariates. Imputation of values in the two treatment arms will be done using the non-missing values from all the patients in the control group. The final decision on the use of the MI-RD vs Copy-Reference will be done at the time of the analysis and reported in the CSR.

The difference between Reparixin and placebo at Day 28 will be displayed together with the corresponding two-sided 90% confidence interval (in order to reflect the one-sided 95% confidence intervals). One-sided p-value (alpha=0.05 one-sided) will also be displayed for descriptive purpose.

7.1.2 Sensitivity analyses

Sensitivity analyses are defined to assess the robustness of results on the two primary endpoints versus assumptions used in the statistical model for the main estimator.

7.1.2.1 Missing at Random assumption

The comparison between treatment and control will be performed under MAR conditions.

Oxygenation Index

The following step will be followed for the missing data imputation.

STEP 1: Imputation of baseline value: the same imputed baseline values for the main analysis will be used.

STEP 2: Day 7 missing data will be imputed by means of MI under Missing at Random (MAR) assumption instead of MNAR. The random seed number will be CCI MI will be implemented as follows. All missing primary endpoint data (due to treatment discontinuation, study discontinuation , or any other reason, whichever the reason) will be imputed using the datasets created in step 1. MI regression model will include treatment, OI baseline value (as described in step 1), gender and age class (<65, >=65 years) as covariates. According to MAR approach, all patients with non-missing values will be used to inform the MI regression model.

STEP 3: Derive change from baseline (using imputed/non imputed data).

STEP 4: Each of the 1000 datasets with observed and imputed data will be analyzed using the ANOVA model.

STEP 5: Rubin's rule will be used for combining results to draw inference.

The adjusted estimated changes from baseline for each treatment arm together with the corresponding 95% confidence intervals will be shown. The difference between Reparixin and placebo at Day 7 will be displayed together with the corresponding two-sided 90% confidence interval (in order to reflect the one-sided 95% confidence intervals). One-sided p-value (alpha=0.05 one-sided) will also be displayed for descriptive purposes.

Ventilatory-free days

The following step will be followed for the missing data imputation.

STEP 1: Missing data at Day 28 will be imputed using the MI regression model specified in section 7.1.1.2 under the MAR conditions (according to MAR approach, all patients with non-missing values

will be used to inform the MI regression model). A total of 1000 datasets will be created. The random seed number will be CCI. These datasets will be used in step #2.

STEP 2: Each of the 1000 datasets with observed and imputed data will be analyzed using the ANOVA model. Rubin's rule will be used for combining results to draw inference.

The difference between Reparixin and placebo at Day 28 will be displayed together with the corresponding two-sided 90% confidence interval (in order to reflect the one-sided 95% confidence intervals). One-sided p-value (alpha=0.05 one-sided) will also be displayed for descriptive purpose.

7.1.3 Supplementary analyses

The following supplementary analyses will be performed for the two primary endpoints.

7.1.3.1 Complete cases

The analysis of the two primary endpoints will be performed on RND set by fitting the ANOVA models described in section 7.1.1.1 on complete cases only i.e., without considering patients with missing primary endpoints, and without implementing any MI.

7.1.3.2 Full Analysis Set

The analysis of the two primary endpoints described in section 7.1.1.1 will be entirely (including MI on baseline and MI-RD on Day 7 data) reproduced on the FAS set instead of RND. For the analysis on the FAS set, the same seeds used for the analysis on RND set will be used. If FAS population will be the same of RND population, the analysis will not be replicated.

7.1.3.3 Per-protocol

The analysis of the two primary endpoints described in section 7.1.1.1 will be entirely (including MI on baseline for OI and MI-RD on Day 7 data for OI and Day 28 data for VFD) reproduced on the PP set instead of RND.
For imputation of baseline OI the random seed number will be CCI.
For imputation of OI at day7 and VFD at Day 28 the random seed number will be CCI.

In the case where in the PP set there are not enough retrieved dropouts (RD) for convergence of MI-RD regression model or there are any convergence issues that prevent the use of RD approach, the Copy Reference (CR) approach will be used, and a new sensitivity analysis will be implemented using CR also in the Randomized Set (this will ensure comparability of estimates in PP and RND set).

Due to the low sample size in the PP population, in case of convergence issues in the final analysis, age covariate will be removed from the imputation models as well as from the ANOVA model.

In summary the following process will be followed:

1. Run the model using Retrieved Drop-Out (RD) approach (using all covariates).
    a) If it converges ok, stop.
    b) If it doesn't converge, follow the next steps.
2. Run the model using Copy Reference (CR) approach (using all covariates).
    a) If it converges ok, stop here and add a new sensitivity on RND set, i.e., run a model using Copy Reference (CR) approach (using all covariates) on the Randomized Set.
    b) If it doesn't converge, follow the next steps.
3. Run the model using Copy Reference (CR) approach by deleting age from covariates.
4. Run a new sensitivity on RND set, i.e., run a model using Copy Reference (CR) approach by deleting age from covariates on the Randomized Set

7.1.3.4 Log-transformed scale

As described in section 7.1.1, in the case the assumption of normality on the primary variables is not met, the primary endpoints will be analyzed also using the log-transformed scale.
For the analysis on the log-transformed data, log-transformation will be applied before the multiple imputation step.
For the analysis of VFD at Day 28, before the log-transformation, a +0.5 will be added to the original scale values.

7.1.3.5 Additional clinically relevant adjustment(s)

The analysis of the two primary endpoints described in section 7.1.1 will be entirely reproduced after updating the regression model used for the analysis with further clinically relevant variables that may result imbalanced at baseline (for example specific comorbidities). This decision will be taken at the BDRM (keeping the study team blinded) or after the database lock (in this case the analyses will be considered as ad-hoc).

The following supplementary analysis will be performed only for the primary endpoint referred to change in OI from baseline to day 7.

7.1.3.6 Change in OI from baseline to Day 7 without imputing death and extubation.

This analysis will be performed only on the subset of complete cases only (i.e., without considering patients with missing endpoint) that reached Day 7 still intubated (imputed values of patients who died or were extubated before or at Day 7 with no OI at Day 7 will be classified as missing). Value and change in OI from baseline to Day 7 will be analyzed by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test (alpha=0.05 one-sided).

7.2 Analysis of secondary efficacy endpoints

7.2.1 Analysis details

Independently of results on primary, all secondary endpoints (Section 0) will be analyzed and compared by treatment by means of descriptive statistics and by appropriate parametric tests depending on the nature of the variable and its distribution. No multiplicity correction is required. Statistical tests for continuous variables will be performed only for the change from baseline.
The assumption of normality requested by parametric statistical tests, will be checked as described in section 4.1, and in case such assumptions are not met, also non-parametric counterpart tests will be performed. Change from baseline value (for continuous variables) and shift tables versus baseline (for categorical variables) may also be summarized for all post-baseline visits, as described in the following sections. Alpha level to be used for secondary endpoints is 0.05 two-sided.

