16.1.9 Documentation of statistical methods

Statistical analysis plan

STATISTICAL ANALYSIS PLAN

PROTOCOL: REPAVID-19

Adaptive phase 2/3, randomized, controlled multicenter study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with COVID-19 pneumonia.

STATEMENT OF CONFIDENTIALITY

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STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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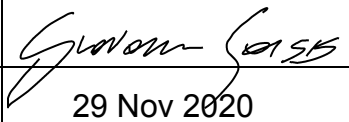
Signature:	
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Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
DMC	Data Monitoring Committee
DRM	Data Review Meeting
ENR	Enrolled set
FAS	Full Analysis set
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IRS	Interactive Response System
ITT	Intent to Treat
IV	Intravenous therapy
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol set
PT	Preferred Term
Q1	1st Quartile
Q3	3rd Quartile
RND	Randomized set
RTF	Rich Text Format
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2
SAS	Statistical Analysis Systems
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TID	Ter in die - three times a day
TLF(s)	Tables, Listings and Figures
VAS	Visual Analog Scale
WHO DD	World Health Organization Drug Dictionary

Revision History

Document Version	Changes Made	Document Date
Final 1.0	First release	29 November 2020

1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of REPAVID-19 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or Case Report Form (CRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.

This SAP is based on study protocol Version n. 1.5 - April 23, 2020[1] and Case Report Form Version 1.0 – April 30, 2020[2].

2. Study Objectives

The objective of this clinical trial is to assess efficacy and safety of reparixin as compared to the Standard of care in hospitalized adult subjects with severe COVID-19 pneumonia.

3. Study Design

General design and plan

The study is designed as an adaptive, randomized, controlled, multicenter study to evaluate efficacy and safety of reparixin in hospitalized adult subjects with severe COVID-19 pneumonia.

In the phase 2 segment of this study, subjects will be randomized 2:1 to reparixin oral tablets 1200 mg (Group 1, active treatment) or standard of care (Group 2, control arm). In case of worsening (e.g. need of Intensive Care Unit (ICU) and/or mechanical ventilation) after the first 24hrs, subjects will be offered a rescue medication based on their physicians' judgement, without any constrain from the sponsor. The administration of rescue medications is allowed, without constituting a protocol deviation.

In the phase 3 segment of this study, it is planned that subjects will be randomized 2:1 to reparixin or standard of care. In case of worsening after the first 24hrs, subjects under the control arm will be offered a rescue medication with the active treatment (reparixin 1200 mg oral tablets TID) or reparixin 2.772 mg/kg body weight/hour IV infusion, if the oral route is unfeasible for the clinical condition. The phase 3 design will be reassessed and decided based on the results of the phase 2.

3.1 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in Table 1. Paragraph no. 7 "Assessments and procedures" of Study Protocol contains additional details about scheduled visits, evaluations and assessments that are performed during the study.

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

Table 1: Schedule of evaluations

Study procedures	Screening	Baseline	Day 1	Day 2	Week 1	End of treatment	End of follow up
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Pregnancy Test	X						X
Randomization		X					
Demographics	X						
Medical History	X						
Previous And Concomitant Medications	X	X	X	X	X	X	X
Clinical severity score	X	X	X	X	X	X	X
Liker scale	X	X	X	X	X	X	X
Dyspnea VAS scale	X	X	X	X	X	X	X
Body temperature	X	X	X	X	X	X	X
Hematology evaluations*	X	X	X	X	X	X	X
Oxigen treatment (time and quantity)	X	X	X	X	X	X	X
Mechanical ventilation (Yes/No)	X	X	X	X	X	X	X
ICU admission (Yes/no)	X	X	X	X	X	X	X
Chest radiologic imaging	X	X§	X§	X§	X§	X	X§
PaO2, SpO2, FiO2	X	X	X	X	X	X	X
CRP, Hs-CRP	X	X	X	X	X	X	X
Cytokine profile **	X	X	X	X	X	X	X
Reparixin blood concentration **			X	X	X	X	X
SARS-CoV-2 virologic counts **		X			X	X	X
Study drug dispensation		X					
Verify study medication dosing compliance			X	X	X	X	
Record AEs / SAEs	X	X	X	X	X	X	X

** Including routine hematology as for local laboratory procedures and predefined hematochemical evaluations required for this study;*
*** Not mandatory; § When deemed appropriate by the investigators.*

3.2 Sample size justification

The sample size of the full phase 2/3 study is calculated based on data from clinical experience and on Sponsor expectations as reported in Table 2:

Table 2: Assumptions for primary endpoints

Primary endpoint*	Standard of care (control)	Reparixin
Time to primary endpoint of phase 2	2 days	5 days
Time to primary endpoint of phase 3	2-4 days	4-8 days

** see section 3.5.1.*

Based on the following assumptions:

- an enrollment phase of 2 months,

- a total follow-up of 21 days,
- a randomization ratio (reparixin:control) of 2:1
- an exponential distribution for survival probability $S(t) = e^{-\lambda t}$,
- a comparison between treatment by means of a log-rank test,
- an interim analysis framework as described in section 4.5, and
- a correction of the type I and II errors by means of O'Brien-Fleming spending functions

a total of 109 events (corresponding to approximately 111 subjects) will allow to provide >80% power to show superiority of reparixin vs standard of care in terms of primary endpoint of phase 3, controlling the type I error under 0.025.

Based on the same assumptions reported above, phase 2 portion of the study will be performed when a total of 46 events (corresponding to approximately 48 subjects) has happened. This allow to achieve approximately 80% power to show superiority of reparixin vs standard of care in terms of (not severe) primary endpoint of phase 2, controlling the type I error under 0.025.

