STATISTICAL ANALYSIS PLAN

PROTOCOL: REP0321

Reparixin 1200 mg three times a day as add-on therapy to standard of care to limit disease progression in hospitalised adult patients with COVID-19 and other community-acquired pneumonia. A multinational, multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase III trial (REPAVID-22).

APPROVAL PAGE

Document Information	
Protocol Number:	REP0321
Version:	V5.0 - Final
Document Date:	29 January 2025

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

Author Statistician details:	
Name:	PPD
Job Role:	Director, Biometry, consultant Dompé
Company:	Dompé farmaceutici S.p.A. [Dompé] PPD
Signature:	PPD
Date of signature:	

Lead Statistician details:	
Name:	PPD
Job Role:	Principal Biostatistician
Company:	PPD
Signature:	PPD
Date of signature:	

Sponsor Approver details:	
Name:	PPD
Job Role:	Medical Director, consultant Dompé
Company:	Dompé farmaceutici S.p.A. [Dompé] PPD
Signature:	PPD
Date of signature:	

Sponsor Approver details:	
Name:	PPD
Job Role:	Senior Clinical Project Manager, consultant Dompé
Company:	Dompé farmaceutici S.p.A. [Dompé] PPD
Signature:	PPD
Date of signature:	

Contents

List of tables

Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
CAP	Community-Acquired Pneumonia
CSR	Clinical Study Report
CRO	Contract Research Organization
eCRF	electronic Case Report Form
DB	Database
DMC	Data Monitoring Committee
DRR	blind Data Review meeting Report
ECMO	Extracorporeal Membrane Oxygenation
ENR	Enrolled set
EU	European Union
FAS	Full Analysis set
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
IRS	Interactive Response System
IRT	Interactive Response Technology
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
NEWS	National Early Warning Score
NIAID-OS	National Institute of Allergy and Infectious Disease Ordinal Scale[Error! Reference source not found.]
CCI	[redacted]
PK	Pharmacokinetic
PP	Per protocol set
PT	Preferred Term
QALY	Quality-Adjusted Life Years
RND	Randomized set
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SEM	Standard error of the mean
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TLF	Tables, Listings and Figures
t.i.d.	Ter in die (three times a day)
US	United States
VFD	Ventilatory-free days

1. Revision History

Table 1: Revision history

Version	Changes Made	Document Date
Final 1.0	First release.	CCI
Final 2.0	CCI CCI	CCI
Final 3.0	CCI CCI CCI	CCI

	CCI	
NtF to Final V3.0	CCI CCI CCI CCI	CCI
Final V4.0	CCI CCI CCI CCI CCI	CCI

	CCI CCI – – 	
Final V5.0	CCI CCI	29 January 2025

2. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of REP0321 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. 2.0 – 20 June 2022 [1] (any exception referring to previous version 1.0 [2] will be declared) and Case Report Form Version No. 8.0 – 11 October 2023 [3].

This SAP also considers the premature closure of the enrolment as a result of the interim analysis who concluded for the study stop for futility, as described in the recommendation letter from the DMC members, dated 26 June 2024 [4].

Interim analysis was based on the previous version of the SAP (V3.0 dated 16May2024 [5] and Note To File to SAP V3.0 dated 30May2024 [6])

For additional details on the changes of the originally planned analysis plan due to the premature closure of the study, please refer to section 7.9.

Considering the premature closure of the study, the final analysis will be performed when all enrolled subjects, already ongoing at the time of the study closure, will have completed/discontinued the study and the study database will be locked.

A summary of the steps followed by the ongoing patients for the study completion/discontinuation is described in section 7.7.2

Pharmacokinetic (PK) analysis is not covered by this SAP.

3. Study Design

3.1 General design and plan

This is a multinational, multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase III trial. As per the planned sample size, it will enroll 526 male and female patients ≥18 years, hospitalized for CAP (including COVID-19), assigned (1:1) to receive either oral reparixin (treatment group) or matched placebo (control group) three times a day (TID) for up to 21 days.

All the patients will receive the standard of care based on their clinical need, including COVID-19 and CAP medications, as per local standard therapy at the trial site and in line with international guidelines.

3.2 Study Objectives and endpoints

The primary objective of this trial is to evaluate the efficacy of oral reparixin plus standard of care versus placebo plus standard of care in limiting disease progression in adult patients hospitalized for community-acquired pneumonia (CAP), including COVID-19.

The effect of reparixin on recovery, ventilatory free days and mortality will be addressed.

The safety of oral reparixin versus placebo in the specific clinical setting will be evaluated.

Definition and derivation of the efficacy endpoints (primary, secondary, CCI is detailed in Section 12.1.

3.2.1 Primary

Objective(s)	Endpoint(s)
• To compare the efficacy of reparixin vs. placebo in proportion of patients dead or requiring IMV (or ECMO) by Day 28.	• Proportion of patients dead or requiring IMV (or ECMO) by Day 28.

3.2.2 Key Secondary

	Objective(s)	Endpoint(s)
#1	• To compare the efficacy of reparixin vs. placebo in all-cause mortality at Day 180.	• All-cause mortality at Day 180.
#2	• To compare the efficacy of reparixin vs. placebo in Proportion of patients alive and discharged at Day 28 -.	• Proportion of patients alive and discharged at Day 28.
#3	• To compare the efficacy of reparixin vs. placebo in Ventilatory-free days (VFD) at Day 28.	• VFD at Day 28.
#4	• To compare the efficacy of reparixin vs. placebo in Proportion of patients with IMV (or ECMO) up to Day 28.	• Proportion of patients with IMV (or ECMO) by Day 28.
#5	• To compare the efficacy of reparixin vs. placebo in length of primary hospital stay.	• Length of primary hospital stay.

3.2.3 Secondary

Objective(s)	Endpoint(s)
• To compare the efficacy of reparixin vs. placebo in clinical failure.	• Clinical failure by Day 3 and Day 7

Objective(s)	Endpoint(s)
• To compare the efficacy of reparixin vs. placebo in ICU-free days.	• 28-day ICU-free days
• To compare the efficacy of reparixin vs. placebo in IMV/ECMO-free days.	• Days free of IMV/ECMO (number of days with NIAID-OS not equal to 7 or 8) at Day 28
• To compare the efficacy of reparixin vs. placebo in Duration of antibiotic therapy (days).	• Duration of antibiotic therapy (days) at Day 28
• To compare the efficacy of reparixin vs. placebo in Hospital free days.	• Hospital free days at Day 28
• To compare the efficacy of reparixin vs. placebo in proportion of patients recovered.	• Proportion of patients recovered at Day 3, Day 7±1, Day 14±2, Day 21±2, Day 28 ±2 or hospital discharge
• To compare the efficacy of reparixin vs. placebo in proportion of patients worsening.	• Proportion of patients worsening at Day 3, Day 7±1, Day 14±2, Day 21±2, Day 28 ±2 or hospital discharge
• To compare the efficacy of reparixin vs. placebo in lung function parameters.	• Change in lung function parameters (PaO2, FiO2, SpO2, PaO2/FiO2 , SpO2/FiO2) at Day 3, Day 7±1, Day 14±2, Day 21±2, Day 28 ±2 or hospital discharge
• To compare the efficacy of reparixin vs. placebo in all-cause mortality incidence.	• All-cause mortality at Day 28, Day 60, and Day 90
• To compare the efficacy of reparixin vs. placebo in hospital re-admission.	• Hospital re-admission by Day 90 and Day 180
• To compare the efficacy of reparixin vs. placebo in time to discharge or to a NEWS of ≤ 2.	• Time to discharge or to a NEWS of ≤ 2 (for 24 hours), whichever occurs first [timeframe: Day 28]
• To compare the efficacy of reparixin vs. placebo in change in inflammatory markers and cytokines.	• Change in inflammatory markers (LDH, CRP, ferritin; D-dimer, PCT) at Day 3, Day 7±1, Day 14±2, Day 21±2, Day 28 ±2 or hospital discharge and change in cytokines at end of treatment
• To compare the efficacy of reparixin vs. placebo in change in quality of life.	• Change in quality of life using EQ-5D-5L at Day 90±7 and Day 180±14
• To compare the efficacy of reparixin vs. placebo in duration of IMV/ECMO.	• Duration of IMV and/or ECMO by Day 90 and Day 180
• To compare the efficacy of reparixin vs. placebo in ICU admission and ICU length of stay.	• ICU admission by Day 90 and Day 180 • ICU length of stay by Day 90 and Day 180
• To compare the efficacy of reparixin vs. placebo in hospital length of stay.	• Hospital length of stay by Day 90 and Day 180

Objective(s)	Endpoint(s)
• To compare the efficacy of reparixin vs. placebo in occurrence of infections.	• Occurrence of infections by Day 90 and Day 180

CCI [redacted]

[redacted]	[redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

3.2.5 Safety

Objective(s)	Endpoint(s)
• To evaluate the safety and tolerability of reparixin vs. placebo, as measured by Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs (TESAEs).	• Incidence of TEAEs and TESAEs from the beginning of study treatment to up to the end of study participation.
• To evaluate the safety and tolerability of reparixin vs. placebo in incidence of lung fungal infections by 28 days.	• Incidence of lung fungal infections by Day 28
• To evaluate the safety and tolerability of reparixin vs. placebo in Haematology and biochemistry tests.	• Change in Haematology/biochemistry tests at Day 3, Day 7±1, Day 14±2, Day 21±2, Day 28 ±2 or at hospital discharge
• To evaluate the safety and tolerability of reparixin vs. placebo in vital signs.	• Change in BP and HR at Day 3, Day 7±1, Day 14±2, Day 21±2, Day 28 ±2 or at hospital discharge
• To evaluate the safety and tolerability of reparixin vs. placebo in ECG.	• Change in ECG at end of treatment

3.3 Schedule of evaluations

Table 2 summarizes the study schedule and the patient visits of the trial. For all measurements, the actual date and time of assessment, including date of sampling, will be recorded in the Source Document and / or eCRFs. Timeframe for each assessment is also shown.

Table 2: Schedule of evaluations

	Screening day -1 or 1	Baseline[3] Day 1	Day 3	Day 7 (±1)	Day 14 (±2)	Day 21 (±2)[11]	Day 28 (±2)	Hospital discharge [20]	Day 90 (±7)	Day 180 (±14)
ELIGIBILITY										
Informed Consent	X[1]									
Inclusion/Exclusion Criteria	X									
Demographics, Medical History	X									
Previous medications	X									
STUDY INTERVENTION										
Randomization		X								
Study product administration[4]		←---------- daily ---------->								
STUDY PROCEDURES										
SARS-CoV-2 RT-PCR		X[12]								
Clinical severity score (NIAID-OS)	X	<---------- daily[15] ---------->								
Physiological parameters (NEWS)[18]		<---------- daily ---------->								
PSI		X[12]								
PaO_2/FiO_2[19]	X[12]		X	X	X	X	X			
Chest imaging review	X[13]	CCI								
Adverse events evaluation		<----------								---------->
Concomitant medications	<----------									---------->
Additional Clinical Findings[10]							X	X		
EQ-5D-5L[2]								X	X	X
Follow-up[16]									X	X
SAFETY PROCEDURES										
Safety Laboratory Tests[6]	X[12]		X	X	X	X	X			
Pregnancy Test[7]	X					X				
Vital signs[14]		X	X	X	X	X	X	X		
ECG		X				X				
RESEARCH LABORATORY										
Cytokines[8]		X				X				

	Screening day -1 or 1	Baseline[3] Day 1	Day 3	Day 7 (±1)	Day 14 (±2)	Day 21 (±2)[11]	Day 28 (±2)	Hospital discharge [20]	Day 90 (±7)	Day 180 (±14)
Inflammatory markers[9]		X[12]	X	X	X	X	X	X		
Serum PK	CCI									

1 Informed consent must be documented before any study-specific screening procedure
2 Telephone interview version
3 Screening and baseline (pre-treatment assessment) may coincide (both as Day 1)
4 Study product will be administered TID up to 21 days
CCI
6 Includes Haematology (RBC count, haematocrit, haemoglobin, WBC count and differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes], platelets count) and Biochemistry (sodium, potassium, chloride, calcium, glucose, creatinine [to calculate eGFR using MDRD], albumin, AST, ALT, total and direct bilirubin).
7 For women of childbearing potential. Positive urine test results will be confirmed with a serum pregnancy test. Study drug must not be administered unless pregnancy test result is negative.
8 Such as IL-1, IL-6, IL-8 (in selected centres), to be checked prior to first IMP administration and at the end of treatment
9 LDH, ferritin, CRP, D-dimer, PCT
10 Include final evaluation of days of hospitalisation, etiologic agents (if identified), ICU admission and total days in ICU, occurrence, and duration of IMV and/or ECMO, if any.
11 Or end of treatment
12 Diagnostic and Laboratory tests performed at the site during current hospitalization will be accepted for determination of eligibility and/or used as baseline data
13 Screening chest imaging, already performed per clinical needs, should be reviewed to confirm new/worsening lung infiltrate(s)
14 Systolic / diastolic blood pressure (BP; mmHg); heart rate (HR; b/min), respiratory rate (RR; n/min)
15 Every morning during hospitalization
16 Phone follow-up to assess re-hospitalization, all-cause mortality (health registry may be used). If re-hospitalized, it should be also collected: duration of IMV and/or ECMO, ICU admission and ICU length of stay, hospital discharge and hospital length of stay, occurrence of infections.
CCI
18 In a scored system, NEWS includes Blood Pressure (BP), Heart Rate (HR), Respiratory Rate (RR), body temperature, level of consciousness (A, V, P, U), SpO2 and use of supplemental oxygen (see 14.4.4)
19 If Arterial Blood Gas (ABG) analysis is not readily available, SpO2 can be used to estimate PaO2 (see appendix 14.4.6)
20 It can occur before or after 28d
21 If not already available, blood urea nitrogen should be measured to calculate PSI. In case the laboratory results are not readily available, and PSI calculated once all laboratory results will be available

4. General definitions

4.1 Investigational drug and study treatment

The Investigational Medicinal Product (IMP) will be either reparixin 600 mg oral tablet or matched placebo. The proposed dose in this clinical study is 1200 mg oral reparixin TID for up to 21 days. Placebo will be administered with the same schedule.