7.2.1.1 Change in OI from baseline to Day 4

Value and change in OI from baseline to Day 4 will be analyzed by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.
Change from baseline to Day 4 is derived similarly to change from baseline to day 7: details on derivation are provided in section 11.1.1.

7.2.1.2 Acute lung injury score

Rules for derivation of Acute lung injury score are reported in section 11.1.
Value and change from baseline in Acute lung injury score will be analyzed at Day 2, Day 3, Day 7, Day 14 (if still intubated) timepoints by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumption of normality is not confirmed, two-sample Mann-Whitney U test.
Acute lung injury score classes (as defined in section 11.1.1.) will also be summarized as a categorical variable: number and percentage of patients in each class for each timepoint will be presented and a shift table will be provided.

7.2.1.3 SOFA scores

Up to CRF V6.0, sites entered in eCRF the single items and the SOFA score was automatically calculated.
Starting from CRF V7.0 sites have either
1) the possibility to complete the single items (if they are all available) and get the SOFA Score automatically calculated
OR
2) they can enter the total SOFA score manually, without completing the single items.
Summaries will not differentiate between these two methods of collecting the total SOFA score (i.e. will report the total score regardless if it is manually entered or automatically calculated from single items).

If both scores (manually and automatically calculated) are present, the value automatically calculated will be used in the analysis.
Value and change from baseline in SOFA score will be analyzed at Day 2, Day 3, Day 7, Day 14 (if still intubated) timepoints by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.

7.2.1.4 Ventilatory ratio

Rules for derivation of Ventilatory ratio are reported in section 11.1.
Value and change from baseline in Ventilatory ratio will be analyzed at Day 2, Day 3, Day 7, Day 14 (if still intubated) timepoints by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.

7.2.1.5 Incidence of ECMO

Rules for derivation of Incidence of ECMO are reported in section 11.1.
The number and proportion of patients requiring ECMO will be reported at Day 14 and compared by means of Fisher's exact test or Chi-squared test, depending on data distribution.

7.2.1.6 Use of vasoactive medications

Vasoactive medication use will be defined as described in Section 11.1.
The proportion of patients with at least one vasoactive medication by Day 14 (as defined in section 11.1.1) will be compared by Fisher's exact test or Chi-squared test, depending on data distribution.

7.2.1.7 CXR assessment of pulmonary edema by "radiographic assessment of lung edema" (RALE) score

Value and change from baseline in RALE score will be analyzed at Day 2, Day 3, Day 7, Day 14 (if still intubated) timepoints by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.

7.2.1.8 Percentage of patients achieving pressure support ventilation equal to 5 cmH2O with PEEP equal to 5 cmH2O for 2 hours (measure of weaning) by day 28 and at hospital discharge

The proportion of patients achieving pressure support ventilation equal to 5 cmH2O with PEEP equal to 5 cmH2O for 2 hours (measure of weaning) by Day 28 and at hospital discharge will be compared by Fisher's exact test or Chi-square's test, depending on data distribution.

7.2.1.9 ICU-free days at Day 28 and at Hospital Discharge

Rules for derivation of ICU-free days are reported in section 11.1.
ICU-free days will be analyzed by means of descriptive statistics as a continuous variable at Day 28 and at hospital discharge. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.

7.2.1.10 Hospital-free days at Day 28

Rules for derivation of hospital-free days are reported in section 11.1.
The hospital-free days by Day 28 will be analyzed by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.

7.2.1.11 Incidence of tracheostomies

Rules for derivation of Incidence of tracheostomies are reported in section 11.1.
The proportion of patients with tracheostomies by Day 28 and at hospital discharge will be compared by Fisher's exact test or Chi-square's test, depending on data distribution.

7.2.1.12 Incidence of transfer to long term acute care (LTAC) facility

Rules for derivation of Incidence of transfer to LTAC facility are reported in section 11.1.
The proportion of patients with transfer to LTAC facility by Day 28 and at hospital discharge will be compared by Fisher's exact test or Chi-square's test, depending on data distribution.

7.2.1.13 All-cause mortality by day 28 and by day 60

Rules for derivation of All-cause mortality by day 28 and by day 60 are reported in section 11.1.
The number and proportion of deaths within Day 28 and within Day 60 will be reported and compared by Fisher's exact test.
Freedom from death will also be analyzed and graphically represented as described in Section 4.1 following a time-to-event approach.
An additional analysis for time to death will be performed where study discontinuations for Adverse Event, Death, and Loss to follow-up will be considered as failure events.

7.2.1.14 Patients discharged by day 28

The number and proportion of patients discharged (alive) at Day 28 (as defined in in section 11.1) will be reported and compared by Fisher's exact test.

7.2.1.15 Change from baseline to Day 3, 7 and 14 in plasma levels of Il-6, IL-8, PAI-1, Plasma TNFr-1, ICAM-1, RAGE

Value and change from baseline to Day 3, 7 and 14 in biomarkers plasma levels of Il-6, IL-8, PAI-1, Plasma TNFr-1, ICAM-1, RAGE will be analyzed by means of descriptive statistics as a continuous variable. Comparison between treatments will be performed by means of two-sample t-test and, if assumptions of normality is not confirmed, two-sample Mann-Whitney U test.
Boxplot for values and changes from baseline will also be graphically represented by treatment at each timepoint.
In the case parameters are reported with a result containing a qualifier (e.g.: "<2.5", ">3.4") the value will be analyzed by stripping out the qualifiers:

- if the value contains a qualifier "<" with a decimal place (<X.X), the value will be analyzed as: X.X;

- if the value contains a qualifier ">" with a decimal place (>X.X) the value will be analyzed as: X.X.

A listing on biomarkers results will be provided as well.

7.3 Analysis of exploratory efficacy endpoints

Not applicable.

8. Evaluation of Safety

8.1 Adverse events

Adverse Events (AEs) started before administration of study treatment will be considered as pre-treatment; any AE started on or after the date of the administration of the first dose of study medication or started prior to the administration of the first dose and worsened in severity after the administration of the first dose will be considered as TEAE.
In case of missing or incomplete dates not allowing a direct allocation to any of the two categories of AEs (pre-treatment/TEAE), an allocation will be done according to the available parts of the onset and the end dates (Table 4 in section 11.1.2). In case of TEAE, the event can be further classified as:

1. On Treatment period, or
2. On Follow-up period

according to the available parts of the onset and the end dates (Table 4).

All AEs will be coded by SOC and PT according to MedDRA Version 25.0 (or later) thesaurus.
In addition, each AE will be graded to capture the relationship to IMP and severity. "Possible", "Probable" and "Highly Probable" or missing relationships will be considered as related to study drug (ADR – Adverse Drug Reaction) for the summary tables. "None" and "Unlikely" relationships will be considered not related to study drug.
Pre-treatment AEs will be presented in the listings only.
TEAE summaries will be presented, displaying frequencies and percentages of patients reporting TEAEs within each SOC in decreasing order of total frequency. Along with TAEs, number of events will be reported. On each of these summaries, patients will be counted only once per SOC and, within each SOC, patients will be counted only once per PT.
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, at least one secondary infection TEAE by Day 28 and by hospital discharge,

- the 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, number of secondary infection TEAEs by Day 28 and by hospital discharge.