The remaining portion of the 111 patients will be enrolled in the phase 3 study segment. Anyhow, due to the novel nature of the COVID-19 pandemic and being the primary efficacy endpoint planned in phase 3 not well established, it may require confirmation based on phase 2 data. For this reason, at the end of the phase 2 portion, power calculations may be reassessed, and sample size may be re-estimated for phase 3.

The adaptive design allows for the assessment of efficacy endpoint in phase 2 which are then seamlessly confirmed in the phase 3. Since primary endpoint of phase 3 will be tested only if superiority of reparixin is shown in phase 2 (at interim or final stage), the overall type I error of the study will be controlled at 0.025 via the hierarchical testing procedure.

3.3 Randomization and blinding

Eligible subjects will be randomized in a 2:1 fashion to either reparixin or standard of care through an Interactive Response System (IRS).

Randomization will be stratified by site to ensure balanced assignment across treatment groups. A stratified permuted block randomization list will be generated with a computer procedure, randomizing an excess of subjects to allow competitive recruitment within each center. Each randomized subject will be allocated with randomization number according to the stratified randomization list.

Given the open-label nature of the trial and the stratification by site, random block sizes will be adopted in the randomization list to avoid that treatment assignments might be forecasted by investigators.

The master randomization list will be kept confidential and will not be disclosed to any other person than those for which is strictly required (i.e. independent statistician who create the list, and IRS provider personnel).

Mis-randomization events will be recorded as major deviation and reported in the final study report.

Randomization codes will not be reused in case of subject's dropouts.

3.4 Overview of planned statistical analyses

The study plans for the following statistical analyses:

- Phase 2:
    - Interim analysis for efficacy or futility: this analysis will be conducted by Data Monitoring Committee (DMC) when half of the planned events of primary endpoint of phase 2 has happened;

  - Final analysis: this analysis will be conducted when all randomized phase 2 subjects has performed the final visit.
- Phase 3 (in case of success of phase 2):
  - Interim analyses for efficacy or futility: this analysis will be conducted by DMC when approximately 55% and 74% of the planned severe events of primary endpoint of phase 3 has happened;
  - Final analysis: this analysis will be conducted all randomized phase 3 subjects has performed the final visit.
- Analyses for the DMC: these analyses will be produced periodically according to the DMC charter. In addition to the above interim analyses, analyses for safety integrity reviews will be performed according to DMC charter.

3.5 Efficacy endpoints

3.5.1 Primary endpoints

- Primary Endpoint for phase 2: Composite endpoint of clinical events (the subject requires at least one of the following: supplemental oxygen requirement, invasive mechanical ventilation use, admission to ICU, and use of a rescue medication for any reason);
- Primary Endpoint for phase 3: Composite endpoint of death and clinical severe events (the subject dies or requires invasive mechanical ventilation use and/or admission to ICU).

3.5.2 Secondary Endpoints:

- Clinical severity score (a seven-category ordinal scale) at any available time point
- Dyspnea severity (Liker categorical scale and VAS continuous scale) at any available time point;
- Changes in body temperature at any available time point;
- Duration and quantity of supplemental oxygen treatment at any available time point;
- Incidence and duration of mechanical ventilation use at any available time point;
- Incidence of ICU admission need at any available time point;
- Lung damage extension changes from baseline (assessed by Chest CT or Rx) at any available time point;
- Change from baseline in lung exudation degree (assessed by Chest CT or Rx) at any available time point;
- PaO2 at any available time point;
- SpO2 at any available time point;
- Partial arteriolar oxygen pressure (PaO2) to fraction of inspiration O2 (FiO2) ratio at any available time point;
- CRP at any available time point;
- Hs-CRP at any available time point;

3.5.3 Exploratory Endpoints (not mandatory):

- Cytokine profile at any available time point;

- Concentration of reparixin in serum over time;
- SARS-CoV-2 virologic counts at any available time point.

3.6 Safety endpoints

- Adverse Events (AEs) and Serious Adverse Events (SAEs) throughout the study.
- Safety Laboratory Tests at any available time point;
- Vital signs at any available time point;
- Pregnancy at any available time point.

4. Statistical Analysis

4.1 General

Appropriate descriptive statistics will be produced, according to the variable:

- for continuous data n, mean, standard deviation (SD), median, Q1-Q3, and range (minimum and maximum) will be presented;
- for categorical data, frequency distributions and percentages will be presented;
- for time-to-event variables, cumulative freedom from event will be evaluated using Kaplan-Meier (KM) method. The degree of uncertainty will be expressed with 95% confidence limits (calculated per the method proposed by Greenwood[3]). Comparison of curves among arms will be performed with the log-rank test. KM graphs will be presented along with the number of subject-at-risk at exact time points. Subjects who have discontinued/terminated the study without an event will be censored at the date of study discontinuation/termination. Subjects ongoing and who are free from event at the time of database lock (for example at interim analyses) will be censored at the last available date.

Unless otherwise specified, hypothesis testing will be carried out at the alpha = 0.050 level (two-sided) when comparing treatments. For all inferential analyses, p-value will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.050. For primary analysis only (section 7.1.2), p-values will be provided at 5th decimal place, in order to compare with efficacy and futility thresholds specified in section 4.5.

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

Derivation rules for efficacy and safety analyses are reported in Table 7 in section 9.

All the data collected and derived in the study will be presented in subject data listings by centre.