The oral route and a dose regimen have been selected based on the clinical data from previous clinical study in COVID-19 population.

The study medication will be provided as a Patient Kit, CCI

4.2 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 Summary" eCRF form.

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 Summary" eCRF form. This value must be consistent with End of treatment date as per "End of Treatment Visit" eCRF form. In case of different dates, the latest will be used as treatment end. If for any reason the End of treatment date as per "End of Treatment Visit" is not present, the last date/time of administration of IMP as per "Study Product Administration Summary" eCRF form will be used

4.3 Study day

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).

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.

4.4 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in Table 2. Additional details about scheduled visits and time windows are provided in the study protocol.

Scheduled visits, time windows, and visit types are:

- Screening (Day -1 or Day 1);
- Baseline (Day 1);
- Day 3;
- Day 7 (±1):

  - Visit as per study protocol during treatment,
  - Follow-Up at the site – after IMP completion/discontinuation;
- Day 14 (±2):
  - Visit as per study protocol during treatment,
  - Follow-Up at the site – after IMP completion/discontinuation,
  - Follow-Up telephone call;
- Day 21 (±2):
  - Visit as per study protocol during treatment,
  - Follow-Up at the site – after IMP completion/discontinuation;
- Day 28 (±2):
  - Follow-Up at the site – after IMP completion/discontinuation,
  - Follow-Up telephone call;
- Day 60 (±7) (only for patients enrolled under protocol version 1.0)
- Day 90 (±7);
- Day 180 (±14).

Patients enrolled under protocol version 1.0 will have last follow-up visit at Day 60 (±7).

For convenience, Baseline, Day 3, Day 7, Day 14, Day 21, Day 28, Day 60, Day 90, and Day 180 have been used throughout the document without reporting the corresponding windows and type of visit.

For efficacy and safety endpoints, data will be evaluated and reported according to the Visit at which they have been collected even if performed out-of-window,, or according to the number of days from Day 1, depending on the type of the endpoint. More details about variable derivations are reported in section 12.1.

In addition, the following visits will be collected in eCRF:

- End of treatment (when the End of treatment date is entered, if the End of treatment date is equal to the Day 21 Visit date, only the End of Treatment form will be displayed, and no other information will be collected for this visit. In this case, the information collected at Day 21 will be used to populate the End of treatment visit),
- Hospital discharge.

4.4.1 Visit re-mapping and data re-allocation

Visit re-mapping

In case data are missing at Day 3, Day 7, Day 14, Day 21, Day 28, Day 60, Day 90, and Day 180 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 (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.

Data Re-allocation

- Data discharge from primary hospitalization / Re-hospitalization:
    - If the date of discharge from primary hospitalization / Re-hospitalization is missing or partial the following approach will be applied:
        - If the patient died, the date of discharge will be imputed equal to the date of death.
        - If the patient did not die the date is set at missing.
    - This decision has been taken during the BDRM and documented in the DRR.

- Data discharge from ICU:
    - If the date of discharge from ICU is missing the following approach will be applied:
        - If the date of hospital discharge is available and date ICU admission ≤ date hospital discharge, the date of discharge from ICU will be imputed equal to the date of hospital discharge;
        - otherwise (if date hospital discharge is not available), if the subject died and date of death is available, the date of discharge from ICU will be imputed equal to the date of death
        - otherwise the date of discharge from ICU is set at missing..

Other decisions regarding data re-allocation not listed in the SAP will be evaluated during the BDRM and, if any, documented in the blind Data Review meeting Report (see section 7.10).

4.5 Baseline

Baseline is defined as the last visit prior to and including date of the randomization visit and 1st IMP intake (Day 1).

Unless otherwise specified, baseline values are defined as the measurements taken during this visit.

For assessments collected daily (NIAID-OS and NEWS)

If Date 1st IMP intake=Baseline Day 1 Visit date, baseline is the last assessment on or prior Date 1st IMP intake (this may include pre-treatment assessments collected only at screening)

In case of multiple measurements (including the screening assessment if performed on the same day of baseline), the highest value (worst case scenario) will be considered as baseline evaluation before start of treatment.

The same rules to define baseline will be applied also for subjects which have first treatment one or more days after the Baseline Day 1 Visit. Due to the missing time of assessment, it is assumed that the assessment is performed before the 1st IMP intake.

For assessments collected by Visit, baseline is the last assessment collected prior to the first IMP intake. In case multiple assessments exist in the same date, the one collected under the schedule visit will be used (unscheduled will only be used if they are the last assessment prior to the first IMP intake). Due to the missing time of assessment, if the assessments happen the same date of the 1st IMP intake it is assumed that the assessment is performed before the 1st IMP intake. If assessment at Day 3 Visit is used as baseline, the same assessment will not contribute to the Day 3 visit.

4.6 Post-baseline

For safety and efficacy evaluations all assessments after Baseline are considered as "post-baseline" assessments.

5. Sample size justification

The sample size of the study is calculated based on results from the phase III randomized controlled trial CCI and literature on CAP.

Sample size was calculated according to the following assumptions:

- randomization ratio 1:1.
- a proportion of patients dead or requiring IMV (or ECMO) by Day 28 [NIAID-OS 7] of CCI in the placebo group.
- an expected group difference ≥CCI in favor of reparixin.
- an interim analysis when half of the planned patients are evaluable, will be performed to evaluate efficacy and futility.

Based on these assumptions, a total sample size of 500 evaluable patients allows to achieve an overall power of 90% to show superiority of reparixin vs placebo in terms of primary endpoint, considering a one-sided alpha of 0.025.

No additional multiplicity correction of alpha is required.

Assuming 5% of subjects will not be evaluable for primary analysis after enrolment, a total of approximately 526 patients is expected to be enrolled.

6. Randomization and blinding

6.1.1 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.

Randomization list will be stratified by disease severity (NIAID-OS 5 vs. NIAID-OS 6) and site to ensure balanced assignment across treatment groups. The stratified 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 IRS. Each Patient Kit number will be randomly associated with a treatment group.

6.1.2 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 Technology (IRT).

Investigators will be allowed to unblind study medication directly through the IRT system and must notify 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.

The sponsor's personnel from the Pharmacovigilance Department of Dompé may 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.

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.

6.2 Overview of planned statistical analyses

The study plans for the following statistical analyses:

- Interim analysis for efficacy or futility: this analysis will be conducted by an independent statistician when half of the planned evaluable patients has reached Day 28 or IMV/ECMO or death or an intercurrent event. Interim analysis results will be reviewed by DMC only.
- Final analysis: this analysis will be conducted when all enrolled subjects have completed the study and the study database has been locked and unblinded.
- Analyses for the DMC: these analyses will be produced periodically according to the DMC Charter.

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

7. Statistical Analysis

7.1 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, Q1 and Q3, range (minimum and maximum) and 95% confidence intervals will be presented.
- For categorical data, frequency distributions and percentages with 95% confidence intervals (Wilson method) per category will be presented.
- For time-to-event variables, cumulative freedom from event will be evaluated using the Kaplan-Meier method. The degree of uncertainty will be expressed with 95% confidence limits (calculated per the method proposed by Greenwood [7]). 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. Only for time to death an additional analysis 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, Death, 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.
- In case of continuous measures, comparisons between treatments will be performed using two-sample t-test (assuming unequal variances) or, if the required normality assumptions are not met, the two-sample Mann–Whitney U test will be used. Whenever needed, analyses will be provided for baseline visit, each post-baseline visit, and their change from baseline. Statistical test will be provided only for change from baseline.
- In case of categorical variables, the Fisher's exact test will be provided in addition to summary description.
- For time to event variables comparison of Kaplan-Meier curves among arms will be performed with the log-rank test.

Considering the premature closure of the study for futility, the analyses have been updated as follows:

The primary analysis, comparison by treatment will be descriptive in nature and the test will be one-sided at alpha level=0.025.

For the key secondary endpoints, no more hierarchy is defined between them and no more multiplicity adjustment is required. Comparison by treatment will be performed by means of tests that will be descriptive in nature and each test will be two-sided at alpha level=0.05.

For other analysis, unless otherwise specified, the significance level for statistical testing will be 0.05 and two-sided tests. For the continuous key secondary endpoints (VFD at Day 28 and length of primary hospital stay), normality assumptions will be checked through visual inspection and statistical tests (Shapiro-Wilk's test). If normality assumptions are met with both checks, only data using original scales will be analyzed. If normality assumptions are not met on at least one of the two checks, data will be analyzed both in the original and transformed scales (or using non-parametric test on the original scale).

For the other continuous secondary endpoints, normality will be checked by the test only.

For the continuous key secondary endpoints (VFD at Day 28 and length of primary hospital stay), in case of deviation of normality assumption the interpretability of the conclusions will be granted by the original scale. A specific focus on the impact of the deviations from normality will be added in CSR for interpreting discordant results between analyses performed on original and transformed scales (or original scale tested using parametric and non-parametric methods).

Additional post-hoc analysis may be produced to further allow comparison between treatment and control, according to the results obtained. Any deviations from the original statistical plan (including unplanned analyses) will be documented in the CSR. These further apply to the possible post-hoc analyses that will be produced in consideration of the latest DMC recommendations after Interim Analysis ("Safety long term issue", [4]), if the already planned descriptive analysis will highlight any signal.

7.2 Analysis sets

A final agreement on the patients to be included in or excluded from each analysis set will be reached before breaking the blind during the Blind Data Review Meeting (BDRM) and fully documented in the blind Data Review meeting Report (DRR).

7.2.1 Screened set (SCR)

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

7.2.2 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).

7.2.3 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.

7.2.4 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 to analyze results on efficacy data.

7.2.5 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.

7.2.6 Per Protocol set (PP)

The PP set will consist of all patients in the FAS population who do not have Major Protocol Deviations. The PP population will be used for sensitivity supplemental analyses.

7.3 Usage of analysis sets

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

Table 3. 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 3).

Table 3: Usage of analysis set

Analysis	SCR	RND	FAS	SAF	PP
Subject enrolment and disposition	X	X			
Protocol deviations		X			
Study discontinuations		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
Analysis of key secondary efficacy endpoints			X		
Analysis of all secondary efficacy endpoints			X		
CCI					
Analysis of pharmacokinetics					
Adverse events				X	
Clinical laboratory evaluation				X	
Vital signs				X	
ECGs				X	

7.4 Estimands

7.4.1 Primary estimand

The primary estimand is defined by the following:

- Population: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- Variable: Patients dead or requiring IMV (or ECMO) by Day 28.
- Intercurrent event: Treatment discontinuation will be handled by the treatment policy strategy. The occurrence of the event is 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.
- Population-level summary: Difference in proportion of patients dead or requiring IMV (or ECMO) by Day 28.