- Summary of TEAEs by primary SOC and PT and by study period (on treatment/follow-up and overall).
- Summary of TEAEs by primary SOC, PT and Severity.
- Summary of Serious TEAEs by Primary SOC and PT and by study period (on treatment/follow-up and overall).
- Summary of Treatment Emergent ADRs by Primary SOC and PT and by study period (on treatment/follow-up and overall).
- Summary of Treatment Emergent ADRs by Primary SOC and PT and Severity.
- Summary of TEAEs leading to IMP Discontinuation by Primary SOC and PT and by study period (on treatment/follow-up and overall).
- Summary of TEAEs leading to study Discontinuation by Primary SOC and PT and by study period (on treatment/follow-up and overall).
- Summary of TEAEs leading to Death by Primary SOC and PT.
- Summary of secondary infection TEAEs by Day 28 and by hospital discharge by Primary SOC and PT.
- Listing of all pre-treatment AEs.
- Listing of all TEAEs.
- Listing of serious TEAE.
- Listing of Treatment Emergent ADR.
- Listing of Serious Treatment Emergent ADR.
- Listing of all TEAEs leading to IMP discontinuation.
- Listing of all TEAEs leading to study discontinuation.
- Listing of all TEAEs leading to death.
- Listing of Deaths.
- A summary of Deaths will also be provided as table reporting mean time to death (time to death as derived as date of death-randomization date+1), Autopsy performed, number of deaths (overall and by day), and the proximate cause of death (overall and by day)
- Listing of secondary infections (as defined in Section 11.1).

8.2 Clinical laboratory evaluation

Analysis of clinical laboratories data will be performed by treatment for Hematology and Biochemistry (including eGFR) tests. In case of different units of measure considered for the same laboratory

parameter, all values will be converted into Standard International units (if applicable) or to the same unit. Even if laboratory are collected at screening and the protocol mention changes from screening, baseline and changes from baseline will be provided: this means that, if for some reason the screening assessment is done after treatment start date (by mistake or any reason), the value will not be considered in the analysis, since the value will not be flagged as "Baseline" (as defined in section 3.2.2). Subsequent timepoints are Day 3, Day 7, Day 14, Day 21, end of treatment, Day 28 and hospital discharge.

The following summaries will be provided:

- A summary table showing for all laboratory tests the values and changes from baseline to each subsequent visit.
- A summary table showing for all laboratory tests the frequency of the investigator's interpretation at each available visit.
- Shift tables presenting the number and the percentage of patients in each bivariate category (baseline versus each post-baseline visit) with regards to investigator's interpretation.

The following graphical representations will be provided for all laboratory parameters:

- Spaghetti plot of individuals' observed data and change from baseline (with x-axis marked by days relative to start of actual treatment);
- Boxplot for values and changes from baseline by actual treatment at each timepoint.

Listings showing hematology results, biochemistry results, abnormal clinically significant hematology results and abnormal clinically significant biochemistry results will be provided.

8.3 Vital signs

Summary statistics by treatment will be provided along with a summary of the change from baseline at each timepoint for Vital signs:

- Respiration Rate (n/min),
- Heart Rate (beats/min),
- Mean Arterial Pressure (mmHg).

Daily assessments through first extubation will be tabulated (considering Study date based on date/time as per section 3.2.1); all the other assessments after extubation will only be listed.

The following graphical representations will be provided for all quantitative vital signs:

- Spaghetti plot of individuals' observed data and change from baseline (with x-axis marked by days relative to start of actual treatment);

- Boxplot for values and changes from baseline by actual treatment at each timepoint.

8.4 ECGs

Summary statistics by treatment of Heart Rate (b/min), PQ interval (msec), QT interval (msec), QTcB (msec) and ECG interpretation will be provided along with summary of the change/shift from baseline at each available timepoint (Day 3, Day 7, Day 14, Day 21, end of treatment, and hospital discharge). Even if ECG are collected at screening and the protocol mention changes from screening, baseline and changes from baseline will be provided: this means that, if for some reason the screening assessment is done after treatment start date (by mistake or any reason), the value will not be considered in the analysis, since the value will not be flagged as "Baseline" (as defined in section 3.2.2).
In addition, summary statistics of the number and frequency of patients with an alteration and the type of alteration will be provided by treatment arm and overall at each available timepoint.
The following graphical representations will be provided for all quantitative ECG values:

- Spaghetti plot of individuals' observed data and change from baseline (with x-axis marked by days relative to start of actual treatment);
- Boxplot for values and changes from baseline by actual treatment at each timepoint.

Listings showing ECG results, as well as abnormal clinically significant ECG results will be provided.

8.5 Physical examination

Not applicable

8.6 Other safety evaluations

Not applicable

9. Tables, Figures and Listings

Mock shells for tables, listings and figures are reported in the appendix attached to this document.

9.1 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, as applicable.
- 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.

9.2 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.

9.3 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 are printed out to 2 more significant digit than the original values.
- Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

9.4 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.

10. Literature

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9. Papazian L, Forel J, Gacouin A et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Eng J Med 2010;363: 1107-1116
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11. Appendices

11.1 Derivations and date conventions

11.1.1 Variable derivation

Table 3: Variable derivation rules

Parameter	Calculation
Screened	A patient is considered screened if (s)he has "Date of Written Informed Consent Signature" filled
Screening failure	A patient is considered screening failure if (s)he when "Did the subject complete the study?" is answered "No" on the End of Study Form and Primary reason for study discontinuation = "Screening Failure"
Enrolled	A patient is considered enrolled if (s)he has been screened and (s)he is not a screening failure.
Treatment completed/discontinued	A patient is considered as a treatment completer when : Primary reason for end of treatment is = "Treatment completed" or [Primary reason for end of treatment is = "IMP Discontinuation Criteria" and the criteria specified is = "The patient is discharged home"]. Otherwise, the patient is considered as Treatment discontinued
Change from baseline	Each change from baseline will be defined as difference between the value (minuend) at each post-baseline assessment and the baseline value (subtrahend).
Patient with past disease (medical history)	A patient is considered with past disease if CRF term "Has the patient experienced any past and/or concomitant diseases or past surgeries?" = YES and at least a medical history term has "Ongoing" not flagged. Otherwise the patient is considered as with no past diseases.
Patient with concomitant disease	A patient is considered with concomitant disease if CRF term "Has the patient experienced any past and/or concomitant diseases or past surgeries?" = YES and at least a medical history term has "Ongoing" flagged. Otherwise the patient is considered as with no concomitant disease.
Time from randomization to study discontinuation (days)	End of Study date – Randomization date + 1
Length of study (days)	Last available date – Randomization date + 1