4.2 Analysis sets

4.2.1 Enrolled set

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

4.2.2 Randomized set

The Randomized set (RND) will consist of all subjects in the ENR set who are randomized to the study,

regardless of whether they receive the Investigational Medicinal Product (IMP) or not.

4.2.3 Safety set

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

4.2.4 Full Analysis set

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

4.2.5 Per Protocol set

The Per Protocol set (PP) will consist of all randomized subjects who receive at least one dose of the IMP without any Major Protocol Deviations. The PP set will be used for sensitivity analyses.

All the protocol deviations will be discussed case by case by the clinical team during the Data Review Meeting (DRM) before the database lock and described in the DRM Report.

4.3 Usage of analysis sets

The usage of the analysis sets (see previous section) for the creation of tables and figures are illustrated in Table 3

Table 3: Usage of analysis set

Analysis	ENR	RND	FAS	SAF	PP
Subject enrolment and disposition	X				
Protocol violations		X			
Study discontinuations		X			
Patient status		X		X	
Demographics and baseline characteristics			X		
Medical/Surgical History and Concomitant Diseases			X		
Prior and concomitant medications			X		
Other baseline characteristics			X		
Treatment information				X	
Exposure to IMP				X	
Analysis of primary efficacy endpoints			X		
Sensitivity analysis			X		X
Analysis of secondary efficacy endpoints			X		
Analysis of exploratory efficacy endpoints			X		
Adverse events				X	
Clinical laboratory evaluation				X	
Vital signs				X	
Pregnancy test over the study				X	

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 in the listing (according to Table 3).

4.4 Sub-group analyses

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

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

- age group (≤65yrs vs >65yrs);
- gender (Male, Female);
- clinical severity score at baseline (<median vs ≥median);
- dyspnea VAS scale at baseline (<median vs ≥median).

Subgroup analysis will be performed if interaction tests are statistically significant at 15% nominal level. In this case all efficacy endpoints will be analyzed within as described in sections 7.1.2, 7.2.1 and 7.2.2.

4.5 Interim analyses

Interim analyses are planned at specific time point during phase 2 and phase 3 for identification of early superiority of reparixin (efficacy) or for early stop of the trial for futility.

O'Brien-Fleming spending functions will be used to control the type I and II errors for analyses of primary endpoints. P-values boundaries for efficacy and futility at interim and final analyses for phase 2 and phase 3 are reported in Table 4 and Table 5, respectively.

Table 4: O'Brien-Fleming spending functions boundaries for primary analysis in phase 2

Analysis	Sample Size	Boundaries for primary endpoint	
		Efficacy	Futility
Interim #1	~27 (23 events)	p-value <0.00258	p-value ≥0.23349
Final	48 (46 events)	p-value <0.02400	p-value ≥0.02400

Table 5: O'Brien-Fleming spending functions boundaries for primary analysis in phase 3

Analysis	Sample Size	Boundaries for primary endpoint	
		Efficacy	Futility
Interim #1	~60 (60 events)	p-value <0.00296	p-value ≥0.26674
Interim #2	~81 (81 events)	p-value <0.00892	p-value ≥0.09841
Final	111 (109 events)	p-value <0.02151	p-value ≥0.02151

The interim analyses will be conducted by DMC who will communicate to the Sponsor the result of the interim analysis and the consequent decision on the continuation of the study.

The following scenarios may emerge from the interim analysis:

- the communication from the DMC to the Sponsor will be "Not enough evidence for demonstrate superiority of reparixin". Since results are not considered enough to draw conclusions on primary

endpoints, the study enrolment will continue up to the next analysis step, and treatments and follow-ups will proceed without modifications.

- the communication from the DMC to the Sponsor will be "Superiority of reparixin is shown". In this case, the following action will be taken according to the study phase:
    - Phase 2:
        - enrollment of subjects in phase 2 is stopped
        - already enrolled subjects continue their residual treatment and follow-up as planned
        - adaptation of phase 3, if needed;
        - enrollment of subjects in phase 3 may start;
    - Phase 3:
        - enrollment of subjects is stopped
        - already enrolled subjects continue their residual treatment and follow-up as planned
        - when last enrolled subject completes the follow-up and database is close, final analysis is performed and clinical study report will be released.
- the communication from the DMC to the Sponsor will be "Superiority of reparixin is excluded". In this case, independently from the study phase, the enrollment (if still ongoing) will be stopped, and all subjects will discontinue the treatment and will be follow-up till the next scheduled visit where they will be notified of the termination of the study.

4.6 DMC Safety Integrity Review

In addition to the above interim analyses, analysis of safety data will be performed for supporting Safety Integrity Review meetings during the trial.

Safety Integrity Review meetings will be performed on ongoing basis (frequency will be defined by DMC members also considering feedbacks from REPAVID-19 Investigators) and at the end of the phase 2 in order to ensure that, in addition to superiority in efficacy, reparixin has an adequate safety profile.

The following information will be analyzed for safety reason at each Safety Integrity Review:

- Major protocol changes,
- Information on subject screening,
- Study accrual by month and by institution,
- Eligibility violations,
- Demographics,
- Length of follow-up data available (pooled by treatment regimen),
- Analyses of adverse events,
- Analyses of vital signs, including basic summaries and longitudinal analyses,
- Analyses of lab values, including basic summaries and longitudinal analyses,
- Discontinuation of medications,
- Information on crossover subjects.

4.7 Study adaptation

REPAVID-19 trial's design will allow for adaptations based on results from efficacy and safety data through the study. The spectrum of possible adaptations for the phase 3 study segment with the corresponding trigger rules is reported in Table 6.