7.4.2 Key secondary estimands

Key secondary endpoint #1 (see section 3.2.2) will be defined by the following estimand:

- Population: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- Variable: Any death up to Day 180.
- Intercurrent event: The occurrence of any intercurrent event is irrelevant. All observed values will be used regardless of occurrence of an intercurrent event. Retrieved Dropouts will be used for data imputation of missing data.
- Population-level summary: Difference in proportion of patients dead by Day 180.

Key secondary endpoint #2 (see section 3.2.2) will be defined by the following estimand:

- Population: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- Variable: Patients alive and discharged at Day 28.
- Intercurrent event: Treatment discontinuation will be handled by the treatment policy strategy. The occurrence of the event is 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 (section 7.8).
- Population-level summary: Difference in proportion of patients alive and discharged at Day 28.

Key secondary endpoint #3 (see section 3.2.2) will be defined by the following estimand:

- Population: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- Variable: Ventilatory free days up to Day 28.
- Intercurrent events:
    - Death within Day 28 will be handled by the composite strategy (set as failure, Ventilatory free days=0);
    - Treatment discontinuation will be handled by the treatment policy strategy. The occurrence of the event is 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).
- Population-level summary: Difference in means of Ventilatory free days up to Day 28.

Key secondary endpoint #4 (see section 3.2.2) will be defined by the following estimand:

- Population: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- Variable: Patients requiring IMV (or ECMO) by Day 28.
- Intercurrent events:
    - Deaths due to a respiratory disease progression within Day 28 will be handled by the composite strategy and considered as an unfavorable event (set as failure);
    - Treatment discontinuation will be handled by the treatment policy strategy. The occurrence of the event is 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 (including missing data due to death for other causes).
- Population-level summary: Difference in proportion of patients requiring IMV (or ECMO) by Day 28.

Key secondary endpoint #5 (see section 3.2.2) will be defined by the following estimand:

- Population: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- Variable: Length of primary hospital stay.
- Intercurrent events:
  - Death during the primary hospital stay will be handled by the composite strategy and considered as an unfavorable event. Length of primary hospital stay will be imputed (as failure) to 28 days (if death before day 28) or date of death if death is >= 28 days).
  - Retrieved dropouts will be used for data imputation of all missing data.
- Population-level summary: Difference in means of length of hospital stay (days).

7.5 Sub-group analyses

Descriptive in nature analyses of primary and key secondary endpoints (sections 3.2.1 and 3.2.2) will be performed within subgroups defined by the following baseline characteristics:

- Age class (<65 yrs, ≥ 65 yrs),
- Sex,
- Baseline Clinical severity score (NIAID-OD <=5 vs. NIAID-OD 6)

7.6 Interim analysis

An interim analysis is planned when half of the planned evaluable patients are evaluable for the primary endpoints at Day 28 (i.e., first 250 randomized patients, ordered by randomization date and afterwards by random number, who meet the FAS definition and who reach Day 28 [including patients reporting "not done"] or death or IMV/ECMO or any intercurrent event prevent the reaching of Day 28) for identification of early superiority of reparixin (efficacy) or for early stop of the trial for futility.

The alpha-spending function method using O´Brien Fleming (OBF) boundaries will be used to control type error for the analyses of primary endpoints. P-values boundaries for efficacy and futility at interim and final analyses are reported in Table 4.

Table 4: OBF's spending functions boundaries for primary endpoints

Analysis	Sample Size (evaluable patients)	Boundaries for primary endpoint	
		Efficacy	Futility
Interim	250	p-value CCI	p-value CCI
Final	500	p-value CCI	p-value CCI

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

- Scenario 1 *(p-value is* CCI *efficacy) but* CCI *(futility)):* The communication will be "Not enough evidence for demonstrate superiority of reparixin". In this case, since results

are not considered enough to draw conclusions on primary endpoints, the enrolment shall continue up to the final analysis step, and treatments and follow-ups will proceed without modifications.

- Scenario 2 *(p-value* CCI *(efficacy))*: The communication will be "Superiority of reparixin is shown". In this case, enrolment of subjects shall be stopped and considered completed. Already-enrolled subjects continue their residual treatment and follow-up as planned.
- Scenario 3 *(p-value is* CCI *(futility))*: The communication will be "Superiority of reparixin is excluded". In this case, the enrolment (if still ongoing) shall be stopped, and all subjects will discontinue the treatment and will be followed-up until the next scheduled visit where they will be notified of the termination of the study. When database is closed, final analysis will be performed, and the clinical study report will be written and released.

To derive the difference estimate, confidence interval, and p-value at interim analysis, the stage-wise ordering of the sample space will be used. The resulting median unbiased estimate, confidence interval, and p-value will be computed and presented in the final report.

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

- Primary efficacy endpoint and variables for the definition of FAS population: all data must be checked in term of missingness and inconsistencies, and all queries resolved up to the Day 28. Consequently, the following forms will be cleaned before performing the analysis:
  - registration / informed consent,
  - inclusion/exclusion criteria and correlated forms,
  - eligibility,
  - randomization and IMP assignment,
  - study product administration summary,
  - end of treatment visit,
  - clinical severity score (NIAID-OS),
  - IMV/ECMO summary,
  - end of study,
  - death report.
- Data not related to the interim analysis: no specific cleaning activities are required at this point.

7.7 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:

- Major protocol changes,
- Information on subject screening,
- Study accrual,
- Eligibility violations,
- Demographics,
- Previous and concomitant medications,
- Medical history and concomitant diseases,
- Length of follow-up data available,

- Adverse events,
- IMV (or ECMO),
- Mortality,
- Vital signs, including basic summaries and longitudinal analyses,
- Lab values, including basic summaries and longitudinal analyses,
- ECGs, including basic summaries and longitudinal analyses,
- Discontinuation of medications.

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

Access to unblinded information on the efficacy analyses is allowed on DMC request 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. Since the DMC does not monitor primary endpoints for early efficacy termination (except for the Interim Analysis), no Type I error adjustment is necessary.

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

7.7.1 Interim Analysis results and DMC recommendations

On 21st June 2024 the DMC meeting for the Interim Analysis performed on 250 patients evaluable for the primary endpoint was held. The Data Monitoring Committee, on the basis of the results received by the unblinded independent statistician (as per DMC Charter), communicated verbally to the Sponsor their recommendation to stop the study for futility (as per Scenario CCI Official communication was sent to the Sponsor on 26 June 2024 as described in the recommendation letter from the DMC members [4].

Below a snapshot of the recommendation letter [4]:

Based on our review, we recommend:

☐ 1. The study may continue without modifications
☐ 2. The study may continue with modifications (see comments)
☒ 3. The study should be terminated (see comments)
☐ 4. The study should be temporarily suspended (see comments)
☐ 5. Other changes (see comments)

The impact on the primary endpoint, sensitivity analysis, secondary analysis and subgroup analysis are described in section 7.1, 10.1.1, 10.1.3, 10.2 and 7.5 respectively.

7.7.2 Interim Analysis: actions

Here below a summary of the steps and actions put in place after the DMC meeting including Interim Analysis:

- 21st JUNE - DMC meeting including Interim analysis (250 patients) assessment occurred
- 21st JUNE - DMC members verbal recommendation to early terminate the study for futility - Dompé team attended the open session and received the communication
- 26th JUNE - DMC written communication was received at Dompé confirming the verbal information of June 21st:
  - *1) Interim analyses of primary endpoint showed futility;*
  - *2) Safety long term issue needs to be explored*
- 26th JUNE - Dompé informed Clinical CRO of study discontinuation
- 27th JUNE – Clinical CRO informed all sites of REP0321 study to stop recruitment and interrupt treatment immediately providing the letter signed by the Dompé representative and dated 21 June [8]
- 04th JULY - Dompé approved and sent to Clinical CRO instruction on EDC completion for ongoing patients;
- 05th JULY - Clinical CRO shared instructions to sites for the patients follow-up management and study discontinuation [9]

Here below the instructions sent to the sites for the follow-up management and study discontinuation of the patients that were ongoing at the time of the Sponsor decision to stop the study.

Last visit performed (before study closure)	Next (last) visit post study closure
• Before Day 14	• Day 14 Visit and Day 28 Visit
• Between Day 14 (included) and before Day 28	• Day 28 Visit
• Between Day 28 (included) and before Day 90	• Day 90 Visit
• Between Day 90 (included) and before Day 180	• Day 180 Visit

These instructions, aligned with the study protocol requirements, were put in place with the aim to capture potential signals of long term safety issues, as suggested by the DMC recommendations. The strategy was shared and approved by the DMC.

End of Study page was requested to be completed by all the patient, with EOS date equal to the last visit completed as for the above table.

If last visit completed was Day 28 or Day 90 the Reason for Discontinuation was set at "Sponsor Decision".

7.8 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.

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.

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.

For the primary and key secondary analyses, all the missing data will be handled by means of Multiple Imputation (MI) as detailed in sections 7.4.1, 7.4.2, 10.1.2, and 10.2.2, using retrieve dropouts (MI-RD). For each endpoint its own "retrieved dropout patients set" will be detected.

7.9 Changes in the planned analysis

The following changes have been included, compared to the protocol [1]:

7.9.1 Changes Prior to Interim Analysis

- Section 12.1: Primary endpoint "Patient dead or requiring IMV (or ECMO) by Day 28": the following clarifications have been reported:
  - Assessment at Day 14 no longer mandatory. The NIAID_OS assessments considered for the endpoint evaluation are the ones collected during hospitalization and at Day 28 visit. Additional IMVs potentially occurring between discharge and Day 28 Visit must be included in the endpoint evaluation and are captured in a specific cumulative CRF form (IMV);
  - deaths occurring in Day 29 and 30 are included in the primary endpoint to be consistent with the time window (±2 days) allowed at Day 28 Visit.
- Section 3.2.2: key secondary endpoint "Occurrence of IMV (or ECMO) by day 28" has been rephrased as "Proportion of patients with IMV (or ECMO) by Day 28".
- Section 3.2.3: all-cause mortality incidence will be evaluated not only at Day 28 and Day 90, but also at Day 60, as per FDA request.
- Section 4.5: an updated definition of baseline is provided compared to the one provided in the protocol synopsis ("Baseline is defined as the parameters prior to and including the date of the randomization visit").
- Section 7.1: for the time-to-event analysis it was specified that all patients who discontinue the study will be handled as censored at the date of discontinuation, whatever the reason. Moreover only for time-to-death an additional analysis will be performed, where specific reasons for discontinuation will be incorporated into the analysis for determining failure status.
- Section 7.4.2: strategy for handling of intercurrent events for the key secondary estimands has been clarified.
- Section 7.4.2: handling of intercurrent events for the estimand of the key secondary endpoint #4 has been rephrased by imputing only death due to a respiratory disease progression as an unfavorable event.
- Section 7.4.2: variable for the estimand of the key secondary endpoint #5 has been updated in length of primary hospital stay, highlighting that the focus is on the primary hospital stay. For the same reason, also the handling of intercurrent events has been rephrased by changing "before hospital discharge" with "during the primary hospital stay".

- Section 7.5: New subgroup analyses have been added compared to protocol. In addition, the need of a sub-group analysis by concomitant disease will be investigated based on its interaction with treatment and, in case, performed.
- Section 7.6: a typo in Table 4 has been modified CCI CCI
- Section 10.1.2: the age class has been added as covariate in the logistic regression model compared to what specified in the protocol. This change impacts all sections who refers to section 10.1.2 for the definition of the analysis models.
- Section **Error! Reference source not found.**: To assess the robustness of the primary analysis, a two-dimensional tipping point analysis will be done. The shift parameters will be applied to both arm (reparixin and placebo) instead of just the reparixin arm. In the tipping point sensitivity analysis, the threshold for defining the tipping point is CCI CCI, depending on when efficacy is shown (at interim or at final analysis, respectively).
- Section 10.3.1.8: in addition to PaO2/FiO2 ratio, other lung function parameters (SpO2 (%), PaO2 (mmHg), FiO2 (0.21 to 1), SpO_2/FiO_2) will be evaluated.
- Section 12.1: the proportion of patients recovered at post-baseline visit will be defined as the proportion of patients with a downward shift from baseline of ≤2 points on the NIAID-OS or live discharge from hospital, not from screening as reported in the protocol.
- Section 12.1: the proportion of patients worsening at post-baseline visit will be defined as the proportion of patients with an upward shift from baseline of at least >1 point of the NIAID-OS, not from screening as reported in the protocol.
- Section 12.1: the derivation of the length of primary hospital stay has been updated accordingly to the estimands defined for the Key Secondary Endpoint #5 in Section 7.4.2.