Parameter	Calculation
Last available date	Most recent visit date/assessment date/procedures date (max: end of study date) defined as follows. last available date = end of study (EOS) date* If reason for discontinuation = "Lost to follow-up", last available date=most recent visit date§ or assessment date^ or procedures date *For patient who dies: end of study date = date of death § at Day 60 visits to be considered only if patient Vital Status = "Alive" in the form "Follow-Up" ^assessment including information from all summary pages (AEs, CM…)
Last available day	Last available date – Day 1 date + 1 Note: Day 1 date for derivation of the Last available day is based on calendar day (i.e., date of first IMP)
Time from Date of diagnosis of moderate to severe ARDS to randomization	Randomization date – Date of diagnosis of moderate to severe ARDS + 1. CRF field: "Date of diagnosis of moderate to severe ARDS as defined in inclusion criterion 3" in "ARDS-SPECIFIC INFORMATION" CRF form
Extent of exposure (hours)	Exposure calculated as total number of hours under treatment: (Date:time of last administration of IMP – Date:time of first administration of IMP) Date/time first and last administration defined in SAP 3.1.1 <u>Date/time first administration of IMP missing:</u> If Date first administration of IMP is not missing and time first administration of IMP is missing then: If Date first administration of IMP = "Date of Randomization" and Time randomization is not missing then time first administration of IMP= time of randomization; Otherwise set time first administration IMP = "00:00" <u>Date/time last administration missing:</u> If Time last administration of IMP is missing then set time last administration IMP = "23:59"
Total number of tablets scheduled during the treatment period	[ROUND(Extent of exposure (hours)/8) + 1]*2 The result has to be taken rounded to the closest integer.
Extent of exposure (days)	Date of last administration of IMP – Date of first administration of IMP + 1.

Parameter	Calculation
On treatment period TEAE	AE start date is on or after treatment start date and on or before end of treatment date. If AE start date is missing and the AE is considered treatment-emergent, it is considered on treatment TEAE. In case of End of treatment date missing or if last IMP intake is after End of Treatment date, the last IMP intake (instead of the End of Treatment) will be considered.
Follow-up period TEAE	AE start date is after end of treatment date. In case of End of treatment date missing or if last IMP intake is after End of Treatment date, the last IMP intake (instead of the End of Treatment) will be considered.
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.

Primary endpoint "Change in oxygenation index (OI) from baseline to day 7 " [study day based on Date/time]	**OI derivation** OI is defined as: % mean airway pressure x FIO2/PaO2, derived as 100 x mean airway pressure x FIO2/PaO2. Following the estimand definition: - If patient dies before Day 7, or at Day 7 (Day 7 date = Day 1 date + 6, since only date of death -no time- is collected) and OI is missing: OI at day 7 = 90th percentile of the distribution of the primary variable at Day 7. - If patient at Day 7 is extubated* and OI is not evaluable (i.e., if the patient results not intubated* in the time range [First IMP Intake Date/Time +132h, First IMP Intake Date/Time +155h and59 min]): OI at day 7 = 10th percentile of the distribution of the primary variable at Day 7. - Otherwise, OI is set to missing. *intubation/extubation status at day 7: check intubations in "Extubation Summary" CRF form. Use the multiple entries of extubation/re-intubation: if the last record of intubations/ extubation prior day 7 is an extubation and there are no intubations at day 7, it means the subject was extubated on Day 7. Subjects should reach day 7 to be eligible for this imputation. **Collection of data on FiO2/PaO2 and mean airway pressure** The implementation of the OI is based on 2 daily forms: "Mechanical Ventilation Parameters" for mean airway pressure, and "Lung Function" for the following parameters: PaO2/FIO2, FIO2, PaO2. FIO2/PaO2, used for the computation of OI, may be derived as 1/(PaO2/FIO2) or by using the individual values of PaO2 and FIO2 (when PaO2/FIO2 is missing) as described in the following section "Missing PaO2/FiO2 or mean airway pressure". **Missing PaO2/FiO2 or mean airway pressure** In case of missing PaO2/FiO2 for a specific visit, derive it based on the individual values of PaO2 and FiO2, if available. If PaO2 is not available set to missing (PaO2 won't be derived). The same applies for mean airway pressure, if not collected on a specific visit, the OI will be missing for that day. **Baseline derivation** 1 - For each assessment performed on or prior treatment start date/time, derive OI as defined below. 1.1 Select the last record of mean airway pressure collected in that day (if on the same date of treatment start date, use only records with time <= time of first exposure to IMP) 1.2 - Select the "FiO2/PaO2" which is closest (and non missing) to the selected "mean airway pressure" and occurring on the same timeframe (but assessed on or prior treatment start date/time). Same timeframe here means that it should be considered the date/time of mean airway pressure (detected in step 1.1) +/- 12 hours BUT always considering prior to the first IMP intake. If there is any FiO2/PaO2 available in this timeframe, take that FiO2/PaO2 assessment. If there is no FiO2/PaO2 available in this timeframe, select the FiO2/PaO2 collected in the same exact date of the selected mean airway pressure (selected in step 1.1). If there is no such match, the OI baseline will set as missing.

Parameter	Calculation
	2 - Select the OI record closest to the treatment start date. Note: It's expected that the OI will be derived from the assessments performed on the same day of treatment start date (day 1). If OI not available on day 1, then use the OI available from exact previous day (TRTSDT-1). In case neither exists, then the baseline will be missing Note: In case of multiple records, use the value collected under "Randomization/baseline" visit, if available. Otherwise, use the one collected under the latest timepoint prior treatment start date (i.e.: by order: 1 - "Screening", 2 - "Daily assessments through extubation"). **Post-baseline daily assessments (i.e., assessment after First IMP intake date/time)** For each post-baseline assessment, select the value of mean airway pressure based on the study day rules considering date and time. Select the value FiO2/PaO2 based on the study day rules considering date and time. If there is one measurement of mean airway pressure and one measurement of FiO2/PaO2 falling in that specific study day (as defined by the rules considering date/time), select these values to compute the OI at that day. Do the same for each post baseline day. (Example for day 7. Both mean airway pressure and FiO2/PaO2 should be collected in the window [First IMP Intake+132h, First IMP Intake+155h and 59min]) For both mean airway pressure and FIO2/PaO2: In case of more assessments at the same day, keep the assessment closer to the midpoint of the time interval. For instance: 2 assessments at day 7 [First IMP Intake Date/Time +132h, First IMP Intake Date/Time +155h and 59 min], the one closer to 144 hours from 1st IMP will be taken. If multiple records exist at the same distance from the midpoint of the time interval, select the first record collected in the eCRF. In case mean airway pressure and/or FiO2/PaO2 is missing at a specific study day, the value of OI for that day is not derived (the 2 records of mean airway pressure and FiO2/PaO2 should be assessed in the same study day, where study day is intended as derived using date/time).
Retrieved drop-out flag for change in OI from baseline to day 7	For “change in OI from baseline to day 7” the retrieved dropouts are the patients that discontinued the study treatment (treatment completers/discontinuers are defined above in this table under “Treatment completed/discontinued”) by day 7 *(day 7 not included) and have the endpoint evaluable by Day 7 (death on the day of the treatment discontinuation not part of the retrieved dropout): Set to 'Y' if Subject discontinued the treatment prematurely by day 7* and patient is alive or have date of death after end of treatment, and the endpoint is not missing for this parameter and timepoint. * date of discontinuation should be prior to the min value for the range of time windows of day 7 (study day using date/time) i.e., discontinuation should happen before First IMP Intake+132h.

Parameter	Calculation
Ventilatory days up to Day 28 [study date based on date/time]	To derive the number of ventilatory days up to day 28, count the days for which the subject was intubated (from the CRF Form: "Extubation Summary") starting from the date of first IMP intake up to day 28 date, where Day 28 date = Day 1 date/time + 28 days. In case of multiple periods of IMV during the first 28 days, the total duration of ventilation considered all periods of ventilation during the index admission. Between the extubation and the subsequent intubation, there should be >= 48h: if between the extubation and the subsequent intubation there is less than 48h, the extubation (from a clinical point of view) is considered unsuccessful, and it will be considered as a single intubation period (therefore that extubation period should not be considered in the calculation). As all subjects are intubated at the beginning of the study the calculation will be: Time from date/time of first IMP intake to first extubation date/time + Time from second intubation to second extubation (if from first extubation and second intubabtion there are >= 48h, otherwise Time from first IMP intake to second extubation) + Time from third intubation to third extubation (if from second extubation and third intubation there are >= 48h, otherwise Time from second intubation to third extubation)) etc. up to day 28 date/time. Note: the only possible range is the range of real number in the interval]0, 28].
Primary endpoint "Ventilator free days (VFD) at day 28" [study day based on Date/time]	Number of days from First IMP Intake to Day 28 date when the patient will be alive and free of invasive ventilation^ . It will be derived as follows: - Patients who will die before or on day 28: VFD= 0*. - If patient is alive at Day 28 (last available day >=26): VFD = 28 – Ventilatory days up to Day 28 - If subject is alive and followed for <26 days (last available date<26) the endpoint is set as missing. ^ intubation/extubation status at day 28: check intubations in "Extubation Summary" CRF form. The only possible range of values is between 0 and 28. *In the case subjects are never been extubated: VFD = 0
Retrieved drop-out flag for ventilatory free days at day 28	For "VFD at Day 28" the retrieved dropouts are the patients that discontinued the study treatment (treatment completers/discontinuers are defined above in this table under "Treatment completed/discontinued") and have the endpoint evaluable by Day 28 (death on the day of the treatment discontinuation not part of the retrieved dropout): Set to 'Y' if Subject discontinued the treatment prematurely and patient is alive or have date of death after end of treatment, and the endpoint is not missing for this parameter and timepoint.

Parameter	Calculation
Change in oxygenation index (OI) from baseline to day 4 [study day based on Date/time]	The endpoint is derived similarly to change from baseline at day 7. - If patient dies before Day 4, or at Day 4 (Day 4 date = Day 1 date + 3, since only date of death -no time- is collected) and OI is missing: OI at day 4 = 90th percentile of the distribution of the primary variable at Day 4. - If patient at Day 4 is extubated* and OI is not evaluable (i.e., if the patient results not intubated* in the time range [First IMP Intake Date/Time +60h, First IMP Intake Date/Time +83h and 59 min]), OI at day 4 = 10th percentile of the distribution of the primary variable at Day 4. - Otherwise, OI is set to missing. *intubation/extubation status at day 4: check intubations in "Extubation Summary" CRF form. Use the multiple entries of extubation/re-intubation: if the last record of intubations/ extubations prior day 4 is an extubation, and there are no intubations at day 4, it means the subject was extubated on Day 4.
ICU stay up to Day 28 and up to hospital discharge (days)	The information on ICU length of stay is collected under "Other Clinical Event Form" at Day 28 Visit and at Hospital Discharge Visit

Parameter	Calculation
ICU-free days at Day 28 and at hospital discharge (days) [study day based on Date]	<u>ICU-free days at Day 28</u> If patient is alive at Day 28 (last available day >=26) and ICU-free days is not missing at Day 28: ICU-free days = 28 – ICU stay up to Day 28.^ Else, If patient is discharged before Day 28 (date of discharge is not missing and date of discharge<Day 28) and the patient died after hospital discharge and before day 28 (hospital discharge<date of death< Day 28) then ICU-free days at day 28= ICU-free days at discharge If patient dies within Day 28 : ICU-free days = 0 If subject is alive and followed for <26 days (last available date<26) the endpoint is set as missing. Otherwise, the endpoint will be set as missing. ^in case of negative values, it is assumed that ICU-free days = 0. Day 28= Day 1 date + 27 <u>ICU-free days at Hospital Discharge</u> If patient is alive at hospital discharge date* (last available date>hospital discharge date*): ICU-free days = [hospital discharge date* – First IMP Intake date + 1] – ICU stay up to hospital discharge date*. ^ If patient is never discharged (date of discharge is missing) and the patient died after day 28 (date of death > Day 28), then ICU-free days at discharge=ICU-free days at day 28 Else (If patient dies within hospital discharge date*) or (if date of death is not missing and it is prior to Day 28 (date of death < Day 28) and discharge date is missing (i.e., subjects died during hospitalization)): ICU-free days = 0 Otherwise, the endpoint is set as missing. ^in case of negative values, it is assumed that ICU-free days = 0. *date of discharge is collected in End of Study form; in the case it is missing it is taken from Visit date in "Hospital Discharge".

Parameter	Calculation
Hospital stay up to Day 28 (days) [study day based on Date]	Hospital stay up to Day 28 : Date of discharge* – First IMP Intake date + 1. If Date of discharge* is after Day 28 date, then Day 28 date will be used instead. If Date of discharge* is missing and date of death>= Day 28 date then date of Discharge = Day 28 date. If Date of discharge* is missing and last available day >= 26 then date of Discharge = Day 28 date. Otherwise the endpoint is set as missing. Day 28 date: Day 1 date + 27 *date of discharge is collected in End of Study form; in the case it is missing it is taken from Visit date in "Hospital Discharge".
Hospital-free days by Day 28 [study day based on Date]	Hospital-free days by Day 28 If patient is alive at Day 28 (last available day >=26): Hospital-free days = 28 – Hospital stay up to Day 28 If patient dies within Day 28: Hospital-free days = 0 Otherwise, If subject is alive and followed for <26 days (last available day <26) the endpoint is set as missing. Day 28= Day 1 date + 27

Parameter	Calculation
Patients discharged (alive) by Day 28 [study day based on Date]	A patient is considered discharged alive by Day 28: - if patient is discharged* before Day 28 (included) (regardless the vital status after discharge). Otherwise, a patient is considered not alive and discharged by Day 28: - if patient dies and date of discharge* is missing, OR - if patient is not discharged* before Day 28 (included) (day of discharge >28) OR - if date of discharge is missing, but subject is in study long enough (last available day >= 26) OR - Discharge date=Death date (assumptions: patient died in the hospital) Otherwise, if the date of discharge is missing and subject is alive and followed for <26 days (last available date<26) the endpoint is set as missing. Day 28: Day 1 + 27 *date of discharge is collected in EOS; in the case it is missing it is taken from Visit date in "Hospital Discharge".
Incidence of ECMO by day 14 [study day based on Date]	Transition to ECMO (Y/N) is collected in "Ventilation - Specific Information" CRF Daily assessments through extubation. Incidence of ECMO at Day 14 : event ="Y" if Transition to ECMO ="Y" and date of daily collection (VSIDAT) is performed between date of 1st IMP intake and Day 14 included. otherwise event ="N" if last available day>=12 (allowed time window of 2 day for Day 14 visit) otherwise event is missing if last available day<12 Day 14= Day1 (date 1st IMP intake) + 13

Parameter	Calculation
Use of Vasoactive Medication by day 14 [study day based on Date/time]	Use of Vasoactive Medications is collected in "Ventilation - Specific Information" CRF Daily assessments through extubation. Use of Vasoactive Medications by Day 14 : event ="Y" if Vasoactive Medications ="Y" and date/time of daily collection is performed between Date/time of 1st IMP intake and Day 14 (date/time). otherwise event ="N" if last available day>=12 (allowed time window of 2 day for Day 14 visit) otherwise event is missing if last available day<12 Day 14= Day1 (date/time 1st IMP intake) + 13
Incidence of tracheostomies by day 28 and hospital discharge [study visit]	Performance of tracheostomy (Y/N) and date of tracheostomy is collected in "Other Clinical Event" CRF Form. <u>Incidence of tracheostomy by Day 28</u> : event ="Y" if date of tracheostomy is performed between date of 1st IMP intake and Day 28 visit date. otherwise event ="N" if ((date of tracheostomy is missing or < date 1st IMP intake) and day 28 visit is present) or (date of tracheostomy > day 28 visit) otherwise event is missing if day 28 visit is missing. <u>Incidence of tracheostomy by hospital discharge</u>: event ="Y" if date of tracheostomy is performed between date of 1st IMP intake and date of Hospital Discharge* (included). In the case the discharge date is missing (but the date of tracheostomy is not missing), it is assumed that the patient is at the hospital (as the tracheostomy can only be performed at the hospital) therefore the event will be = "Y". otherwise event ="N" if ((date of tracheostomy is missing or < date 1st IMP intake) and date hospital discharge* is present) or (date of tracheostomy > hospital discharge*) otherwise event is missing . note: if date hospital discharge is missing and patient died then date hospital discharge* = date death. *date of discharge is collected in EOS; in the case it is missing it is taken from Visit date in "Hospital Discharge".

Parameter	Calculation
Incidence of LTAC facility by day 28 and hospital discharge [study visit]	Performance of LTAC facility (Y/N) and date of LTAC facility is collected in "Other Clinical Event" CRF Form. <u>Incidence of LTAC facility by Day 28 :</u> event ="Y" if date of LTAC facility is performed between date of 1st IMP intake and Day 28 visit date. otherwise event ="N" if ((date of LTAC facility is missing or < date 1st IMP intake) and day 28 visit is present) or (date of LTAC facility > day 28 visit) otherwise event is missing if day 28 visit is missing <u>Incidence of LTAC facility by hospital discharge:</u> event ="Y" if date of LTAC facility is performed between date of 1st IMP intake and Date of Hospital Discharge* (included). In the case the discharge date is missing (but the date of LTAC facility is not missing), it is assumed that the patient is at the hospital therefore the event will be = "Y". otherwise event ="N" if ((date of LTAC facility is missing or < date 1st IMP intake) and date hospital discharge* is present) or (date of LTAC facility > hospital discharge*) otherwise event is missing if hospital discharge is missing note: if date hospital discharge* is missing and patient died then date hospital discharge* = date death *date of discharge is collected in EOS; in the case it is missing it is taken from Visit date in "Hospital Discharge".

Ventilatory Ratio (VR) [study day based on date/time]	As per Protocol Section 14.4.4. (From: Sinha P et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med 2019; 199: 333-341) VR = [minute ventilation (ml/min) × PaCO2 (mm Hg)]/[predicted body weight × 100 (ml/min) × 37.5 (mm Hg)] Where: Predicted body weight (PBW): Males = 50 + 2.3 [height (inches) – 60], where height(inches) = height(cm)/2.54 Females = 45.5 + 2.3 [height (inches) – 60], where height(inches) = height(cm)/2.54 minute ventilation (ml/min)= the product of the tidal volume and breathing frequency. - Tidal volume (ml) is collected under "Mechanical Ventilation Parameters" at "randomization and baseline assessments "and during the daily assessment through extubation. Mechanical Ventilation Parameters are collected at a specific date and time. - Breathing frequency is collected under "Respiration Rate (n/min) in "Vital Signs" collected at "randomization and baseline assessments", during the daily assessments through extubation, during "assessments from extubation to hospital discharge (every 48h+/-8h) ". Vital Signs are collected at a specific date and time. -PaCO2 (mm Hg)= collected under "Lung Fuction" at "Screening day -1 or 1", "randomization and baseline assessments" during the "daily assessment through extubation", during "assessments from extubation to hospital discharge (every 48h+/-8h) ", at day 28 and at hospital discharge *Ventilatory Ratio (VR) at baseline:* *1 - For each day on or prior treatment start date/time, derive VR as defined below.* *"Ventilatory Rate" derivation for each pre-treatment start day:* *1.1 - Select the last record of "Tidal Volume" collected in that day (if on the same date of treatment start date, use only records with time <= time of first exposure to IMP)* *1.2 - Select the "Respiratory Rate" closest to the selected "Tidal Volume" and occurring on the same timeframe (tidal volume date/time +/- 12h) but assessed on or prior treatment start date/time. If no value exists in the timeframe of +/- 12h, use the value of "Respiratory Rate" that is closest to the selected "Tidal Volume" date/time but collected in the exact same date (only consider values collected prior treatment start date/time). If there is no match, set the at baseline as missing.* *Note: In case of multiple records at same distance, use the value collected under "Randomization" visit, if available. Otherwise, use the one collected under the latest timepoint*

Parameter	Calculation
	prior treatment start date (i.e.: by order: 1 - "Screening", 2 - "Daily assessments through extubation"). *1.3 - Select the "PaCO2" closest to the selected "Tidal Volume" and occurring on the same timeframe (tidal volume date/time +/- 12h) but assessed on or prior treatment start date/time. If no value exists in the timeframe of +/- 12h, use the value of "PaCO2" that is closest to the selected "Tidal Volume" date/time but collected in the exact same date (only consider values collected prior treatment start date/time). If there is no match, set the baseline as missing* *Note: In case of multiple records at same distance, use the value collected under "Randomization" visit, if available. Otherwise, use the one collected under the latest timepoint prior treatment start date (i.e.: by order: 1 - "Screening", 2 - "Daily assessments through extubation").* *1.4 - Derive the "VR" using the values selected above.* *2 - Select the VR record closest to the treatment start date.* *Note: It's expected that the VR will be derived from the assessments performed on the same day of treatment start date (day 1). If VR not available on day 1, then use the VR available from exact previous day (TRTSDT-1). In case neither exists, then the baseline will be missing.* <u>*Ventilatory Ratio (VR) at day 2:*</u> day 2 will be derived as per section 3.2 based on date and time (i.e., for day 2 from 12h after 1st IMP intake to 35h and 59 minutes after 1st IMP intake): if in the pre-specified window for day 2, there are measurements of tidal volume and respiration rate and PaCO2 (they do not need to be collected the same date/time), then VR is computable. Otherwise, it will be set as missing. If more than one assessment is available within the window of day 2, keep the assessment closer to the midpoint of the time interval. For instance: 2 assessments at day 2, the one closer to 24hours from 1st IMP will be taken. If multiple records exist at the same distance from the midpoint of the time interval, select the first record collected in the eCRF. Derive the VR using the selected values. In case PaCO2 and/or minute ventilation is missing at a day, the value of VR for that day is not derived. <u>Ventilatory Ratio at day 3, 7, 14 :</u> same as for day 2.

Acute lung injury score [by visit and date/time]

As per study protocol, acute lung injury score is a composite value of PaO2/FIO2 ratio, PEEP, lung compliance (plateau airway pressure minus PEEP/TV) and extent of pulmonary infiltrates.

		Value
1. Chest X-ray (Number of quadrants with alveolar infiltrates)		
0		0
1 quadrant		1
2 quadrants		2
3 quadrants		3
4 quadrants		4
2. Hypoxemia score (PaO2/FiO2 mmHg)		
PaO2/FiO2	≥300	0
PaO2/FiO2	225-<300	1
PaO2/FiO2	175-<225	2
PaO2/FiO2	100-<175	3
PaO2/FiO2	<100	4
3. PEEP score (cmH2O)		
PEEP	≤5 cmH2O	0
PEEP	6-8.99 cmH2O	1
PEEP	9-11.99 cmH2O	2
PEEP	12-14.99 cmH2O	3
PEEP	≥15 cmH2O	4
4. Compliance (ml/cmH2O)		
Compliance	≥80 ml/cmH2O	0
Compliance	60-79.99 ml/cmH2O	1
Compliance	40-59.99 ml/cmH2O	2
Compliance	30-39.99 ml/cmH2O	3
Compliance	≤29.99 ml/cmH2O	4

* Abbreviations: Pao/Flo2 = arterial oxygen tension to inspired oxygen concentration ratio; PEEP =: positive end-expiratory pressure.

The value of acute injury score is obtained by a mean of the items reported in the table above i.e., by dividing the aggregate sum by the number of components that were used (Protocol Section 14.4.5).

The acute injury score is computable only if 3 over 4 items (of the table above) are not missing.

The score will be classified as follows:

	Score
No lung injury	0
Mild-to-moderate lung injury	0.1-2.5
Severe lung injury (ARDS)	>2.5

Alveolar infiltrates are collected under "Chest Imaging" collected at "Screening day -1 or 1", "randomization and baseline assessments", at day 2, day 3, day 7, day 14

Parameter	Calculation
	PaO2/FiO2 (mmHg) is collected under "Lung Function" at "Screening day -1 or 1", "randomization and baseline assessments", during the "daily assessment through extubation", during "assessments from extubation to hospital discharge (every 48h+/-8h) ", at day 28 and at hospital discharge. PEEP (cmH2O) and Compliance (ml/cmH2O) is collected under "Mechanical Ventilation Parameters" at "randomization and baseline assessments" and during the daily assessment through extubation. Mechanical Ventilation Parameters are collected at a specific date and time Rules to match assessments for Acute Lung Injury score: 1. keep date of Chest Imaging assessment from the i-th visit (namely, day 2,3,7,14) 2. link date of LF (Lung Function) and MV (Mechanical Ventilation) assessments with the date of CI (Chest Imaging), i.e., the assessments should be at the same date. 3. If no link is feasible Acute Lung Injury Score at that Visit will be missing. If chest imaging date is missing, please use study day based on date/time as follows: Select the value of Lung Function assessment based on the study day rules considering date and time. Select the value Mechanical Ventilation assessment based on the study day rules considering date and time. If there is one measurement of LF and one measurement of MV falling in that specific study day (as defined by the rules considering date/time), select these values to compute the Acute Lung Injury score at that day. Do the same for each applicable post baseline day. (Example for day 7. Both LF and MV assessments should be collected in the window [First IMP Intake+132h, First IMP Intake+155h and 59min]). In case of more assessments at the same day, keep the assessment closer to the midpoint of the time interval. For instance: 2 assessments at day 7 [First IMP Intake Date/Time +132h, First IMP Intake Date/Time +155h and 59 min], the one closer to 144 hours from 1st IMP will be taken. If multiple records exist at the same distance from the midpoint of the time interval, select the first record collected in the eCRF.
SOFA score [study day based on date/time]	The SOFA score is calculated as per Study Protocol section 14.4.2, and it is collected in CRF at "randomization and baseline assessments "and during the daily assessment through extubation. SOFA score is calculated every 24 hours using (for each organ system) the worst variable recorded within the same 24 hours. The best possible score corresponds to 0 whereas the worst score corresponds to 24. The SOFA total score will be considered as collected in CRF. Study day will be presented using date/time (as described in section 3.2). In the case more than one assessment is eligible for the time windows described in section 3.2 for a specific day, the assessment closest to the midpoint of that day will be considered.

Parameter	Calculation
RALE score [by visit]	The RALE score is calculated as per Study Protocol section 14.4.3, and it is collected in CRF under "Chest Imaging" at "Screening day -1 or 1", "randomization and baseline assessments", at day 2, day 3, day 7, day 14. The RALE score will be considered as collected in CRF. Study day will be presented by visit.
Secondary infections	Secondary infections are flagged in the AE CRF Form via the field "Is the AE a secondary infection? " (Y/N) Secondary infections by Day 28: are defined as those secondary infections collected up to day 30 (upper limit of Day 28 visit) Secondary infections by Hospital Discharge: are defined as those secondary infections collected up to the subject's date for Hospital discharge*. If the subject has no hospital discharge it is assumed is because the subject was not discharged, so it is assumed that the infection was during the hospitalization; if the subject has no hospital discharge and also no secondary infection, the subject will not be considered in the analysis. *date of discharge is collected in EOS; in the case it is missing it is taken from Visit date in "Hospital Discharge".
All-cause mortality by day 28 and by day 60 [study day based on Date]	The following algorithm is implemented. Death at day 28: If patient died up to Day 28* (included) then endpoint ="Y" Else if Last available day>=26* then endpoint = "N" Else If Last available day<26* endpoint is missing. Death at day 60*: use the time window (+/-2) If patient died up to Day 60* (included) is endpoint ="Y" Else if Last available day>=58* then endpoint = "N" Else If Last available day<58* endpoint is missing. *Day 28= Day1 (date 1st IMP intake) + 27; similar derivation for day 26, 60, 58 mentioned above