In case of decision of continuation of the study, results of the phase 2 portion of study will be submitted to the competent authority with the final version of the Phase 3 segment of the study (as an amendment to study protocol) prior to proceed. In that case, the SAP will be updated accordingly.

Table 6: Adaptations and triggers

Action	Trigger
Modification of the experimental treatment route of administration.	Safety reasons based on DMC recommendation or Sponsor evaluation.
Confirmation or modification of the primary, secondary and exploratory endpoints (at beginning of phase 3).	DMC indication based on review of phase 2 results.
Refining the sample size.	In case of relevant discrepancies between sample size assumptions (section 3.2) and phase 2 results.
Population enrichment.	Based on safety and efficacy results (including subgroup analyses), it may be identified a subset of subjects most likely to benefit from treatment.
Change the allocation ratio of subjects to trial arms.	Safety and ethical reasons based on DMC recommendation or Sponsor evaluation.

4.8 Handling of missing and incomplete data

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

4.9 Changes in the planned analysis

No change has been implemented in this SAP.

However, in order to clarify the analysis of the primary endpoint, a clarification of the meaning of "supplemental oxygen treatment" is provided: since all patients enrolled in this study had a respiratory distress, it is intended in all the analysis that the term "supplemental" refers to additional and/or increased oxygen requirement as compared to the baseline. In fact, all patients were expected to be already on oxygen treatment before the start of treatment. Details are provided in section 9.1.

4.10 Data Review Meeting

A DRM will be held before final database lock.

4.11 Software

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

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

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

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

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

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

Listings will be provided based on ENR set.

5.2 Protocol violations

All the protocol violations will be discussed case by case with the clinical team during the DRM and described in the DRM Report.

Number of occurrences and of subjects with at least one major and minor protocol violations will be summarized for each treatment.

5.3 Study discontinuations

The following information will be summarized by treatment and overall:

- Trial completers;
- Subjects who discontinued the IMP (and reasons);
- Subjects who discontinued the trial prematurely (and reasons);
- Subjects who discontinued the IMP but complete the study;
- Subjects who discontinued the IMP and discontinued the trial prematurely.

If more than 30% of randomized subjects discontinue the study prematurely, the distribution of the time from randomization to discontinuation will be summarized using time-to-event method. Subjects who have not prematurely discontinued the trial will be censored at study termination.

5.4 Patient status

The following information will be summarized by treatment at each time point:

- Subjects continuing treatment with oral reparixin/standard of care (yes, no, NA);
- Subjects switching to rescue medication (yes, no, NA);
- Subjects continuing treatment with IV reparixin (yes, no, NA), if applicable;

5.5 Demographics and baseline characteristics

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

The following demographic and baseline characteristics will be reported:

- Demography
- Age (years)
- Gender (Male, Female)
    - If female, potential childbearing (yes, no)
- Race (White / Caucasian, Black or African American, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not Reported)
- Pregnancy test result (Positive or Negative), if appropriate

5.6 Medical/Surgical History and Concomitant Diseases

A disease is considered as medical/surgical history if it is ended before screening visit. A disease is considered as concomitant disease if it is ongoing at screening visit.

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

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

5.7 Prior and concomitant medications

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

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

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

In case of missing or incomplete dates/times not directly allowing allocation to any of the two categories of medications, a worst-case allocation will be done according to the available parts of the start and the end dates (see Table 9). The medication will be allocated to the first category allowed by the available data, according to the following order:

- concomitant medication;
- prior medication.

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

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

5.8 Other baseline characteristics

The following information at baseline will be descriptively reported by means summary statistics:

- Clinical severity score (categorical)
- Dyspnea VAS scale (continuous)
- Respiratory parameters (continuous)
    - FiO2 (%)
    - Respiration rate (Breath/min)
    - PaO2 (mmHg)
    - SpO2 (%)
    - PaO2/FiO2 (Ratio)
        - Acute Respiratory Distress Syndrome (ARDS) severity

  and their categorical evaluation, if applicable.
- Additional information
    - Did the subject experience any Adverse Events? (yes, no);
    - Has the subject been admitted to the ICU? (yes, no);
    - Was oxygen administered to the subject? (yes, no);
    - Has the subject been mechanically ventilated? (yes, no).

6. Evaluation of Treatment Compliance and Exposure

6.1 Treatment information

Descriptive analyses of the following parameters will be presented at each available time point:

- For subjects treated with oral reparixin:
    - Total number of oral treatment days
    - Total n° oral tablets administered
- For subjects treated with standard of care:
    - Total number of oral treatment days
- For subjects treated with IV reparixin (if applicable):
    - Total number of IV treatment days

- Total n° IV Vials administered

6.2 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 7.

7. Evaluation of Efficacy

As described in section 0, possible modifications in the phase 3 study might be introduced as adaptation from phase 2. In this case, all the impacted below sections will be amended.

7.1 Analysis of primary efficacy endpoints

7.1.1 Testing strategy and multiplicity adjustment

7.1.1.1 Phase 2

The following null hypothesis is defined: the freedom from composite endpoint (section 3.5.1) in reparixin is lower or equal than control:

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

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

where $T_{REPARIXIN}$ and $T_{CONTROL}$ are the freedoms from composite endpoint for reparixin and standard of care, respectively. The null hypothesis H_0 will be rejected, and preliminary (to be confirmed in phase 3) superiority of reparixin shown if log-rank 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 O'Brien-Fleming spending function boundaries and are reported in Table 4.