CCI

- CCI
- CCI
- CCI CCI CCI

CCI

CCI

CCI

CCI

CCI

CCI

-

7.9.3 Other changes after stop of the study not relate to futility

- 3.2.3: secondary endpoint: For the following endpoints:
  - "Duration of IMV and/or ECMO at Day 90 and Day 180",
  - "ICU admission at Day 90 and Day 180",
  - "ICU length of stay at Day 90 and Day 180",
  - "Hospital length of stay at Day 90 and Day 180",
  - "Occurrence of infections at Day 90 and Day 180"

  "at" has been replaced by "by". This is to clarify that the cumulative information from Day1 to Day 90 (Day 180) will be evaluated.
- Section 8.6 – Prior Medication have been split into two groups: the Prior Medication and the "Other Prior Medication" to distinguish between those stopped in the 7 days before the screening or, however, prior to administration of the first dose of study treatment from those stopped earlier.
- Section 9.1: for IMP compliance calculation, a fourth daily administration for subjects having the drug intakes 6h apart, not mentioned in the study protocol, was also considered.

- Section 12.1 – some general adaptation and clarification to the derived variables has been added

7.10 Blind Data Review Meeting

BDRM will be held before DB lock. Any decision regarding protocol deviations and Analysis sets will be taken during the BDRM and documented in the DRR. Any further possible data re-allocation will be discussed during the BDRM and documented in the DRR.

7.11 Software

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

8. Evaluation of Demographic and Baseline Characteristics

8.1 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, %).
- Subjects randomized but not treated by treatment group, and overall (N, %).
- Subjects in each analysis set (FAS, SAF, PP) and reasons for exclusion by treatment group, and overall (N, %),
- Subjects who completed each planned visit (N, %).

The Table is based on the SCR set.

For the 2nd and 3rd bullet point the percentage denominator will be the number of ENR subjects;

For the 4th bullet point the percentage denominator will be the number of RND subjects within each arm, while for overall the denominator will be the number of ENR subjects.

For the other bullet points the percentage denominator will be the number of RND subjects.

Listings of patient disposition and subjects enrolled but not randomized will be provided based on ENR set.

A listing on screening failures will also be provided on the Screened Set.

8.2 Protocol deviations

All the protocol deviations will be discussed case by case before unblinding of the treatment code with the clinical team during the BDRM and described in the BDRM Report. Any deviation from these protocol procedures will be reported in the study-specific Protocol Deviation form.

Number of occurrences and of subjects with at least one major and minor protocol deviation will be summarized for each treatment and overall. Major deviations are the deviations impacting the primary efficacy analysis while minor deviations are the deviations not impacting the primary efficacy analysis. Major and minor protocol deviations will be tabulated and listed separately. A listing of protocol deviations classified as “No Analysis deviation” (not impacting any analysis) will also be provided.

As an example, a non-exhaustive list of Major 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*

As a result of the discussion at the BDRM, the following rules will be put in place for the subjects receiving a medication kit different from the one assigned by the RTSM system:

- The PD have been classified as Major PD at the time of the blinded DRM;
- After the unblinding procedures, they will be considered:
    - Major PD if the IMP of at least one dispensed Kit is different from the IMP of the Kit assigned by the RTSM system.
    - Minor PD: if the IMP of the dispensed Kit is equal to the IMP of the Kit assigned by the RTSM system.

*The **sources** to detect Protocol Deviations for the statistical analysis (SAS DRM outputs, clinical PD Log…), will be listed and properly described in the DRR.*

8.3 Study discontinuations

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

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

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

The same tables will be provided for FAS set and for randomized patients not included in the FAS set (not treated).

8.4 Demographics and baseline characteristics

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

The following demographic information will be reported:

- Geographic region (country and continent) of the site.
- 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 no,
    - Reasons for not performing
  - If yes,
    - Result of urine dipstick (Negative, Positive)
    - If positive,
      - confirmed by performing the serum pregnancy test? (Yes, No)
      - If no,
        - Reasons for not performing
      - If yes,
        - Result of serum pregnancy test
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino).
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other);
- Height (cm),
- Weight (Kg)
- BMI (BMI≤25kg/m^2 vs 25kg/m^2<BMI≤30kg/m^2 vs BMI>30kg/m^2).

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))
- 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))

The following information on influenza will be reported:

- Has the patient recently performed a test for influenza? (Yes, No)
- If yes,
  - Influenza test result (Positive or Negative);
- Did the patient receive vaccination for influenza? (Yes, No)
- If yes,
  - Total number of doses received

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

- Was the sample collected? (Yes, No)
- If no,
  - Reasons for not performing
- If yes,
  - SARS-CoV-2 RT-PCR test result (Positive, Negative)
  - Quantitative result
- 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 onset of COVID-19 signs and symptoms to randomization
- Symptoms
- Time from hospital/ED admission to randomization

The following information on Pneumonia will be reported:

- Time from Date of onset of Community-Acquired Pneumonia signs and symptoms to randomization
- Symptoms

8.5 Medical/Surgical History and Concomitant Diseases

A disease is defined:

- "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) dictionary and reported in separate tabulations. Frequency distributions and percentages will be summarized by treatment, by System Organ Class (SOC) and Preferred Term (PT).

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.

8.6 Prior and concomitant medications

Based on the start/end medication date(s) reported in the eCRF (see Table 7 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 case of missing information not directly allowing allocation to the above categories of medications, the medication will be considered as concomitant.

Other Prior, Prior and/or concomitant medications will be coded using World Health Organization Drug Dictionary 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.

Subjects taking more than one medication classified in the same category will be counted only once.

Other Prior medication category will only be listed.

8.7 Other baseline characteristics

No statistical testing will be carried out for comparing baseline characteristics.

8.7.1 Clinical severity score (NIAID-OS)

Baseline NIAID-OS will be descriptively summarized by treatment and overall as an ordinal variable. Assessments reported during the "Baseline – Day 1" visit and assessment at baseline as per Baseline definition given in section 4.5 will be presented. Information on the NIAID-OS assessment (performed/not performed) will be reported, with reasons in case of not execution.

NIAID-OS at screening and NIAID-OS at randomization (IWRS) will also be descriptively summarized.

8.7.2 Lung function

Baseline lung function parameters:

- SpO_2 (%),
- PaO_2 (mmHg),
- FiO_2 (0.21 to 1),
- PaO_2/FiO_2 ratio (mmHg) (see Table 5 for more details on the derivation of PaO_2/FiO_2)

will be descriptively summarized by treatment and overall as a continuous variable. Investigator's interpretation (Normal, Abnormal NCS, Abnormal CS, No Result) for each parameter (except FiO_2 (0.21 to 1)) will be reported as well. Information on the lung function assessment (performed/not performed) will be reported, with reasons in case of not execution.

8.7.3 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 / already performed for clinical needs) will be reported, with reasons in case of not execution. The following information will be reported:

- Method (X-rays, CCI , Lung Ultrasound)
- Confirmation of lung involvement and inflammation (Yes, No) (for patients enrolled under Protocol version 1.0)
- Confirmation of new/increased pulmonary infiltrate(s) (Yes, No) (for patients enrolled under Protocol version 2.0)
- Clinical evaluation(s)

8.7.4 Child Pugh Score and Class.

Baseline Child Pugh Score will be descriptively summarized by treatment and overall as a continuous variable along with the corresponding classes. Information on the Child Pugh Score assessment (performed/not performed) will be reported.

8.7.5 Physiological parameters

Baseline NEWS will be descriptively summarized by treatment and overall as a continuous variable. Information on the NEWS assessment (performed/not performed) will be reported.

8.7.6 Pneumonia Severity Index (PSI)

Baseline PSI (total score) will be descriptively summarized by treatment and overall as continuous variable. Information on the PSI assessment (performed/not performed) will be reported, with reasons in case of not execution.

9. Evaluation of Treatment Compliance and Exposure

9.1 Compliance to IMP

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 tables 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 12.1.

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.

9.2 Exposure to IMP

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 the formula reported in Table 5.

10. Evaluation of Efficacy

Rules for ***derivation of clinical endpoints*** are reported in section 12.1.

Primary endpoint and key secondary endpoints will be presented as categorical / continuous variable, depending on the nature of the variable, with the pertinent univariate test statistic (Fisher exact test

or t-test/Mann-Whitney for categorical and continuous variable respectively) and by multivariate models as described in section 10.1.2 and 10.2.2.3.

10.1 Analysis of primary efficacy endpoint

10.1.1 Testing strategy and multiplicity adjustment

The hypothesis testing of the primary efficacy endpoint was originally planned as follows:

The following null hypothesis is defined: the proportion of patients dead or requiring IMV (or ECMO) by Day 28 in reparixin ($T_{REPARIXIN}$) is greater or equal than control ($T_{CONTROL}$):

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

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

Where $T_{REPARIXIN}$ and $T_{CONTROL}$ are the proportions of patients dead or requiring IMV (or ECMO) at Day 28 for reparixin and control groups, respectively. The null hypothesis H_0 will be rejected, and superiority of reparixin is declared if primary analysis p-value will be lower than pre-specified threshold, depending at which analysis (interim or final) the test is performed. Thresholds are calculated according to OBF's spending function boundaries and are reported in Table 4.

Considering the premature closure of the study for futility, the analysis of the primary endpoint will be descriptive in nature.

The test will be kept as one-sided at alpha level=0.025 for consistency with the analysis performed at the Interim Analysis; the thresholds defined by the OBF's spending function boundaries will no longer be applied.

10.1.2 Analysis details

The primary endpoint will be analyzed by means of a logistic regression model adjusting by pre-defined factors (treatment, baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6), sex, age class (<65 vs >=65 yrs.) and presence of concomitant disease as fixed) and a one-sided test will be used to test for differences between treatment groups.

MI-RD will be used to handle missing data. Retrieved dropout patients are defined as 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. Consequently, MI will be performed based on the subjects' allocated treatment arm and observed values as covariates in a MI regression model using data from retrieved dropout patients that have the primary endpoint assessment done. Only data up to Day 28 will be used to impute primary endpoint missing data.

For the imputation of missing data a logistic regression model will be created by including treatment, baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6), sex, age class (<65 vs >=65 yrs.) and presence of concomitant disease as covariates (for convenience we will refer to this method as "MI regression model"). One thousand data sets will be generated. MI will be implemented in the following steps:

1. Missing primary endpoint data 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 datasets with observed and imputed data will be analyzed using the logistic regression model. Rubin's rule will be used for combining results to draw inference.

If there are not enough retrieved dropouts for convergence of the MI regression model, a reference-based MI approach will be adopted to consider a Missing Not at Random (MNAR) mechanism for missing data: imputation of values in the reparixin arm (above step #1) will be done using the non-missing values from all the patients in the control group (this approach will be referred as "Copy Reference"). This approach does not assume benefits for reparixin in case of missingness due to discontinuation or other reasons and limits a post-missing clinical effect to that of placebo.

If, after applying the Copy-Reference approach with the full MI regression model, the convergence issues are still present, the Copy-Reference approach will be used with a reduced set of covariates. Covariates will be removed from the model with the following order:

- presence of concomitant disease removed as first (sex, age (<65 vs >=65 yrs.) and baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6) as covariates)
- in case of persistent convergence issues, sex removed as second (age (<65 vs >=65 yrs.) and baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6) as covariates)
- in case of persistent convergence issues, age removed as third (baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6) as covariates)
- in case of persistent convergence issues, baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6) removed as last (only treatment in the model)

The final decision on the use of the MI-RD (primary method) vs Copy-Reference for the imputation of the missing primary endpoint will be done at the time of the analysis and reported in the CSR.

In the case a significantly small number of events occurs, this may potentially lead to cells with zero events and thus lead to issue in estimating treatment effect and its standard error with the logistic regression model.

In this case, the removal of covariates from the model (as detailed above) will be adopted with the same order of removal.

If none of the logistic models will be able to provide estimates for the treatment effect and its standard error, the comparison between treatments in terms of p-value will be provided by the univariate Fisher's exact test.

Whether for MI-RD or Copy-Reference approach, the covariate adjusted absolute risk difference between reparixin and placebo at Day 28 will be displayed together with the corresponding two-sided 95% confidence intervals and the one-sided p-value. In addition to absolute risk difference, the covariate adjusted odds ratio and its 95% confidence interval will be provided.