Parameter	Calculation
Percentage of patients achieving pressure support ventilation equal to 5 cmH2O with PEEP equal to 5 cmH2O for 2 hours (measure of weaning) by day 28 and at hospital discharge [study day: date]	As per study protocol, CPAP (Continuous Positive Airway Pressure) is defined as use of pressure support ventilation equal to 5 cmH2O with PEEP equal to 5 cmH2O for 2 hours. The CRF Field: "Number of attempts at weaning defined as continuous positive airway pressure (CPAP) trial (CPAP 5 cmH2O plus PEEP 5 cmH2O) of 2 hours duration" (in CRF Form: "Ventilation-Specific Information" in Daily assessments through extubation") counts the number of attempts at weaning as =1 each time that a CPAP 5 cmH2O + PEEP 5 cmH2O has been performed for 2 hours. <u>Number of patients achieving pressure support ventilation equal to 5 cmH2O with PEEP equal to 5 cmH2O for 2 hours (measure of weaning) by day 28</u> event ="Y" if at least one "Number of attempts at weaning defined as continuous positive airway pressure (CPAP) trial (CPAP 5 cmH2O plus PEEP 5 cmH2O) of 2 hours duration" >0 and date of daily collection (VSIDAT) is performed between Day 1 (date of 1st IMP intake) and Day 28. otherwise event ="N" if all assessments are available (i.e., no missing values are present) between date of 1st IMP intake and Day 28 (or, in general, for all days of intubation) and they are all = 0 otherwise, event is missing. Day 28= Day1 (date 1st IMP intake) + 27 <u>Number of patients achieving pressure support ventilation equal to 5 cmH2O with PEEP equal to 5 cmH2O for 2 hours (measure of weaning) by hospital discharge</u> event ="Y" if at least one "Number of attempts at weaning defined as continuous positive airway pressure (CPAP) trial (CPAP 5 cmH2O plus PEEP 5 cmH2O) of 2 hours duration" >0 and date of daily collection (VSIDAT) is performed between Day 1 (date of 1st IMP intake) and date of discharge*. event ="N" if all assessments are available (i.e., no missing values are present) between date of 1st IMP intake and Hospital discharge* and they are all = 0 otherwise, event is missing. *date of discharge is collected in EOS; in the case it is missing it is taken from Visit date in "Hospital Discharge".. If the subject has no hospital discharge it is assumed is because the subject was not discharged, so it is assumed that the event was during the hospitalization
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

Parameter	Calculation
General rule	For calculation of a time interval, in case time is available, it is considered in the formula. Time intervals will be expressed in hours in if less than 24 hours and days if more than 24 hours.

11.1.2 Partial date conventions

Table 4: 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	If AE start date > max(Date of last IMP intake, End of Treatment) then "Follow-up", otherwise "Treatment" period.
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	
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 5: 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 first dose of IMP, assign as prior If medication stop date >= date of first dose of IMP, 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 first dose of IMP, assign as prior If medication stop date >= date of first dose of IMP, assign as concomitant
	Missing	Assign as concomitant
Partial	Known	If medication stop date < date of first dose of IMP, assign as prior. Impute medication start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), If medication stop date >= date of first dose of IMP and start date >= date of first dose of IMP and before end of study day, 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), and impute medication start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If medication stop date < date of first dose of IMP, assign as prior If medication start date >= date of first dose of IMP and before end of study day and stop date >= date of first dose of IMP, then assign as concomitant
	Missing	Impute medication start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If medication start date >= date of first dose of IMP and before end of study day, then assign as concomitant
Missing	Known	If medication stop date < date of first dose of IMP, assign as prior.
	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 first dose of IMP, assign as prior

11.2 Seed numbers to be used for MI strategies

Table 4: Seed numbers

Analysis	Seed number
Imputation baseline for OI	CCI
Main analysis OI	CCI
Main analysis VFD	CCI
Sensitivity analysis - OI (MAR)	CCI
Sensitivity analysis - VFD (MAR)	CCI
Imputation baseline for OI (PP)	CCI
Main analysis OI (PP)	CCI
Main analysis VFD (PP)	CCI

11.3 SAS Codes

SAS Code below details for programming specific analyses.

Note: the codes are just examples and should not be copied as they are. For the sake of programming the code can be adapted.

PROC MI for numerical endpoints using retrieved dropout

CCI

Proc Mixed / MIanalyze for ANOVA model

CCI

CCI

CCI

CCI

PROC MI for numerical endpoints using copy-reference

CCI

PROC MI for numerical endpoints using MAR

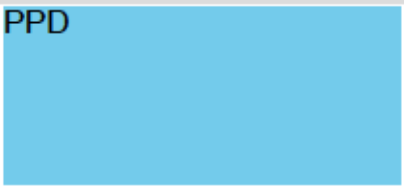
CCI

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with Docusign: REP0122_SAP_2.0_2025-07-30_clean.docx
Source Envelope:
Document Pages: 78
Signatures: 4
Envelope Originator:
Certificate Pages: 5
Initials: 0
PPD
AutoNav: Enabled
PPD
EnvelopeId Stamping: Disabled
IP Address: PPD
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
30-Jul-25 | 04:40
Holder: PPD
PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required), Login with SSO	PPD  Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 30-Jul-25 | 04:48 Viewed: 30-Jul-25 | 04:49 Signed: 30-Jul-25 | 04:51
Electronic Record and Signature Disclosure: Accepted: 30-Jul-25 | 04:49 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (Required)	PPD  Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): Approvo il documento	Sent: 30-Jul-25 | 04:48 Viewed: 30-Jul-25 | 05:34 Signed: 30-Jul-25 | 05:35
Electronic Record and Signature Disclosure: Accepted: 30-Jul-25 | 05:34 ID: PPD		

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Drawn on Device Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): Approvo il documento	Sent: 30-Jul-25 | 04:48 Viewed: 30-Jul-25 | 04:56 Signed: 30-Jul-25 | 04:56
Electronic Record and Signature Disclosure: Accepted: 30-Jul-25 | 04:56 ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I am the author of this document	Sent: 30-Jul-25 | 04:48 Viewed: 30-Jul-25 | 04:48 Signed: 30-Jul-25 | 04:51
Electronic Record and Signature Disclosure: Not Offered via Docusign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	30-Jul-25 | 04:48
Certified Delivered	Security Checked	30-Jul-25 | 04:48
Signing Complete	Security Checked	30-Jul-25 | 04:51
Completed	Security Checked	30-Jul-25 | 05:35

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 13-Dec-21 | 12:58
Parties agreed to: PPD

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