7.1.1.2 Phase 3

The following null hypothesis is defined: that the freedom from severe composite endpoint (section 3.5.1) in reparixin is lower or equal than control:

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

H_1: $\Pi_{REPARIXIN} > \Pi_{CONTROL}$

where $\Pi_{REPARIXIN}$ and $\Pi_{CONTROL}$ are the freedoms from severe composite endpoint for reparixin and standard of care, respectively. The null hypothesis will be rejected, and superiority of reparixin concluded if log-rank p-value will be lower than pre-specified threshold, depending at which analysis (first or second interim or final) the test is performed. Thresholds are calculated according to O'Brien-Fleming spending function boundaries and are reported in Table 5.

Phase 3 null and alternative hypotheses will be tested only if superiority of reparixin is shown in phase 2. Null hypotheses of both phases must be rejected in order to claim superiority of reparixin over standard of care. Consequently, no multiplicity correction of type I error will be applied on primary analyses.

7.1.2 Analysis details

The composite endpoints for phase 2 and phase 3 (section 3.5.1) will be summarized along with their single component by a binomial response rate at each time point (only the first event will be considered). The Clopper-Pearson method will be used to estimate the two-sided 95% CIs.

Primary analyses on time to composite endpoint(s) will be performed using the KM methodology and the one-

sided log-rank test will be used to test for differences between treatment groups. See section 4.1 for more details on time-to-event analysis and representation.

The primary endpoint of phase 2 will be assessed also in phase 3 as secondary analysis, and vice versa.

7.1.3 Sensitivity analysis

7.1.3.1 Phase 2

Results of primary analysis will be assessed in sensitivity analyses as detailed below.

- The comparison between treatment and control will be performed by means of a Cox regression model, using age class, gender and clinical severity score at baseline as covariates, to assess the robustness of results on primary endpoint versus the presence of confounding factors. Additional covariates might be included after DRM in case relevant baseline imbalance will be identified between groups, despite randomization. The assumptions of proportionality will be investigated with a time-dependent exploratory variable, which is defined as treatment*{log[time to event]}. If the p-value from the Wald Chi-squared statistic for this variable is less than 5% there is evidence of a departure from the adjusted model assumptions. In case of non-proportional hazards, a Weibull model will be assumed as parametric form of the distribution of survival times. The treatment group will be included in the model as covariate.
- Time to event for each single component of the primary endpoint will be performed separately in order to adjust for the presence of possible competing risks. The following events:
    - first supplemental oxygen requirement,
    - first mechanical ventilation use,
    - first admission to ICU, and
    - first use of a rescue medication for any reason

  will be analyzed according to survival analysis methodology detailed in section 4.1 with the following modifications:
    - the common representation of survival curves using the Kaplan-Meier estimator will be replaced by the cumulative incidence function,
    - the presence of other competing event(s) is/are treated as censored.
- A modified composite endpoint of phase 2 will be analyzed adding “death” as fifth component. It will be analyzed according to section 7.1.2 to assess the robustness of results on primary endpoint versus the presence of censoring due to fatal events.

Decision to proceed/not proceed to phase 3 will be based only on primary analysis results, despite inconsistencies with sensitivity analyses. Sensitivity results will be interpreted and discussed in the clinical study report and will be used to eventually adjust adaptations for the phase 3.

7.1.3.2 Phase 3

Results of primary analysis will be assessed in sensitivity analyses as detailed below.

- The comparison between treatment and control will be performed by means of a regression model, using the same method (Cox or Weibull model) and covariates identified during phase 2, to assess the robustness of results on primary endpoint versus the presence of confounding factors.
- Time to event for each single component of the severe primary endpoint will be performed separately in order to adjust for the presence of possible competing risks. The following events:
    - death,
    - first invasive mechanical ventilation use, and
    - first admission to ICU

will be analyzed according to survival analysis methodology detailed in section 4.1 with the following modifications:

- the common representation of survival curves using the Kaplan-Meier estimator will be replaced by the cumulative incidence function,
- the presence of other competing event(s) is/are treated as censored.

- The comparison between treatment and control will be performed in the PP population instead of FAS as described in section 7.1.2, to assess the robustness of trial results versus the adherence to protocol.

7.2 Analysis of secondary efficacy endpoints

7.2.1 Descriptive Analysis

Descriptive in nature analyses will be performed on all secondary endpoints (section 3.5.2) at each available time points by means of descriptive statistics (section 4.1).

In case of continuous measures, analyses will be provided for:

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

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

7.2.2 Comparison between treatments

Along with the above summary statistics, comparisons between treatments will be performed as detailed in the next sub-sections. Parametric test (i.e. two-sample t-test for continuous variables, Chi-square test for categorical) will be adopted as first choice. In case the required assumptions are not met, the corresponding non-parametric counterpart will be used (i.e. the two-sample Mann–Whitney U test for continuous variables, and the Fisher's Exact test for the categorical). Normality of continuous data is assessed by Kolmogorov-Smirnov test.

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

7.2.2.1 Composite endpoint of phase 2 using Oxygen Delivery System Classification

The composite endpoints will be summarized along with their single component by a binomial response rate at each time point (only the first event will be considered). The Clopper-Pearson method will be used to estimate the two-sided 95% CIs.

Time to composite endpoint(s) will be performed using the KM methodology and the one-sided log-rank test will be used to test for differences between treatment groups.

7.2.2.2 Changes in clinical severity score

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects with a clinical severity score improvement of at least two points compared to randomization or live discharge from the hospital will be calculated and compared.

7.2.2.3 Dyspnea severity (Liker scale and VAS scale)

The comparison of the Liker scale between the two study treatment arms will be performed by means of Wilcoxon signed-rank test, given its ordinal nature.