10.1.3 Sensitivity analyses

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

10.1.3.1 Missing at Random assumption

The comparison between treatment and control will be performed by means of MI under Missing at Random (MAR) assumption instead of MNAR. MI will be implemented in the following steps (except for death as intercurrent event: in this case an unfavorable value will be imputed to the primary endpoint):

- Missing primary endpoint data will be imputed using the MI regression model (section 10.1.2). 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. These datasets will be utilized in Step #2.
- Each of the 1000 datasets with observed and imputed data will be analyzed using the logistic regression model. Rubin's rule will be used for combining results to draw inference.

The adjusted estimated treatment odds ratio between reparixin and placebo at Day 28 will be displayed together with the corresponding two-sided 95% confidence intervals and p-value. In addition to the absolute risk difference, the odds ratio and its 95% confidence interval will be provided.

10.1.3.2 Copy-Reference

In case the Copy-Reference approach will not be used for the primary analysis (instead of MI-RD), it will we performed for sensitivity purposes. See details in 10.1.2.

10.1.4 Supplementary analyses

10.1.4.1 Complete cases

The analysis of primary endpoint will be performed by fitting the logistic regression model described in section 10.1.2 on complete cases only i.e., without considering patients with missing primary endpoint and without implementing the MI.

10.1.4.2 Per-protocol

The analysis of primary endpoint described in section 10.1.2 will be entirely (including MI) reproduced on the PP set instead of FAS.

10.2 Analysis of key secondary efficacy endpoints

10.2.1 Testing strategy and multiplicity adjustment

The analysis of the key secondary efficacy endpoints was originally planned hierarchically (in a conditional sequence manner) according to the following rule:

in case the analysis of the primary endpoints leaded to rejection of null hypothesis, the following key secondary endpoints will be tested in a conditional sequential manner to show superiority of reparixin versus control (at alpha one-sided 0.025) according to the following ranking:

1. *All-cause mortality at Day 180,*
2. *Proportion of patients alive and discharged at Day 28,*
3. *VFD at Day 28,*
4. *Proportion of patients with IMV (or ECMO) by Day 28,*
5. *Length of primary hospital stay.*

This hierarchical test strategy protects the family-wise false positive error rate at the overall one-sided 0.025 level.

Considering the premature closure of the study for futility, all key secondary endpoints will be analyzed independently of results on primary endpoint. No hierarchy is established between the key

secondary endpoints and no more multiplicity correction is required. Comparison by treatment will be performed by means of tests that will be descriptive in nature and each test will be two-sided at alpha level=0.05.

10.2.2 Analysis details

Analysis of key secondary endpoints are detailed below in sections 10.2.2.1 – 10.2.2.5. P-values for comparison between treatments are the following:

1. P-value associated with treatment variable from logistic regression model on proportion of patients died within Day 180,
2. P-value associated with treatment variable from logistic regression model on proportion of patients alive and discharged at Day 28,
3. P-value associated with treatment variable from ANOVA regression model on VFD at Day 28,
4. P-value associated with treatment variable from logistic regression model on proportion of patients with IMV (or ECMO) by Day 28,
5. P-value associated with treatment variable from ANOVA regression model on length of primary hospital stay.

10.2.2.1 All-cause mortality at Day 180

The number and proportion of died patients within Day 180 will be reported. The proportion will be analyzed with the same MI approach and logistic regression model described in section 10.1.2 for the primary efficacy endpoints.

In addition, time-to-event method (section 7.1) will be used to summarize the time to death events from Day 1.

10.2.2.2 Proportion of patients alive and discharged at Day 28

The number and proportion of patients alive and discharged at Day 28 will be reported. The proportion will be analyzed as described in section 10.1.2.

10.2.2.3 VFD at Day 28

VFD will be analyzed by means of an ANOVA adjusting by pre-defined factors (treatment, baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6), sex, age class (<65 vs >=65 yrs.) and presence of concomitant disease as fixed effect) and a two-sided test will be used to test for differences between treatment groups. If assumption of normality is not confirmed (by both visual inspection of distribution and the Shapiro-Wilk's test), the analysis will also be performed using the log-transformed scale. For the analysis on the log-transformed data, log-transformation will be applied only after the multiple imputation step. The imputation process will force the imputed values to be within the range 0-28. Before the log-transformation, a +0.5 will be added to the original scale values. In this case zero values will be avoided.

For the imputation of missing VFD data at Day 28, a MI regression model will be created by including treatment, baseline disease severity (NIAID-OS ≤5 vs. NIAID-OS 6), sex, age class (<65

vs >=65 yrs.) and presence of concomitant disease as covariates. One thousand data sets will be generated. MI will be implemented in the following steps:

1. Missing VFD 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 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.

If there are not enough retrieved dropouts for convergence of MI regression model, the Copy Reference approach will be used. The same process as in section 10.1.2 will be applied. 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 treatment differences between reparixin and placebo at Day 28 will be displayed together with the corresponding two-sided 95% confidence intervals and p-value.

10.2.2.4 Proportion of patients with IMV (or ECMO) by Day 28

The number and proportion of patients with IMV (or ECMO) by Day 28 will be reported. The proportion will be analyzed as described in section 10.1.2.

10.2.2.5 Length of primary hospital stay

Length of primary hospital stay will be analyzed by means of an ANOVA as described in section 10.2.2.3.

10.3 Analysis of all secondary efficacy endpoints

10.3.1 Analysis details

Independently of results on primary and key secondary endpoints, all secondary endpoints (sections 3.2.2 and 3.2.3) will be analyzed and compared by treatment by means of tests that will be descriptive in nature. No multiplicity correction is required.

10.3.1.1 Clinical failure by Day 3 and Day 7

The number and proportion of patients who experienced a clinical failure by Day 3 and by Day 7 will be reported at each available timepoint and compared by means of Fisher's exact test.

A bar-plot by treatment and by Day will be provided.

10.3.1.2 ICU-free days at Day 28

The ICU-free days at Day 28 will be analyzed according to MI approach and ANOVA model described in section 10.2.2.3Death within Day 28 will be handled as an unfavorable event and ICU-free days will be set at 0. An additional analysis without imputing death as unfavorable event will be performed; no MI will be implemented and comparison will be performed using the two-sample Mann-Whitney U test. Assumption of normality will be checked by Shapiro-Wilk's test only.

10.3.1.3 Days free of IMV/ECMO at Day 28

The IMV/ECMO-free days at Day 28 will be analyzed according to MI approach and ANOVA model described in section 10.2.2.3. Death due to progression of the respiratory disease within Day 28 will be handled as an unfavorable event and IMV/ECMO-free days at Day 28 will be set at 0. An additional analysis without imputing death due to progression of the respiratory disease as unfavorable event will be performed; no MI will be implemented and comparison will be performed using the two-sample Mann-Whitney U test. Assumption of normality will be checked by Shapiro-Wilk's test only..

10.3.1.4 Duration of antibiotic therapy (days) at Day 28

The duration of antibiotic therapy (days) at Day 28 will be reported and compared by means of the Mann-Whitney U test.

10.3.1.5 Hospital free days at Day 28

The hospital-free days at Day 28 will be analyzed according to MI approach and ANOVA model described in section 10.2.2.3. Death within Day 28 will be handled as an unfavorable event and Hospital-free days will be set at 0. An additional analysis without imputing death as unfavorable event will be performed; no MI will be implemented and comparison will be performed using the two-sample Mann-Whitney U test. Assumption of normality will be checked by Shapiro-Wilk's test only

10.3.1.6 Proportion of patients recovered at each available timepoint

The number and proportion of patients recovered will be reported at each available timepoint and compared by means of Fisher's exact test.

A bar-plot by treatment and by visit will be provided.

10.3.1.7 Proportion of patients worsening at each available timepoint

The number and proportion of patients worsened will be reported at each available timepoint and compared by means of Fisher's exact test.

A bar-plot by treatment and by visit will be provided.

10.3.1.8 PaO_2/FiO_2 at each available timepoint

PaO_2/FiO_2 ratio (mmHg) and other lung function parameters (SpO_2 (%), PaO_2 (mmHg), FiO_2 (0.21 to 1), SpO_2/FiO_2), and their changes from baseline will be analyzed at each available timepoints by means of descriptive statistics. In case of different units of measure considered for the same parameter, all values will be converted into Standard International units (if applicable) or to the same unit.

Comparison between treatments will be performed by means of two-sample t-test or, if assumption of normality is not confirmed (by the Shapiro-Wilk's test), the analysis will also be performed using the two-sample Mann-Whitney U test.

For each parameter:

- The observed medians and median changes from baseline will be graphically represented by treatment at each timepoint.
- The change from baseline will be evaluated by means of a mixed model for repeated measurements adjusting for baseline value, treatment, baseline disease severity (NIAID-OS

≤5 vs. NIAID-OS 6), sex, age class (<65 vs >=65 yrs.), presence of concomitant disease, visit, and treatment-visit interaction as fixed factors and patient as random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom. If the model does not converge with the unstructured covariance matrix, then the model will be simplified using only baseline value, treatment, visit, and treatment-visit interaction as fixed factors and patient as random effect. If the model still does not converge, different covariance structures will be used, following the below order:

- a heterogeneous Toeplitz covariance structure,
- a Toeplitz covariance structure,
- a compound symmetry (CS) structure.

The adjusted estimated treatment differences between reparixin and placebo at each visit will be presented together with the p-value and the corresponding 95% confidence interval. The tests of the fixed effects will be presented, together with the estimated least squares means and the corresponding 95% confidence interval.

- Summary statistics of investigator's interpretation (Normal, Abnormal NCS, Abnormal CS) will be provided by treatment arm at each timepoint. The comparison between the two study treatment arms will be performed by means of a Fisher's exact test at each timepoint.
- 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 will be presented.

10.3.1.9 All-cause mortality at Day 28, Day 60 and Day 90

The number and proportion of died patients within Day 28, 60 and 90 will be reported. The proportion will be analyzed as described in section 10.1.2.

10.3.1.10 Hospital re-admission by Day 90 and Day 180

The number and proportion of patients with hospital re-admission by Day 90 and Day 180 will be reported at each available timepoint and compared by means of Fisher's exact test.

A bar-plot by treatment and by visit will be provided.

10.3.1.11 Time to discharge or to a NEWS of ≤ 2

Time to discharge or to a NEWS of ≤ 2 (for 24 hours), whichever occurs first, will be analyzed and graphically represented as described in section 7.1 following a time-to-event approach.

10.3.1.12 Change in inflammatory markers (LDH, CRP, hs-CRP, ferritin; D-dimer, PCT) and cytokines at each available timepoint

Inflammatory markers and cytokines values and their change from baseline will be analyzed at each available timepoint by means of descriptive statistics. Comparison between treatments will be performed by means of two-sample t-test or, if assumption of normality is not confirmed (by the Shapiro-Wilk's test), the analysis will also be performed using the two-sample Mann-Whitney U test.

For each parameter, the observed medians and median changes from baseline will be graphically represented by treatment at each timepoint.

If applicable, summary statistics of investigator's interpretation (Normal, Abnormal NCS, Abnormal CS) and Indicators will be provided by treatment arm at each timepoint. The comparison between the two study treatment arms will be performed by means of a Fisher's exact test at each timepoint.

10.3.1.13 Change in quality of life using EQ-5D-5L at Day 90 and Day 180

The number and proportion of patients of each level (1 - no problems, 2 - slight problems, 3 - moderate problems, 4 - severe problems, 5 - extreme problems) for each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be reported. Shift tables from hospital discharge to Day 90 and Day 180 will be produced to show the change in numbers and proportions between the two timepoints and discharge. The shift tables will be shown by treatment arm. A Chi-squared test will be used to assess the independence between the hospital discharge and Day 90/Day 180 for each treatment arm.

The EQ-VAS score at hospital discharge, Day 90, and Day 180, and their changes will be analyzed by means of descriptive statistics as a continuous variable. The Undiscounted Quality-adjusted life years (QALYs) between Hospital Discharge and Day 90 and between Hospital Discharge and Day 180 will also be analyzed by means of descriptive statistics as a continuous variable. The 95% CIs for the mean will also be shown. Comparison between arms will be performed by means of unpaired t-tests. In case of normality is not confirmed (by the Shapiro-Wilk's test), the analysis will also be performed using the Mann-Whitney U test.

See Section 12.5 for more details on the EQ-5D-5L.

10.3.1.14 Duration of IMV and/or ECMO by Day 90 and Day 180

The duration of IMV and/or ECMO at Day 90 and Day 180 will be reported and compared by means of the Mann-Whitney U test.