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects with

any improvement (improved vs not-improved) will be calculated and compared.

VAS scale comparison between treatments will be performed according to its continuous nature.

7.2.2.4 Changes in body temperature

Comparison between treatments in change from baseline of the body temperature will be performed according to the continuous nature of the variable.

7.2.2.5 Incidence of supplemental oxygen treatment

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects who worsened according to PaO2/FiO2 and to Oxygen Delivery System Classification based on oxygen support will be calculated and compared.

At each time point the number and proportion of patients within each class (Severe, Moderate, or Mild for PaO2/FiO2; Invasive, High Flow, or Low Flow for the type of support) will be provided.

Finally, summary of cumulative quantity (L) and cumulative duration (hours) of oxygen treatment will be performed at 7 days and subsequent time points considering the variable as continuous.

7.2.2.6 Incidence and duration of mechanical ventilation use

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects requiring mechanical ventilation will be calculated and compared.

Comparison between treatments in cumulative duration (hours) of mechanical ventilation will be performed at 7 days and subsequent time points considering the variable as continuous. Analysis will be performed overall and stratified by Invasive/Non-invasive mechanical ventilation.

7.2.2.7 Incidence of ICU admission need

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of subjects requiring ICU admission will be calculated and compared.

Comparison between treatments in duration (days) of ICU stay will be performed considering the variable as continuous.

7.2.2.8 Change from baseline in lung damage extension and lung exudation degree (assessed by Chest CT or Rx)

The comparison of the clinical evaluation of lung damage extension and lung exudation between the two study treatment arms will be performed by means of Wilcoxon signed-rank test.

7.2.2.9 Respiratory parameters

Change from baseline of FiO2, Respiration rate, PaO2, SpO2 and PaO2/FiO2 will be compared between treatments considering the continuous nature of these variables.

7.2.2.10 CRP and Hs-CRP

CRP (mg/L) and Hs-CRP (mg/L) will be compared between treatments considering their continuous nature.

7.3 Analysis of exploratory efficacy endpoints

Explorative endpoints (section 3.5.3) will be analyzed at each available time points by means of descriptive statistics. Specifically, analyses will be provided for baseline visit, each post-baseline visit, and the change from baseline measurements to each visit. Comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality is not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.

In case of different units of measure considered for the same laboratory parameter, all values will be converted

into Standard International (SI) units (if applicable) or to the same unit.

8. Evaluation of Safety

8.1 Adverse events

Any AE which starts at or after the first administration of study treatment will be considered a Treatment Emergent Adverse Event (TEAE). Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only. In case of missing or incomplete dates not allowing a direct allocation to any of the two categories of AEs, a worst-case allocation will be done according to the available parts of the onset and the end dates (see Table 8). The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE;
- Pre-treatment AE.

All AEs will be assigned to a PT and will be classified by primary SOC according to the MedDRA thesaurus. In addition, each AE will be graded according to severity definitions as “Mild”, “Moderate” or “Severe”.

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

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

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

- An overview of TEAEs including the number of subjects 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, number of TEAEs, number of non-serious TEAEs, number of TESAEs, number of ADRs, number of serious ADRs, number of deaths, number of subjects who temporarily interrupted IMP due to a TEAE, number of subjects who permanently interrupted IMP due to a TEAE;
- Summary of TEAEs by primary SOC and PT;
- Summary of TEAEs by primary SOC, PT and Severity;
- Summary of Serious TEAEs by Primary SOC and PT;
- Summary of ADRs by Primary SOC and PT;
- Summary of ADRs by Primary SOC and PT and Severity;
- Summary of TEAEs leading to IMP temporary interruption by Primary SOC and PT;
- Summary of TEAEs leading to IMP permanently interruption by Primary SOC and PT;
- Summary of TEAEs leading to Death by Primary SOC and PT;
- Listing of all AEs by Subject;
- Listing of SAEs by Subject;
- Listing of ADR by Subject;
- Listing of Deaths.

8.2 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 into SI units (if applicable) or to the same unit.

The following summaries will be provided:

- A summary table showing for all laboratory tests the values and changes from baseline to each subsequent time points;
- A summary table showing for all laboratory tests the frequency of subjects reporting laboratory values out of normal range (yes, no) at baseline and at subsequent time points.

8.3 Vital signs

Summary statistics by treatment will be provided at each available time point:

- Weight (Kg),
- Height (cm) if applicable,
- Systolic Blood Pressure (mmHg),
- Diastolic Blood Pressure (mmHg),
- Heart Rate (bpm),
- Body temperature (°C),
- Respiration Rate (breath / min)

8.4 Pregnancy test over the study

A summary table showing test results (Negative/Positive) over the study will be produced by treatment group, where applicable.

9. Derivations and date conventions

9.1 Variable derivation

Table 7: Variable derivation rules

Parameter	Derivation
ARDS Severity classification based on PaO2/FiO2	According to PaO2/FiO2 (RESPIRATORY PARAMETERS form) the classification is: • if 200 ≤ PaO2/FiO2 < 300 mmHg then ARDS Severity=Mild • if 100 ≤ PaO2/FiO2 < 200 mmHg then ARDS Severity=Moderate • if PaO2/FiO2 < 100 mmHg then ARDS Severity=Severe
Worsening based on PaO2/FiO2	A patient with ARDS (PaO2/FiO2<300 mmHg) is considered "Worsened" in case of a decrease of PaO2/FiO2 of at least one third (-33,3%) from the baseline PaO2/FiO2 value.
Oxygen Delivery System Classification based on type of oxygen support	According to Type of oxygen support (RESPIRATORY PARAMETERS form) the classification is: • If "Invasive Medicinal Ventilation" or "ECMO" then Class=Invasive • Else if "High Flow Nasal Cannula" or "BIPAP or CPAP" then Class=High Flow • Else if "Nasal Cannula" or "Mask" then Class=Low Flow
Worsening based on Oxygen Delivery System Classification	A patient is considered "Worsened" after baseline if he/she increase the level of severity within the oxygen delivery system classification (Invasive > High Flow > Low Flow).
Last available date (for censoring time-to-event analysis)	Last date will be considered as the most recent dates collect in: • Last assessment, • Start and stop dates of AEs Last date = max (date of last assessment, start AEs, Stop AEs)

Parameter	Derivation
Composite endpoint of phase 2 and Time to event (days)	From ADDITIONAL INFORMATION form: • if "Has the patient been admitted to the ICU?" = "Yes", then component1 = "Yes" and date of event1 = Date of Visit • if "Has the patient been admitted to the ICU?" = "No", then component1 = "No" From PATIENT STATUS form: • if "Is the subject eligible to switch to rescue medication?" = "Yes", then component2 = "Yes" and date of event2 = Rescue treatment start date o If Rescue treatment start date is missing, then Date of Visit will be used • if "Is the subject eligible to switch to rescue medication?" = "No", then component2 = "No" From ADDITIONAL INFORMATION and MECHANICAL VENTILATION forms: • If "Has the patient been mechanically ventilated?" = "Yes" and type = "Invasive mechanical ventilation", then component3 = "Yes" and date of event3 = mechanical ventilation start date o If mechanical ventilation start date is missing, then Date of Visit will be used • If "Has the patient been mechanically ventilated?" is not empty and type ≠ "Invasive mechanical ventilation", then component3 = "No" From "Worsening based on PaO2/FiO2" (see above): • if a patient is classified as "Worsened", then component4 = "Yes" and date of event4 = Date of Visit • if a patient is classified as not "Worsened" (excluding missing classification), then component4 = "No" The composite endpoint is equal to "Yes" if at least one post-baseline component (1-4) is equal to "Yes" and the date of event is the corresponding date of event. In case of more component equal to "Yes", the first date will be used. Otherwise, if all component (1-4) are equal to "No" the composite endpoint will set as "No". The date of event will be last date where is known that all components are equal to "No". Time to composite endpoint (days) = Date of event - Date of randomization

Parameter	Derivation
Modified Composite endpoint of phase 2 and Time to event (days) [sensitivity analysis]	From ADDITIONAL INFORMATION form: • if "Has the patient been admitted to the ICU?" = "Yes", then component1 = "Yes" and date of event1 = Date of Visit • if "Has the patient been admitted to the ICU?" = "No", then component1 = "No" From PATIENT STATUS form: • if "Is the subject eligible to switch to rescue medication?" = "Yes", then component2 = "Yes" and date of event2 = Rescue treatment start date o If Rescue treatment start date is missing, then Date of Visit will be used • if "Is the subject eligible to switch to rescue medication?" = "No", then component2 = "No" From ADDITIONAL INFORMATION and MECHANICAL VENTILATION forms: • If "Has the patient been mechanically ventilated?" = "Yes" and type = "Invasive mechanical ventilation", then component3 = "Yes" and date of event3 = mechanical ventilation start date o If mechanical ventilation start date is missing, then Date of Visit will be used • If "Has the patient been mechanically ventilated?" is not empty and type ≠ "Invasive mechanical ventilation", then component3 = "No" From "Worsening based on PaO2/FiO2" (see above): • if a patient is classified as "Worsened", then component4 = "Yes" and date of event4 = Date of Visit • if a patient is classified as not "Worsened" (excluding missing classification), then component4 = "No" From DEATH REPORT form: • If "Date of death" is not missing, then component5 = "Yes" and date of event5 = date of death • Otherwise component5 = "No" The composite endpoint is equal to "Yes" if at least one post-baseline component (1-5) is equal to "Yes" and the date of event is the corresponding date of event. In case of more component equal to "Yes", the first date will be used. Otherwise, if all component (1-4) are equal to "No" the composite endpoint will set as "No". The date of event will be last date where is known that all components are equal to "No". Time to composite endpoint (days) = Date of event - Date of randomization

Parameter	Derivation
Composite endpoint of phase 3 and time to event (days)	From ADDITIONAL INFORMATION form: • if "Has the patient been admitted to the ICU?" = "Yes", then component1 = "Yes" and date of event1 = Date of Visit • if "Has the patient been admitted to the ICU?" = "No", then component1 = "No" From ADDITIONAL INFORMATION and MECHANICAL VENTILATION forms: • If "Has the patient been mechanically ventilated?" = "Yes" and type = "Invasive mechanical ventilation", then component3 = "Yes" and date of event3 = mechanical ventilation start date o If mechanical ventilation start date is missing, then Date of Visit will be used • If "Has the patient been mechanically ventilated?" is not empty and type ≠ "Invasive mechanical ventilation", then component3 = "No" From DEATH REPORT form: • If "Date of death" is not missing, then component5 = "Yes" and date of event5 = date of death • Otherwise component5 = "No" The composite endpoint is equal to "Yes" if at least one post-baseline component (1, 3 and 5) is equal to "Yes" and the date of event is the corresponding date of event. In case of more component equal to "Yes", the first date will be used. Otherwise, if all component (1, 3) are equal to "No" the composite endpoint will set as "No". The date of event will be last date where is known that all components are equal to "No". Time to composite endpoint (days) = Date of event - Date of randomization