10.3.1.15 ICU admission by Day 90 and Day 180

The number and proportion of patients requiring ICU admission will be reported at Day 90 and Day 180 and compared by means of Fisher's exact test.

A bar-plot by treatment and by visit will be provided.

10.3.1.16 ICU length of stay by Day 90 and Day 180

The length of ICU stay at Day 90 and Day 180 will be reported and compared by means of the Mann-Whitney U test.

10.3.1.17 Hospital length of stay by Day 90 and Day 180

The length of hospital stay at Day 90 and Day 180 will be reported and compared by means of the Mann-Whitney U test.

10.3.1.18 Occurrence of infections by Day 90 and Day 180

The proportion of patients with at least one infection within Day 90 and Day 180 Visits will be reported and compared by means of Fisher's exact test. In addition, the number and the rate of infections up to Day 180 will be presented. The rate will be calculated as

$$Infections\ rate\ (up\ to\ Day\ 180) = \frac{total\ number\ of\ \text{infections from Day 1 to Day 180}}{cumulative\ followup\ from\ Day\ 1\ to\ Day\ 180}$$

The rate will be analyzed by Poisson regression using an off-set of log (follow-up time until Day 180) and treatment, baseline disease severity, sex, age class and presence of concomitant disease as covariates.

10.3.1.19 Clinical severity score (NIAID-OS) at each available timepoint

NIAID-OSs will be analyzed at each available timepoint by means of descriptive statistics as an ordinal variable. Comparison between treatments will be performed by means of two-sample Mann-Whitney U test.

Boxplot by treatment and by visit will be provided.

10.3.1.20 Physiological parameters at each available timepoint

NEWS score will be analyzed at each available timepoint by means of descriptive statistics as an ordinal variable. Comparison between treatments will be performed by means of two-sample Mann-Whitney U test.

Boxplot by treatment and by visit will be provided.

CCI

CCI

CCI

CCI

CCI

11. Evaluation of Safety

Safety will be evaluated on the SAF set. SAF set will be based according to the actual treatment received at randomization.

11.1 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 6). In case of TEAE, the event can be further classified as:

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

according to the available parts of the onset and the end dates (Table 6).

All AEs will be coded by SOC and PT according to MedDRA 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 AEs within each SOC in decreasing order of total frequency. Along with AEs, 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 lung fungal infection TEAE by Day 28,
  - 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 lung fungal infection TEAEs by Day 28.

- 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 ADRs by Primary SOC and PT and by study period (on treatment/follow-up and overall).
- Summary of 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 lung fungal infection TEAEs by Day 28 by Primary SOC and PT.
- Listing of all AEs by Patient.
- Listing of all AEs leading to IMP discontinuation.
- Listing of all AEs leading to study discontinuation.
- Listing of SAEs by Patient.
- Listing of ADR by Patient.
- Listing of Deaths.

11.2 Clinical laboratory evaluation

Analysis of clinical laboratories data will be performed by treatment for Hematology and Biochemistry tests. In case of different units of measure considered for the same laboratory parameter, all values will be converted according to the units reported in the table below:

Test Name	Analysis Unit
Albumin	g/dL
Alanine Aminotransferase	U/L
Aspartate Aminotransferase	U/L
Basophils	10^3/uL
Direct Bilirubin	mg/dL
Bilirubin	mg/dL
Calcium	mmol/L
Chloride	mmol/L
Creatinine	mg/dL
C Reactive Protein	mg/L
D-Dimer	ug/mL
Eosinophils	10^3/uL
Ferritin	ng/mL
Glomerular Filtration Rate, Estimated	mL/min/1.73m2
Glucose	mmol/L
Hematocrit	%

Hemoglobin	g/dL
Interleukin 1 Alpha	ng/ml
Interleukin 1 Beta	pg/ml
Interleukin 6	pg/ml
Interleukin 8	pg/ml
Prothrombin Intl. Normalized Ratio	RATIO
Potassium	mmol/L
Lactate Dehydrogenase	U/L
Lymphocytes	10^3/uL
Monocytes	10^3/uL
Neutrophils	10^3/uL
Procalcitonin	ug/L
Platelets	10^3/uL
Erythrocytes	10^6/uL
Sodium	mmol/L
Leukocytes	10^3/uL

Leukocyte differential counts

For the following laboratory tests: Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils:
in case the values recorded in the CRF are collected as "%" (part of the total count of WBC), the absolute values for each parameter will be derived by applying the following algorithm:

<lab test result in %> x WBC count / 100.

This derivation will only be applied when the absolute value for the laboratory test is not available, and both results (lab test and WBC count) are collected in the same sample (same date and visit).

D-Dimer and Cytokines

If the D-Dimer or Cytokines parameters are reported with a result containing a qualifier (e.g.: "<2.5", ">3.4") the value will be analyzed by striping 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.

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);
- Observed medians and median changes from baseline plots by actual treatment

11.3 Vital signs

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

- Systolic Blood Pressure (mmHg),
- Diastolic Blood Pressure (mmHg),
- Heart Rate (b/min),
- Respiration Rate (n/min).

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);
- Observed medians and median changes from baseline plots by actual treatment

11.4 ECGs

Summary statistics by treatment of Heart Rate (b/min), PQ interval (msec), QT (msec), QTcB (msec) and ECG interpretation will be provided along with summary of the change/shift from baseline at each available timepoint. 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);
- Observed medians and median changes from baseline plots by actual treatment

12. Derivations and date conventions

12.1 Variable derivation

Table 5: Variable derivation rules

For efficacy and safety endpoints, data will be evaluated and reported according to the Visit at which they have been collected, even if performed out-of-window, or according to the number of days from Day 1, depending on the type of the endpoint (the number of days from Day1 is used when in the derived parameter the specification "(days)" is reported).

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 completed when Primary reason for end of treatment is = "Day 21 treatment completed" or [Primary reason for end of treatment is = "IMP Discontinuation Criteria" and the criteria specified is = "The patient is discharged from the hospital"]; 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).

Parameter	**Calculation**
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.
CCI	
CCI	
CCI	
Antibiotic therapy	A medication in "Prior and Concomitant Medication" is considered an antibiotic therapy if classified with the following ATC codes: • J01 • J02AA • J04AB • J05

Parameter	Calculation
Infection	An AE is considered infection if the MedDRA SOC = "Infections and infestations"
Lung fungal infection	An AE is considered Lung Fungal Infection if the MedDRA SOC = "Infections and infestations" and MedDRA PT="Pneumonia fungal"
Time from randomization to study discontinuation (days)	End of Study date – Randomization date + 1
Length of study (days)	Last available date – Randomization date + 1
Last available date	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^ If reason for discontinuation = "Sponsor Decision" and EOS date≥"27Jun2024" and EOS date<> any study visit date@, last available date=most recent visit date§ or assessment^ **For patient who dies → end of study date = date of death* *§at Day 90 and Day 180 visits to be considered only if patient Vital Status = "Alive" in the form "Phone Follow-Up Assessments"* *^assessment including information from all summary pages (AEs, CM…)* *@patients who discontinue >= 27th Jul 2024; investigator did not perform any phone call*
COVID-19 patients	If SARS-COV-2 VIROLOGY (RT-PCR) result (screening or baseline) = Positive. If SARS-COV-2 VIROLOGY (RT-PCR) result (screening or baseline) = Negative, then patients will be considered as "non COVID-19 patients". In case of missing assessment, patients will not be classified.

Parameter	Calculation
Time from Date of last COVID-19 vaccination to randomization	Randomization date – Date of last COVID-19 vaccination +1
Time from Date of onset of COVID-19 signs and symptoms to randomization	Randomization date – Date of onset of COVID-19 signs and symptoms + 1.
Time from Date of onset of Community-Acquired Pneumonia signs and symptoms to randomization	Randomization date – Date of onset of Community-Acquired Pneumonia signs and symptoms + 1.
Extent of exposure (hours)	Exposure (hours) is calculated as total number of hours under treatment: (Date:time of last administration of IMP – Date:time of first administration of IMP), as defined in section 4.2 Date/time first administration of IMP missing: 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" Date/time last administration missing: 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
Extent of exposure (days)	Date of last administration of IMP – Date of first administration of IMP + 1.

Parameter	Calculation
Patient dead or requiring IMV (or ECMO) by Day 28	A patient is considered as dead or requiring IMV (or ECMO) by Day 28: - if at least one NIAID-OS assessment up to Day 28 Visit* is equal or greater than 7, OR - if patient dies before Day 28^ (included). Otherwise, a patient is considered as not requiring IMV (or ECMO) by Day 28: - if all the expected NIAID-OS assessments up to Day 28 Visit* are lower than 7, AND - if patient does not die before Day 28^ (included). Otherwise, the endpoint is set as missing. **The NIAID_OS assessments considered for the endpoint evaluation are the ones collected during hospitalization and at Day 28 visit. Additional IMVs potentially occurring between discharge and Day 28 Visit must be considered. They are captured in a specific cumulative CRF form (IMV). These cases will be considered for the analysis only if occurring up to Day 30 (included).* *^Deaths occurring at Day 29 and 30 are included to be consistent with the time window (±2) allowed at Day 28 Visit*
Last available day (days)	Last available date – Day 1 date + 1 Note: if patient dies, last available day = time to death

Any death up to Day 180 [Day XX] (days)	A patient is considered a death up to Day 180 (failure): if patient dies on or before Day 180 (included) [time to death<=180] (otherwise) A patient is considered not a death up to Day 180: if patient is alive at Day 180 Visit (performed at Day 166 or after, [[last available day>=166]) or dies after Day 180 [time to death>180] (otherwise) For the following cases the endpoint is set as missing*: - patients alive at Day 180 Visit, with visit performed before Day 166 (i.e., <(Day 180 – 14 days); [last available day <166]) - patients who discontinue the study before Day 180 visit The algorithm for Death up to Day 28, 60 and 90 is the same. 180 will be replaced by 28, 60 , 90. Time window changes as follows: -Any death up to Day 28 -> time window 2 days (alive with visit performed before Day 26 → outcome set at missing) -Any death up to Day 90 -> time window 7 days (alive with visit performed before Day 83 → outcome set at missing) -Any death up to Day 60 -> time window 7 days (alive with visit performed before Day 53 → outcome set at missing) For the "time-to-event" variable (For Day 180 only) the following specifications should also be followed: - the cases where the endpoint is set at missing (identified by the * above) are censored at the last available date: An additional analysis of the time-to-event variable will consider study discontinuation as follows: - for patients discontinuing the study before Day 180 (included) due to Adverse Event or Lost to follow-up, the endpoint is set as failure with time to event set at the last available date;

Parameter	Calculation
	- patient discontinuing the study before Day 180 (included) for other reasons will be censored at the last available date
Time to discharge	Date of discharge – Day 1 date + 1
Patients alive and discharged at Day 28 (days)	A patient is considered not "alive and discharged" at Day 28: - if patient dies before Day 28 (included) [died and time to death<=28], OR - if patient is not discharged before Day 28 (included) [time to discharge>28 OR (discharge never occurred and last available day >= 26)]. Otherwise, a patient is considered alive and discharged at Day 28: - If subject followed (last available date) for the minimum period defined for "Day 28 +/- 2 days" visit (last available day >= 26) Otherwise, the endpoint is set as missing.
Ventilatory days up to Day 28 (days)	For all uses of IMV or ECMO during the first 28 days (between Day 1 date and Day 28 date): Sum of [min(End date, last available date) – Start date + 1] If End date (or last available date) is after Day 28 date, then Day 28 date will be used instead.
VFD at Day 28 (days) [10]	If patient is alive at Day 28 (last available day >=26): VFD = 28 – Ventilatory days up to Day 28 If patient dies within Day 28: VFD = 0 Otherwise, If subject is alive and followed (last available date) for <26 days (28 days +/- 2) the endpoint is set as missing.

Parameter	Calculation
Patient requiring IMV (or ECMO) by Day 28	A patient is considered as requiring IMV (or ECMO) by Day 28: - if at least one NIAID-OS assessment up to Day 28* is equal to 7, OR - patient is died by Day 28^ for a progression of the respiratory disease# Otherwise, a patient is considered as not requiring IMV (or ECMO) by Day 28: - if all expected NIAID-OS assessments up to Day 28* are lower than 7. Otherwise, the endpoint is set as missing. **The NIAID_OS assessments considered for the endpoint evaluation are the ones collected during hospitalization and at Day 28 visit. Additional IMVs potentially occurring between discharge and Day 28 Visit must be considered. They are captured in a specific cumulative CRF form (IMV) These cases will be considered for the analysis only if occurring up to Day 30 (included).* *^Deaths occurring in Day 29 and 30 are included to be consistent with the time window (±2) allowed at Day 28 Visit* *#progression of respiratory disease identified as fatal SAEs by the following condition: [SOC_NAME="Respiratory, thoracic and mediastinal disorders" and HLT_NAME in ("Respiratory failures (excl neonatal)", "Lower respiratory tract infections NEC", "Respiratory tract disorders NEC", "Viral upper respiratory tract infections")]*
Length of primary hospital stays (days)	If a patient is alive at discharge, then: Length = Date of discharge –Hospital admission date* + 1 In case of death during the primary hospital stay AND before Day 28: Length = 28 days In case of death during the primary hospital stay AND on or after Day 28: Length = Date of death – Hospital admission date* + 1 *if a patient died and date of discharge is missing it is assumed that the death occurred during hospital stay: Date of discharge=Date of death Otherwise, the endpoint is set as missing. If Date of Hospital admission is before Day 1 date, then Day 1 date (*start of treatment*) will be used instead*.

Parameter	**Calculation**
Clinical failure by Day 3 [Day 7] (days)	A patient is considered as experiencing clinical failure by Day 3 [Day 7]: - if patient dies before Day 3 [Day 7] (included), OR - if patient requires IMV (or ECMO) by Day 3* [Day 7*^], OR - if patient uses vasopressor§ before Day 3 [Day 7] (included). A patient is considered as not experiencing clinical failure by Day 3 [Day 7]: - If subject followed (last available date) for the minimum period defined for "Day xx" (Day 3: last available day >= 3; Day 7: last available day>=7) AND - if patient does not die before Day 3 [Day 7] (included), AND - if patient does not require IMV (or ECMO) by Day 3* [Day 7*^], *(all the expected NIAID-OS assessments up to Day 3* [Day 7*^] are lower than 7)*AND - if patient does not use vasopressor§. Otherwise, the endpoint is set as missing. **Day 3 and Day 7 NIAID_OS assessments collected only during hospitalization. For subjects who discharge before Day3 (Day7) with all NIAID_OS<7 the next mandatory visit is Day 14 and the outcome at Day 3 (Day 7) will be set at missing, unless, after hospitalization, additional IMVs (or ECMO) captured in the specific cumulative CRF form (IMV) and occurring by Day 3 [Day 7] are reported.* *^ For Day 7 evaluation, the NIAID-OS assessment collected at Day 6 as last assessment during hospitalization is considered valid* *§ A patient starting Vasopressor medication before Day 1 (Start of IMP intake) and continue on or after Day1 is not classified as Clinical failure. It is a Clinical Failure only in case the Vasopressor medication start in Day 1 or after*

Parameter	Calculation
ICU stay up to Day 28 (days)	For all admissions to ICU between Day 1 date and Day 28 [Day XX] date: Sum of [min(Date of ICU discharge, last available date) – Date of ICU admission + 1] If Date of ICU discharge is after Day 28 date, then Day 28 date will be used instead. If Date of ICU admission is before Day 1 date, then Day 1 date will be used instead. Note: if an ICU admission is on multiple consecutive records (representing consecutive days), the ICU admission is the admission recorded on the 1st record and the date of ICU Discharge is the discharge recorded in the last record. If discharge in the last record is not present, counts the daily occurrences. In case date of ICU discharge is missing the following rule to impute the missing date is used: If date hospital discharge is available and date ICU admission≤ date hospital discharge then; date ICU discharge = date hospital discharge otherwise (if date hospital discharge is not available) if patient died and date of death is available then; date ICU discharge = date of death otherwise date ICU discharge = missing
ICU-free days at Day 28 (days)	If patient is alive at Day 28 date (last available day >=26): ICU-free days = 28 – ICU stay up to Day 28 If patient dies within Day 28: ICU-free days = 0 Otherwise, If subject il alive and followed (last available date) for <26 days (28 days +/- 2) the endpoint is set as missing.

Parameter	Calculation
Days free of IMV/ECMO at Day 28 (days)	If patient is alive at Day 28 (last available day >=26): - IMV/ECMO-free days = 28 - Sum of days with an available NIAID-OS >=7 or IMV/ECMO occurring up to Day 28 If patient dies before or at Day 28: - if dies for a progression of the respiratory disease# within Day 28: IMV/ECMO-free days = 0; Otherwise, If subject is alive or death not related to respiratory disease and followed (last available date) for <26 days (28 days +/- 2) IMV/ECMO free days will be set as missing. *#progression of respiratory disease identified as fatal SAEs by the following condition:* *[SOC_NAME="Respiratory, thoracic and mediastinal disorders" and HLT_NAME in ("Respiratory failures (excl neonatal)" , "Lower respiratory tract infections NEC", "Respiratory tract disorders NEC", "Viral upper respiratory tract infections")]*
Duration of antibiotic therapy at Day 28 (days)	For all antibiotic therapies between Day 1 date and Day 28 date: Sum of [min(Date of end antibiotic therapy, last available date) – Date of start antibiotic therapy + 1] If Date of end antibiotic therapy is after Day 28 date, then Day 28 date will be used instead. If Date of start of antibiotic therapy is before Day 1 date, then Day 1 date will be used instead. If subject is followed (last available date) for <26 days (28 days +/- 2) the endpoint is set as missing. In case of overlapping period the duration is counted once. Start date imputation: - In case start date is partial, impute the earliest date possible. - In case date is missing, use treatment start date. End date imputation: - In case the end date is partial, impute the latest date possible. - In case date is missing, use treatment start date + 27 (Day 28).

Parameter	**Calculation**
Hospital stay up to Day 28 (days)	For all hospitalization between Day 1 date and Day 28 date: Sum of [min(Date of discharge, last available date) – Hospital admission date+ 1)] If Date of discharge is after Day 28 date or is missing, then Day 28 date will be used instead. If Date of Hospital admission is before Day 1 date, then Day 1 date will be used instead*. In case of overlapping period the duration is counted once. **it measures the number of days from start of treatment (Day 1)*
Hospital-free days at Day 28 (days)	If patient is alive at Day 28: 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 (last available date) for <26 days (28 days +/- 2) the endpoint is set as missing.

Parameter	Calculation
Proportion of patients recovered at Day 28 [Day XX]	Based on Visit dates A patient is considered as recovered at Day 28 [Day XX] if: - the patient is alive at Day 28 Visit [Day XX] (included) AND - [NIAID-OS assessment at Day 28 [Day XX] Visit (included) is diminished from baseline of at least (>=) 2 points (regardless of being discharged), OR - (NIAID-OS assessment at Day 28 [Day XX] Visit (included) is diminished from baseline of 1 point AND the patient is discharged from hospital before or at Day 28 Visit [Day XX] (included))] Otherwise, a patient is considered as not recovered at Day 28 [Day XX] if: - patient dies before Day 28 Visit [Day XX] (included) OR - NIAID-OS assessment at Day 28 Visit [Day XX] (included) is diminished from baseline of less than 2 points AND the patient is NOT discharged from hospital before or at Day 28 Visit [Day XX] (included), OR - NIAID-OS assessment at Day 28 Visit [Day XX] (included) is diminished from baseline of less than 1 point AND the patient is discharged from hospital before or at Day 28 Visit [Day XX] (included), - . Otherwise, the endpoint is set as missing.
Proportion of patients worsening at Day 28 [Day XX].	Based on Visit dates A patient is considered as worsened at Day 28 [Day XX] if: - NIAID-OS assessment at Day 28 Visit [Day XX] is increased from baseline OR - the patient dies before Day 28 Visit [Day XX] (included). Otherwise, a patient is considered as not worsened at Day 28 [Day XX] if: - (NIAID-OS assessment at Day 28 Visit [Day XX] is not increased from baseline AND - the patient is not died before Day 28 Visit [Day XX] (included). Otherwise, the endpoint is set as missing.

Parameter	**Calculation**
Hospital re-admission by Day 90 and Day 180 (days)	**Set Hospital re-admission by Day 90 [Day 180] to "Y" if**: • Any hospitalization* recorded with start date^ on or after date of primary hospital discharge date and before study day 90 (same for visit "Day 180", but using 180 as cutoff). **Otherwise, set to "N" if**: • Subject primary hospital discharge date is prior day 90 [day 180], **AND** • Subject followed for the minimum amount of time (last available day >= 83) [>=166 in case of Day 180] **Otherwise**, endpoint will be set as missing. *cases from both "Other Hospitalizations" and/or "ICU" admissions to be considered. ^if the start date of the hospitalization is missing, then set to "Y" if the end date is also missing OR end date is after the primary hospitalization discharge date.

Parameter	Calculation
PaO2 and PaO2/FiO2 ratio	When the PaO_2 is not reported in the eCRF (i.e. the value is missing) but the values for SpO_2 is available, the PaO_2 and the PaO_2/FiO_2 ratio will be derived by applying the conversion from SpO2 (%) to PaO2 (mmHg). The conversion used the Ellis inversion [12] of the Severinghous equation [13]. As stated by Brown et al "The Ellis inversion of the Severinghaus equation provides a useful non-linear method for imputing PaO2 from SaO2" [14] Here below the equation for the conversion from SpO2 (%) to PaO2 (mmHg). The derived PsO2 will be used to derive the PaO_2/FiO_2 ratio. The non-linear equation utilized by this calculator is deriven in Brown et al Chest 2016 $$PO_2 = \left\{\frac{11{,}700}{(1/S - 1)} + \left[50^3 + \left(\frac{11{,}700}{1/S - 1}\right)^2\right]^{1/2}\right\}^{1/3} + \left\{\frac{11{,}700}{(1/S - 1)} - \left[50^3 + \left(\frac{11{,}700}{1/S - 1}\right)^2\right]^{1/2}\right\}^{1/3}$$ Non-linear* Note: if SpO2 = 100, the conversion will be done by considering SpO2=99%. The derived PaO_2 will be presented in the listing using 1 decimal place The derived PaO_2/FiO_2 ratio will be presented in the listing using 2 decimal places
Time to discharge or to a NEWS of ≤ 2 (for 24 hours)	Min(Date of discharge, Date of NEWS of ≤ 2 (for 24 hours)) – Day 1 date + 1 Patients who discontinued before discharge not reaching the event for NEWS<=2 for 24 hours will be censored at date of discontinuation
Date of NEWS of ≤ 2 (for 24 hours)	Given two consecutive days with NEWS of ≤ 2, the date of the first assessment will be considered.

Parameter	Calculation
Duration of IMV/ECMO by Day 90 [Day 180] (days)	At Day 90 - Duration = Sum of days with IMV/ECMO or NIAID-OS =7 between Day 1 and min(Day 90, last available day), if last available day >=83 days - *If subject not followed for the minimum amount of time (last available day< 83) [<166 in case of Day 180] endpoint will be set as missing.* The same for Day 180 Info from the INVASIVE MECHANICAL VENTILATION / ECMO form and NIAID-OS daily score
ICU Admission by Day 90 and Day 180 (days)	For derivation at "Day 90" [Day 180] **Set ICU Admission by Day 90 [Day 180] to "Y" if**: • Any ICU Admission* occurs before study day 90 (same for visit "Day 180", but using 180 as cutoff). **Otherwise, set to "N" if**: • Subject followed for the minimum amount of time (last available day >= 83) [>=166 in case of Day 180] **Otherwise**, endpoint will be set as missing. *cases from "ICU" admissions to be considered.

Parameter	Calculation
ICU length of stay by Day 90 [Day 180] (days)	At Day 90: - Duration = Sum of [Date of ICU discharge – ICU admission date + 1] between Day 1 and min(Day 90, last available day), if last available day >=83 days - *If subject not followed for the minimum amount of time (last available day< 83) [<166 in case of Day 180] endpoint will be set as missing.* If Date of ICU discharge is after Day 90 or is missing, then Day 90 date will be used instead. If Date of ICU admission is before Day 1 date, then Day 1 date will be used instead The same for Day 180 Info from the ICU FORM.
Hospital length of stay by Day 90 [Day 180] (days)	At Day 90: - Duration = Sum of [Date of discharge – Hospital admission date + 1] between Day 1 and min(Day 90, last available day), if last available day >=83 days - *If subject not followed for the minimum amount of time (last available day< 83) [<166 in case of Day 180] endpoint will be set as missing.* If Date of hospital Discharge is after Day 90 or is missing, then Day 90 will be used instead. If Date of hospital admission is before Day 1, then Day 1 will be used instead The same for Day 180 Info from the PRIMARY HOSPITALIZATION, OTHER HOSPITALIZATION form, ICU FORM. In case of overlapping period the duration is counted once.

Parameter	Calculation
Occurrence of Infection by Day 90 and Day 180 (days)	Analysis of proportions: For derivation at "Day 90" [Day 180] **Set Occurrence of Infection by Day 90 [Day 180] to "Y" if**: • Any infection occurs before study day 90 (same for visit "Day 180", but using 180 as cutoff). **Otherwise, set to "N" if**: • Subject followed for the minimum amount of time (last available day >= 83) [>=166 in case of Day 180] **Otherwise**, endpoint will be set as missing. Analysis of the infection rate up to Day 180: # and rate of infections up to min(last Available Day, Day 180) (each patient contributing to the denominator of the rate with his/her own follow-up time up to Day 180).
CCI	
CCI	

Parameter	Calculation
[redacted]	
Conversion of Time Intervals	If a time interval was calculated in minutes, hours or days and needs to be converted into months or year the following conversion factors will be used: • 1 hour = 60 minutes • 1 day = 24 hours • 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days
General rule	For calculation of 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.

12.2 Partial date conventions

Table 6: 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 7: Algorithm for Other Prior/Prior/Concomitant medications

MEDICATION START DATE	MEDICATION STOP DATE	RULE for prior or concomitant categorization
Known	Known	If medication stop date < date of screening - 7, assign as other prior 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 screening - 7, assign as other prior 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 or Missing	Known	If medication stop date < date of screening - 7, assign as other prior 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 screening - 7, assign as other prior 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

12.3 Seed numbers to be used for MI strategies

Table 8: Seed numbers

Analysis	Seed number
Primary analysis	CCI
Sensitivity analysis (MAR)	CCI
Sensitivity analysis (CR)	CCI
Supplementary analysis (PP)	CCI
All-cause mortality at Day 180	CCI
Proportion of patients alive and discharged at Day 28	CCI
Ventilatory-free days at Day 28	CCI
Proportion of patients with IMV (or ECMO) by Day 28	CCI
Length of primary hospital stay	CCI
28-day ICU-free days	CCI
Days free of IMV/ECMO at Day 28	CCI
28-day hospital-free days	CCI

12.4 National Institute of Allergy and Infectious Disease - Ordinal Scale (NIAID-OS)

Table 9: NIAID-OS

SCORE	Descriptor
OS 1	Not hospitalized, no limitations on activities
OS 2	Not hospitalized, limitation on activities and/or requiring home O2
OS 3	Hospitalized, no supplemental O2 – no longer requires ongoing medical care
OS 4	Hospitalized, no supplemental O2 – requiring ongoing medical care
OS 5	Hospitalized, requiring supplemental O2
OS 6	Hospitalized, on non-invasive ventilation or high-flow oxygen devices
OS 7	Hospitalized, on invasive mechanical ventilation or ECMO
OS 8	Death

12.5 EQ-5D-5L

The EQ-5D consists of 2 modules: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale that ranges between 0 and 100, where the endpoints are labelled 'The best health you can imagine' (VAS=100) and 'The worst health you can imagine' (VAS=0).

In addition to the by dimension score, other variables will be derived by using the EQ-5D instrument:

- EQ-5D-5L index value, a summary number which reflects how good or bad a health state is according to the preferences of the general population of a country/region [11]. If for a given country/region the value set is not available, the value set of the top enroller country will be used. States including '9' will be set as missing.
- QALYs (see below).

QALY

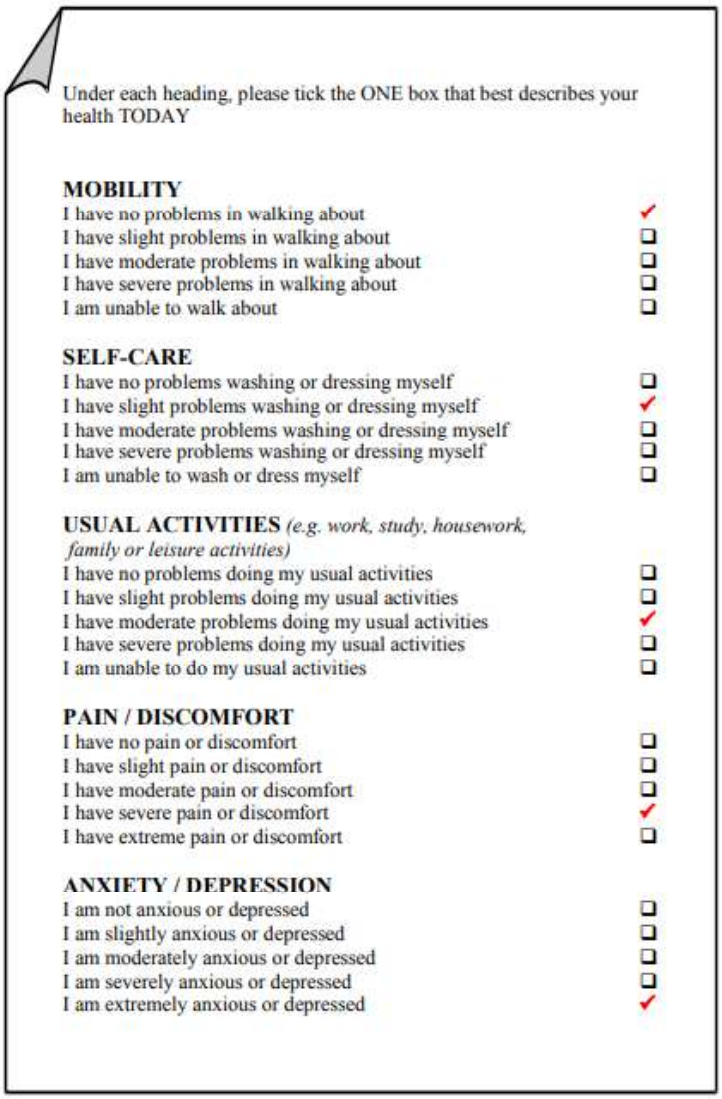
EQ-5D-5L answers to each dimension will be converted into a single index value and then converted in quality-adjusted life years (QALYs). The idea underlying the QALY is that a year of life lived in perfect health is worth 1 QALY (1 Year of Life × 1 Utility = 1 QALY) and that a year of life lived in a state of less than this perfect health is worth less than 1. In order to determine the exact QALY value, it is requested to multiply the index value associated with a given state of health by the years lived in that state. Specifically, the steps to obtain a QALY are:

1. Each dimension of the EQ-5D-5L questionnaire will be scored as follow:
    - Level 1 will be coded as '1'
    - Level 2 will be coded as '2'
    - Level 3 will be coded as '3'
    - Level 4 will be coded as '4'
    - Level 5 will be coded as '5'
    - Missing or ambiguous values (e.g. 2 boxes are ticked for a single dimension) will be coded as '9'.

    All five responses are then combined for a five-digit health state. For each five-digit health state there is a correspondent health related quality of life or score. The example in Figure 2 identifies the state '12345'.
2. Each individual response to EQ-5D-5L will be converted into a single summary index value by applying EuroQol specific country value set (if the value set of a country is not available, the value set of the top enroller country will be used). States including '9' will be set as missing.
3. The index values will be calculated for each patient at each available time point. An averaged index value will be calculated for each time interval between two consecutive time-points (i.e., between two consecutive assessments) as:

    $$QALY_{Vi \rightarrow Vj} = k * (QALY_{Vi} + QALY_{Vj})/2$$

    where $QALY_{Vi \rightarrow Vj}$ is the averaged utility value between Vi and Vj, $QALY_{Vi}$ and $QALY_{Vj}$ are the utility values at visit Vi and Vj respectively, and k is a weight representing the portion of year that each time-interval covers (for example, in case of 30 days: k = 30/365.25).
4. The (undiscounted) QALY at a specific time point Vt is given by the sum of all time-interval QALY from initial date to Vt.



Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
- ✓ I have no problems in walking about
- ☐ I have slight problems in walking about
- ☐ I have moderate problems in walking about
- ☐ I have severe problems in walking about
- ☐ I am unable to walk about

SELF-CARE
- ☐ I have no problems washing or dressing myself
- ✓ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ✓ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

PAIN / DISCOMFORT
- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ✓ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

ANXIETY / DEPRESSION
- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ✓ I am extremely anxious or depressed

Levels of perceived problems are coded as follows:

- ✓ ☐ ☐ ☐ ☐ Level 1 is coded as a '1'
- ☐ ✓ ☐ ☐ ☐ Level 2 is coded as a '2'
- ☐ ☐ ✓ ☐ ☐ Level 3 is coded as a '3'
- ☐ ☐ ☐ ✓ ☐ Level 4 is coded as a '4'
- ☐ ☐ ☐ ☐ ✓ Level 5 is coded as a '5'

13. Tables, Figures and Listings

13.1 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.
- 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.

13.2 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.

13.3 Table Conventions

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

- Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

13.4 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 split in two different parts.

14. References

1. REP0321 Clinical Study Protocol "Reparixin 1200 mg three times a day as add-on therapy to standard of care to limit disease progression in hospitalised adult patients with COVID-19 and other community-acquired pneumonia. A multinational, multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase III trial. (REPAVID-22)" Version No. 2.0 – CCI .
2. REP0321 Clinical Study Protocol "Reparixin 1200 mg three times a day as add-on therapy to standard of care to limit disease progression in hospitalised adult patients with COVID-19. A multinational, multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase III trial" Version No 1.0 – CCI .
3. Case Report Form Version No. 8.0 – 11 October 2023.
4. REP0321_DMC_IA_DRM_2_Recommendation_Signed_Updated, 26 June 2024
5. REP0321_SAP_V3.0_CCI _signed, CCI
6. REP0321_SAP_V3.0CCI _signed, CCI
7. Kalbfleisch, J.D.a.P., R. L. , The Statistical Analysis of Failure Time Data, ed. J.W. Sons. 1980, New York.
8. DOMPE REP0321_Study Early Termination_Site Communication_27th June 2024
9. DOMPE_REP0321_Visit Guidance and EDC completion_Study Closure_4Jul24_Site Communication, 05 July 2024
10. Yehya N, Harhay MO, Curley MAQ, et al. Reappraisal of Ventilator-Free Days in Critical Care Research. Am J Respir Crit Care Med 2019; 200:828–836.
11. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/
12. Ellis RK. Determination of PO2 from saturation. Journal of applied physiology. 1989; 67(2): 902
13. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol Respir Environ Exerc Physiol. 1979 Mar;46(3):599-602
14. Brown et al, Chest 2016; 150(2):307-313
15. Dolan, P. (2000). Chapter 32: The measurement of health-related quality of life for use in resource allocation decisions in health care. Handbook of Health Economics. 1 (B) p1723-60.

15. Appendix – 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.

15.1 SAS Code for the primary and binary endpoints

15.1.1 Details for programming

CCI

Since no random effects are foreseen in the model, the logistic regression model for the step 2 (defined as in section 10.1.2) will be analyzed in SAS by the PROC LOGISTIC procedure.

The estimate of the adjusted risk difference between reparixin and placebo at Day 28 will be derived by using the following SAS Macros available and downloadable from the SAS Support web pages:

- CCI

which manages estimates from imputed data. Details are provided in CCI

CCI

CCI

15.2 SAS Code for other endpoints

CCI

CCI

CCI

SAS Code for Value set for EQ-5L-5L

CCI Value Set

Computing EQ-5D-5L index values with SAS CCI

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'.

If they are given different names the syntax code below will not work properly.

The 5 variables should contain the values for the different dimensions

in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the EQ-5D-5L index values on the basis of the[redacted] set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
**********************************************************************
*SAS syntax code for the computation of index*
*values with the [redacted] (Finch et al) value set*
**********************************************************************
```

[redacted]

CCI

CCI Value Set

Computing EQ-5D-5L index values with SAS CCI

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'.

If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions

in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the EQ-5D-5L index values on the basis of the CCI set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
**********************************************************************
*SAS syntax code for the computation of index*
*values with the CCI TTO value set*
**********************************************************************
```

CCI

CCI

[redacted]

CCI Value Set (top recruiter)

Computing EQ-5D-5L index values with SASCCI

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'.

If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions

in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the

EQ-5D-5L index values on the basis of theCCI set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
**********************************************************************
*SAS syntax code for the computation of index*
*values with the CCI Ttand with all countries with no available value set*
**********************************************************************
```

CCI

CCI

[redacted]