Parameter	Derivation
Composite endpoint of phase 2 and Time to event (days) using Oxygen Delivery System Classification	From ADDITIONAL INFORMATION form: • if "Has the patient been admitted to the ICU?" = "Yes", then component1 = "Yes" and date of event1 = Date of Visit • if "Has the patient been admitted to the ICU?" = "No", then component1 = "No" From PATIENT STATUS form: • if "Is the subject eligible to switch to rescue medication?" = "Yes", then component2 = "Yes" and date of event2 = Rescue treatment start date o If Rescue treatment start date is missing, then Date of Visit will be used • if "Is the subject eligible to switch to rescue medication?" = "No", then component2 = "No" From ADDITIONAL INFORMATION and MECHANICAL VENTILATION forms: • If "Has the patient been mechanically ventilated?" = "Yes" and type = "Invasive mechanical ventilation", then component3 = "Yes" and date of event3 = mechanical ventilation start date o If mechanical ventilation start date is missing, then Date of Visit will be used • If "Has the patient been mechanically ventilated?" is not empty and type ≠ "Invasive mechanical ventilation", then component3 = "No" From "Worsening based on Oxygen Delivery System Classification" (see above): • if a patient is classified as "Worsened", then component4 = "Yes" and date of event4 = Date of Visit • if a patient is classified as not "Worsened" (excluding missing classification), then component4 = "No" The composite endpoint is equal to "Yes" if at least one post-baseline component (1-4) is equal to "Yes" and the date of event is the corresponding date of event. In case of more component equal to "Yes", the first date will be used. Otherwise, if all component (1-4) are equal to "No" the composite endpoint will set as "No". The date of event will be last date where is known that all components are equal to "No". Time to composite endpoint (days) = Date of event - Date of randomization
Time from randomization to discontinuation (days)	Time from randomization to discontinuation (days) = Date of study withdrawal – Date of randomization
Extent of exposure (days)	Extent of exposure (days) = Date of last drug administration - Date of first drug administration

Parameter	Derivation
Time to supplemental oxygen requirement (days)	Time to supplemental oxygen requirement (days) = First Administration start date - Date of randomization
Time to mechanical invasive ventilation use (days)	Time to (invasive) mechanical ventilation use (days) = First (invasive) Mechanical Ventilation start date - Date of randomization
Time to admission to ICU (days)	Time to admission to ICU (days) = Admission date - Date of randomization
Time to rescue medication (days)	Time to rescue medication (days) = First rescue treatment start date - Date of randomization
Overall survival (days)	Overall survival (days) = Date of death - Date of randomization
Subject with improvement based on Liker scale	Improvement = any of these answers: • 1 = minimally better, • 2 = moderately better, and • 3 = markedly better
Cumulative quantity (L) of oxygen treatment	Cumulative quantity of oxygen treatment (L) = Sum of all Quantity (L) in CONCOMITANT OXYGEN TREATMENT form, from randomization to time point of interest. It is defined as supplemental oxygen requirement any increased used of oxygen compared to baseline.
Cumulative duration (hours) of oxygen treatment	Cumulative duration of oxygen treatment (hours) = Sum of duration of oxygen administration (hours) in CONCOMITANT OXYGEN TREATMENT form, from randomization to time point of interest. Duration of oxygen administration (hours) = Administration end date/time - Administration start date/time / 60
Cumulative duration (hours) of mechanical ventilation	Cumulative duration of mechanical ventilation (hours) = Sum of duration of mechanical ventilation (hours) in MECHANICAL VENTILATION form, from randomization to time point of interest. Duration of mechanical ventilation (hours) = End date/time - Start date/time / 60
Duration (days) of ICU stay	Duration of ICU stay (days) = Discharge date - Admission date
Change from baseline	For changes from baseline the baseline value will constitute the minuend and the later value the subtrahend.
Conversion of Time Intervals	If a time interval was calculated in minutes, hours or days and needs to be converted into months or years 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

9.2 Partial date conventions

Table 8: Algorithm for Treatment Emergence of Adverse Events

START DATE	STOP DATE	ACTION
Known	Known, Partial or Missing	If start date < IMP start date, then not TEAE If start date >= IMP start date, then TEAE
Partial, but known components show that it cannot be on or after IMP start date	Known, Partial or Missing	Not TEAE
Partial or Missing	Known	If stop date < IMP start date, then not TEAE If stop date >= IMP start date, then TEAE
	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 stop date < IMP start date, then not TEAE If stop date >= IMP start date, then TEAE
	Missing	Assumed TEAE

Table 9: Algorithm for Prior/Concomitant medications

START DATE	STOP DATE	ACTION
Known	Known	If stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent and start date > end of treatment, assign as post study
	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 stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and 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 stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < date of informed consent, assign as prior If stop date >= date of informed consent, assign as concomitant Cannot be assigned as 'post treatment'
	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 stop date < date of informed consent, assign as prior If stop date >= date of informed consent, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

10. Tables, Figures and Listings

10.1 Output conventions

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

10.2 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.

10.3 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 "-".

10.4 Listing Conventions

- Listings will be sorted for presentation in order of subject number, treatment groups, and visit.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000).

11. Reference

1. Adaptive phase 2/3, randomized, controlled multicenter study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with COVID-19 pneumonia, Version n. 1.5 April 23, 2020
2. Case Report Form, Version 1.0 – 30 April 2020
3. Kalbfleisch, J. D., and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons.