16.1.1 Protocol and protocol amendments

Protocol REP0220 – Final Version 3.0, 09 April 2021

REP0220 – Final Version 3.0_09April 2021

CLINICAL STUDY PROTOCOL

EudraCT Number: 2020-005919-51

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

Short Title: REPAVID-19 Phase 3

Protocol Number: REP0220

Investigational compound: Reparixin

Study period	Projected starting date (first-patient-in):	January 2021
	Projected study end date (last-patient-last-visit):	May 2021

Sponsor: Dompé farmaceutici Spa. Via Santa Lucia 6, 20122, Milan, Italy.

Coordinating Investigator: Prof. Giovanni Landoni. Centro di Ricerca Anestesia e Rianimazione. Ospedale San Raffaele. Milan, Italy.

Scientific Board:

- PPD

STATEMENT OF CONFIDENTIALITY

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1. SIGNATURES

SPONSOR'S SIGNATURE PAGE

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

Version 3.0 09 April 2021

COORDINATING INVESTIGATOR'S SIGNATURE PAGE

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

Version 3.0 09 April 2021

Investigator's Statement

I have read this study protocol and agree that it contains all the information required to conduct this study.

Name of Coordinating Investigator (block letters): GIOVANNI LANDONI

Signature: PPD Date: PPD

INVESTIGATOR'S SIGNATURE PAGE

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

Version 3.0 09 April 2021

Investigator's Statement

I have read this study protocol and agree to conduct the study as outlined in the protocol, and in accordance with the Declaration of Helsinki, ICH-GCP E6 (R2) and any local regulations, being responsible for personally supervise the study conduct and ensure study staff complies with protocol requirement.

Name of Principal Investigator (block letters):_____

Signature: _____ Date: _____

2. CONTACT INFORMATION

SPONSOR	Dompé farmaceutici S.p.A., Via S. Martino 12, 20122 Milan, Italy Phone: +39.02.583831 Fax: +39.02.58383324
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Medical Expert	PPD
Clinical Operations Director	PPD
Clinical Operations Manager	PPD
SAE Reporting	PPD
Clinical Research Organization	PPD
CRO Project Manager :	PPD

3. LIST OF ABBREVIATIONS

AE	Adverse Event
ALI	Acute Lung Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAL	Broncho-Alveolar Lavage
CDE	Cat Dander Extract
CIF	cumulative incidence function
Cmax	Maximum concentration
CRO	Contract Research Organization
CRP	C-Reactive Protein
COVID	Corona Virus Disease
Css	Concentration, steady state
CT	Computerized Tomography
CXC	Cisteina X Cisteina (chemochine)
CYP	Cytochrome P450
DB	Data Base
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
EC	Ethics Committee
CCI	[redacted]
ECMO	Extracorporeal Membrane Oxygenation
eCRF	electronic Case Record Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EoS	End of Study
EoT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	Fraction of inspiration O_2
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
Hct	Hematocrit
HR	Heart Rate
ICF	Informed Consent Form
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INR	International Normalized Ratio
IRB	Institutional Review Board

IRS	Interactive Response System
ITT	Intentio to Treat
KM	Kaplan-Meier
LD50	Lethal Dose 50%
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Milliliters
NCI-CTCAE	National Cancer Institute, Common Terminology Criteria for Adverse Events
OATP	Organic-Anion-Transporting Polypeptides
PaO_2	Partial pressure of oxygen
PCR	Polymerase Chain Reaction
P/F	PaO_2 / FiO_2
Pk	Pharmacokinetic
PMN	Polymorphonuclear cell
PP	Per Protocol
PT	Preferred Term
RR	Respiratory Rate
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SCM	Single Challenge Model
SmPC	Summary of Product Characteristics
SpO_2	peripheral capillary oxygen saturation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TID	Three times daily
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
XDP	Cross-Linked Fibrin Degradation Product
yrs	years
WBC	White Blood Cell
WHO	World Health Organization
WHO-OS	WHO Ordinal Scale

4. PROTOCOL SYNOPSIS

Date and version of protocol synopsis: 09 April 2021 / version 3.0

Sponsor: Dompè Farmaceutici, Milano

Protocol Number: REP0220

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

Short Title: REPAVID-19 Phase 3

Investigational Medicinal Products (IMP): Reparixin oral tablets and corresponding placebo.

Phase of development: phase 3

Planned study period: from IVQ2020 to IVQ2021 (from start-up activities to CSR)

Planned number of study centers and locations: approximately 15 study Centers at European level and approximately 3 centres in USA

Number of subject to be randomized: A total number of 312 subjects will be randomized with a 2:1 randomization ratio (208 in the reparixin group; 104 in the placebo group). No significant drop-out rate is foreseen which could impact on the number of the study population.

Overall Study Design: This clinical trial is designed as a randomized, placebo-controlled, multicentre study to evaluate the efficacy and safety of Reparixin in hospitalized adult patients with severe COVID-19 pneumonia. Patients will be randomized based on an unbalanced randomization scheme (2:1) to Reparixin oral tablets (2 x 600 mg TID) for up to 21 days or to placebo. CCI [redacted] The placebo control arm is justified by the unavailability of a well-defined "standard of care" for subjects with COVID-19 pneumonia who are candidates for this study. All patient will receive the standard supportive care based on the patient's clinical need, eventually including anticoagulants, corticosteroids, antibiotics, among others, as per local standard therapy and in line with international guidelines. Follow-up information on the patient's clinical condition and survival will be collected until day 90.
An interim analysis for efficacy and futility is planned when half of the planned patients has reached the primary endpoint.

Study Objectives and Endpoints

Study Objectives:
Efficacy and safety of Reparixin treatment as compared to placebo (both on top of standard treatment) in adult patients with severe COVID-19 pneumonia.

Primary Endpoint:

- Proportion of patients alive and free of respiratory failure at Day 28, i.e. with no need of invasive mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO) or admission to Intensive Care Unit (ICU) linked to worsening of respiratory parameters compared to baseline.

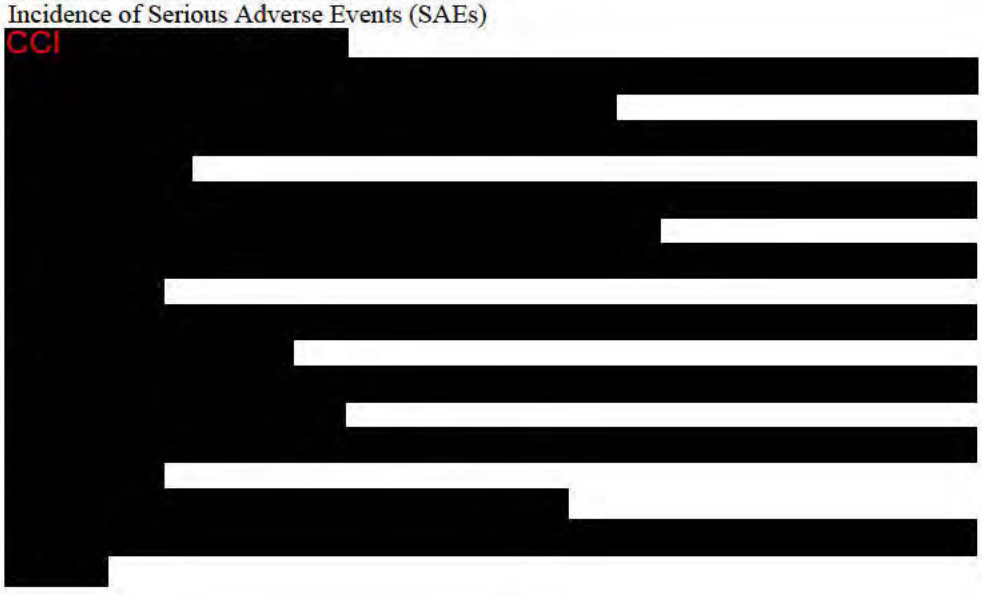
Key Secondary Endpoints:

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

Additional Secondary Endpoints:

- Proportion of subjects alive and free of respiratory failure (as described for the primary endpoint) at fixed time-points: days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) -60 (±2) after randomization (*randomization = day 1*),
- Mean changes in clinical severity score based on the 7-point WHO-OS as measured at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) - 90 (±2) after randomization,
- Time to clinical improvement 1 (decline of 1 category in the 7-point WHO-OS) up to Day 28,
- Time to clinical improvement 2 (decline of 2 categories in the 7-point WHO-OS) up to Day 28,
- Time to discharge from hospital (up to day 28),
- Clinical status at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) - 90 (±2) either in hospital or at home (7-point WHO-OS). When patient is at home, his/her clinical status can be assessed by phone,
- Dyspnea severity (Likert scale and VAS scale) at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Duration of supplemental oxygen treatment (days) up to Day 28,
- Incidence of invasive mechanical ventilation use, or ECMO up to Day 60,
- Duration of invasive mechanical ventilation, or ECMO (days) up to Day 60,
- Duration of non-invasive mechanical ventilation (days) up to Day 28,
- Duration of ICU admission (days) up to Day60,
- Duration of hospitalization since randomization (days) up to Day 28,
- Partial pressure of oxygen (PaO_2): change from baseline to the firstly available daily value at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO_2): change from baseline to the firstly available daily value at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- P/F ratio [partial arteriolar oxygen pressure (PaO2) to fraction of inspiration O_2 (FiO_2) ratio] from baseline to days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Hs-CRP: change from baseline to days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge (alternatively, CRP),
- Mortality rates up to Day 60 and Day 90,
- Freedom from (time to) death or respiratory failure (as described for the primary end-point).

Safety Endpoints:

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

Study Population:
Hospitalized, adult (≥18 <90 years old) patients with rt-PCR-confirmed severe COVID-19 pneumonia. Patients were considered to have severe disease in the presence of respiratory distress and requiring supplemental oxygen. No gender and/or ethnicity restrictions will apply.

Inclusion/exclusion criteria

Inclusion Criteria:

1. Age 18 to 90, male and female subject of any race
2. Reverse transcriptase Polymerase Chain Reaction (rt-PCR)-confirmed COVID-19 infection based on a nasal / oropharyngeal swab within 10 days before randomization
3. At least one of the following: 1) Respiratory distress with tachypnea (RR ≥ 24 breaths/min without oxygen); 2) Partial arterial oxygen pressure (PaO_2) / Fraction of inspiration O_2 (FiO_2) >100 and <300 mmHg (1mmHg = 0.133kPa), 3) $SpO_2 \leq 94\%$ while breathing ambient air.
   Calculation through validated Sat/FiO2 scales is allowed.
   P/F value of reference if the last available before the signature of consent
4. Need of supplemental oxygen (i.e. new use of supplemental oxygen, or increased oxygen requirement if on chronic oxygen) requiring low- or high-flow oxygen or non-invasive mechanical ventilation (7-point WHO-OS category 4 or 5)
5. Radiological chest imaging (X-rays, CT scan) confirms lung involvement and inflammation (presence of ground-glass opacities, and/or inter/intra lobular septal thickening, and/or consolidations in a patchy distribution).
6. Inflammatory status as documented by at least one of the following: Lactate dehydrogenase (LDH) > normal range, C-reactive protein (CRP) ≥ 100 mg/L or IL-6 ≥ 40 pg/mL, serum ferritin ≥ 900 ng/mL, XDP > 20 mcg/mL.
7. Females of child-bearing potential and with an active sexual life must not wish to get pregnant within 30 days after the end of the study and must be using at least one of the following reliable methods of contraception:
   i) Hormonal contraception, systemic, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit until 30 days after final visit
   ii) A non-hormonal intrauterine device [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit until 30 days after final visit
   iii) A male sexual partner who agrees to use a male condom with spermicide
   iv) A sterile sexual partner
   Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted. For all female subjects, with child-bearing potential, pregnancy test result must be negative before first drug intake.

Exclusion Criteria:

1. Cannot obtain informed consent.
2. hepatic dysfunction with Child Pugh score B or C, or ALT or AST > 5 times the upper limit;
3. renal dysfunction with estimated glomerular filtration rate (MDRD) < 50 mL/min/1.73 m^2 or patient receiving continuous renal replacement therapy, hemodialysis, or peritoneal dialysis.
4. Bacterial sepsis (besides COVID-19 sepsis)
5. Positive test for influenza virus, if tested during the current illness (note: influenza testing is not required by protocol)
6. Known congenital or acquired immune deficiency,
7. Patients with hypersensitivity to ibuprofen or to more than one non-steroidal anti-inflammatory drug or to more than one medication belonging to the class of sulfonamides (e.g. sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib
   Hypersensitivity to sulphanilamide antibiotics, e.g. sulfamethoxazole, does not qualify for exclusion).
   Know allergy to any medication (either investigational or non-investigational) which is planned at study entry for use during the study.
8. Patients receiving other not allowed medications (*see Section: Not allowed medications*)

9. Severe, active bleeding such as hemoptysis, gastrointestinal bleeding, central nervous system bleeding, and nosebleeds within 1 month before enrollment.
10. Evidence of COVID-19 disease progression during previously initiated treatment with remdesivir (alone on in any combination with other antiviral treatments), protease inhibitors (e.g. ritonavir, lopinavir, darunavir – atazanavir), tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib), convalescent plasma or intravenous immunoglobulin for COVID-19, or investigational treatments
11. More than three infusions of remdesivir, including the loading dose, prior to randomization
12. Subject participating in other interventional clinical trials. Subject having received investigational therapy in the previous 3 days, or at least 5 half-lives.
13. At the time of enrollment, patients not in a clinical condition compatible with the oral administration of the study drug.
14. P/F < 100 mmHg
15. Pregnancy:
    a) positive or missing pregnancy test before first drug intake or day 1;
    b) pregnant or lactating women;
    Women of childbearing potential and fertile men who do not agree to use at least one primary form of contraception for the duration of the study

Study treatments:
Patients who satisfy the predefined inclusion and exclusion criteria for this trial will be randomized 2:1 to one of the following groups for in-hospital treatment:

Group 1: Reparixin oral tablets 1200 mg TID (2 tablets, 600 mg each, TID) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care.

Group 2 (control): placebo, 2 tablets TID (identical to Reparixin tablets) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care.

Randomization will be performed through an Interactive Response System (IRS). Each Patient's Kit number will be randomly associated with a treatment group. The randomization list will be provided to the facility responsible for IMP packaging/labelling for the purpose of IMP preparation. Each randomized patient will be allocated with randomization number according to the stratified randomization list. Dropouts after randomization will not be replaced.

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

Unblinding:
For each randomized subject, individual code breaks will be accessible in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. Only the responsible investigator, or authorized delegates, can break the code via the IRT.
Any breaking of the treatment code by the investigational staff must be reported immediately to the Sponsor and must include an explanation for breaking the code. The sponsor should be contacted to discuss the case, if possible, prior to unblinding.
A general rule is that breaking the code is only allowed if the knowledge of the actual treatment is necessary for an appropriate decision on actions / treatments for the safety of the patient.
The DMC will have access to group-unblinded and/or fully unblinded DMC reports.

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.

Additional therapy :
Any additional therapy must be considered as local standard of care treatment, and it must be able to be administered to all patients enrolled in the study. Investigators are allowed to provide any medications having received final or conditional approval for the treatment of the COVID-19 infection, or used off-label at the Investigator's discretion and justified by scientific evidence of effectiveness against the COVID-19 infection without to stop study treatment.

Not allowed medications:
Not allowed medications (either at screening, or introduced during the trial) include concomitant drugs for which a significant drug-drug interaction leading to metabolic alterations is suspected based on the respective metabolic pathways.
Reparixin is catalysed by CYP2C9 and to a lesser extent by CYP2C19. Reparixin has some potential *in-vitro* for a non-competitive inhibition of the human hepatic enzyme CYP3A4.
However, at the present time, clinically significant untoward pharmacological interactions are not known for reparixin.
For remdesivir (*recently receiving conditional approval for the treatment of COVID-19; June 2020*) no clinical interaction studies have been performed and the overall potential of this drug for interactions is currently unknown. However, reparixin is not a substrate of the microsomal enzymes of which remdesivir is an *in-vitro* inhibitor (CYP3A4, OATP1B1, OATP1B3) or inducer (CYP1A2, CYP3A).
Patients should remain under close observation during the days of remdesivir administration if given concomitantly with reparixin.

Study duration:
The treatment duration will be up to a maximum of 21 days, with a follow-up period lasting up to 90 days since baseline.
The treatment will be interrupted upon the Investigator's clinical judgment of the patient's improvement, even if the patient is still hospitalized but no longer requiring supplemental oxygen or significant medical care.
The treatment is not foreseen to be continued at home.
For subjects discharged home before the completion of the 21-day treatment period, follow-up visits (preferably in person at the Center, or via a telephone call) will be held at days 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) -60 (±2) and/or 90 (±2) depending on the discharge time point.

End of study (EOS) definition: EOS is defined as the last day the last patient completes the last study assessment (including the follow-up assessments), or withdraws the consent to participate in the study including refusal to undergo follow-up, or is deceased or otherwise lost to follow-up.

End of treatment (EOT) definition: EOT is defined as the last treatment day in a randomized patient. EOT occurs upon completion of the scheduled treatment period (up to 21 days) for clinical judgment of improvement, or at the time of discharge from hospital, or at any time the treatment is interrupted early for any reason (e.g. for adverse events, ineffectiveness, withdrawal of consent for treatment). Patients randomized but with no actual treatment initiated, will have their EOT on the date of randomization.

Stopping criteria for individual subjects:
Subjects should be prematurely discontinued from study treatment for any of the following reasons:

- subject no longer consents to participate in the treatment phase of the study, yet consenting for the continuation of the collection of information in the follow-up phase of the study (specific consent to be signed). Patient may eventually decide to withdraw the consent for the study continuation including the collection of information in the follow-up phase,
- physician decision that it is in the best interest of the subject to be discontinued from study treatment,
- physician decision because of poor efficacy or poor tolerability of the investigational treatment
- the treatment will be interrupted in case of significant worsening of the renal function with eGFR (MDRD) falling to below 30 ml/min/1.75m^2 or an increase of serum creatinine by more than 50% since randomization
- severe protocol deviations

All study subjects, including 'treatment' drop-outs for any reason, will have to be followed up until the End of Study, unless the patient withdraws his/her consent to the study continuation including the follow-up.

Stopping criteria for the clinical trial:
The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.
The recommendations of the Data Monitoring Committee will be taken into consideration in this regard.
If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

Data Monitoring Committee (DMC): An independent Data Monitoring Committee (DMC) will be appointed with the responsibility of safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the clinical trial. These tasks will be accomplished on an ongoing basis throughout the trial. The DMC will provide recommendations about stopping or continuing the trial. In order to contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol- specified regimens and retention of participants, and the procedures for data management and quality control.
The DMC will be advisory to the clinical trial leadership group (the Scientific Committee of the study). The Scientific Committee will be comprised of the sponsor's study team and lead study investigators, who jointly will have responsibility for the design, conduct and analysis of the clinical trial. The Scientific Committee will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in the study conduct are required.

Statistical plan:
The sample size of the study is calculated based on results from the REPAVID-19 study (phase II, open label study) with Reparixin.

Each patient will be randomly allocated to Reparixin or Control according to a randomization ratio of 2:1 and followed for the entire treatment and follow-up duration for collecting the efficacy endpoints.

Considering a randomization ratio 2:1 (Reparixin:placebo) and a one-sided alpha of 0.025, a total of 264 evaluable patients will allow to achieve an overall power of 90% to detect a group difference ≥20% in proportion of patients

alive and free of respiratory failure at Day 28 in favor of reparixin, assuming that the proportion of patients alive and free of respiratory failure in the placebo group will be approximately 60%. Assuming that 15% of subjects will not be evaluable for primary analysis, a total of approximately 312 subjects is expected to be enrolled.

An interim analysis for efficacy and futility is planned when half of the planned patients has reached the primary endpoints. O'Brien-Fleming spending functions will be used to control the type I and II errors. No additional correction for multiplicity is required. The DMC will be involved in the evaluation of the interim analysis results and in the consequent decision on the continuation of the study.

Summary statistics have been defined for quantitative variables (number of observations, mean, standard deviation, median, minimum and maximum) and qualitative variables (number and percentage per category). If appropriate, confidence intervals around the mean or the proportions will be presented. For time-to-event variables, cumulative freedom from event will be evaluated using Kaplan-Meier (KM) method and 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.

Primary endpoint will be analyzed by means of logistic regression adjusting by pre-defined baseline factors. Since patients who discontinue the IMP will not be withdrawn from the study but will be asked to complete safety and efficacy assessments, missing data will be addressed by modeling patients with missing data after retrieved drop-outs, assuming that missing data would have been like retrieved drop-outs if they were assessed.

Results of primary analysis will be assessed in sensitivity analyses to assess the robustness of results on primary endpoint versus adherence to protocol and presence of missing data.

If the primary analysis of primary endpoint leads to rejection of the null hypotheses, key secondary endpoints will be tested in a conditional sequential manner to show superiority of reparixin versus placebo according to the pre-defined ranking sequence. Independently of the results on primary endpoints, all secondary endpoints will be analyzed at each available time points by means of summary statistics and by appropriate parametric tests depending on the nature of the variable and its distribution. All analyses will be descriptively in nature. Data transformation might be used in order to satisfy the assumption of normality requested by parametric statistical tests. In case such assumptions are not met, non-parametric counterpart tests will be used. Change from baseline value (for continuous variables) and shift tables versus baseline (for categorical variables) will also be summarized for all post-baseline visits.

AEs will be presented in terms of the number of AEs and incidence. Other safety parameters will be summarized by treatment at each available visit by means of descriptive statistics.

The Safety and the Full Analysis Set population will consist of all patients who will be randomized and received at least one dose of the investigational product. Safety population will be analyzed according to the actual treatment received; Full Analysis Set population will be analyzed according to ITT principle, i.e. by treatment allocation. The Per Protocol (PP) population will consist of all patients in the FAS population who do not have Major Protocol Deviations. Primary and secondary efficacy analyses will be conducted on the FAS population while SAF and PP populations will be used for safety and sensitivity analyses, respectively.

The Study Statistical Analysis Plan (SAP) with more technical and detailed elaboration of the principal features of statistical analyses will be finalized before interim analysis. Any deviation from the original statistical plan will be described in the Clinical Study Report.

SCHEDULE OF ASSESSMENTS

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

Study procedures	Screening	Baseline Day 1	Day 3	Day 7 (±1)	Day 14 (±2)	Day 21 (±2) or EoT [1]	Day 28 (±2) or discharge or EoS [1]	Day 60 (±2) or discharge or EoS [1]	Day 90 (±2) or EoS[1]
CCI [redacted]		[redacted]				[redacted]			
CCI [redacted]		[redacted]	[redacted]	[redacted]					
samples for Reparixin concentration [8]			X						
CCI [redacted]		[redacted]				[redacted]			
SARS-CoV-2 virology (rt-PCR)	<---------- X						X		
Use of additional therapy [9]			<---------- X						
Study drug administration		<---------- X ---------->							
Record AEs / SAEs	<---------- X ---------->								

[1] EoT: End of Treatment. EoS: End of Study
EoT is the last day of treatment administration The investigational treatment will last up to 21 days. Reasons for earlier treatment termination are: Investigator's decision based on clinical judgment of improvement, even if the patient is still hospitalized but no longer requiring supplemental oxygen or significant medical care ; occurrence of adverse events; patient's withdrawal of consent to the treatment. After EoT, laboratory and clinical examinations shall be collected on the day of patient's discharge from hospital, or on Day 28. The collection of follow-up information should be continued after EoT until EoS (Day90), unless the patient also withdraws the consent to the follow-up. For subjects discharged home before the completion of the 21-day treatment period, follow-up (preferably in person at the Center, or via a telephone call) at days 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) and/or 90 (±2) depending on the discharge time point.
EoS is defined as the last day the last patient completes the last study assessment (including the follow-up assessments), or withdraws the consent to participate in the study, including follow-wp. Subjects with EoS before Day 28 should undergo a full evaluation (as required on Day 28). Subjects with EoS after Day 28 but earlier than Day 90 should undergo evaluation as required on Day90.
[2] Time between onset of symptoms and initiation of the investigational treatment (days); Time between hospitalization and initiation of the investigational treatment (days)
[3] to be recorded over the whole duration of the hospitalization (total number of days to be reported). For supplemental oxygen, please record daily (average) delivery as < 6 L/min, 6 - 10 L/min, >10 L/min
[4] When deemed appropriate by the investigators
[redacted]
[8] Samples for the determination of Reparixin concentrations collected immediately before and one hour (± 15 min) after first dosing at day 3

1. INTRODUCTION

1.1 Background

IN DECEMBER 2019, A NEW IDENTIFIED CORONAVIRUS (SARS-COV-2) OUTBREAK IN WUHAN CAUSED PUBLIC HEALTH CRISIS IN CHINA AND SPREAD WORLDWIDE. On February 11, 2020, the World Health Organization officially named the disease caused by the new coronavirus: "COVID-19". The symptoms of human infection with SARS-CoV-2 are generally fever, fatigue, dry cough and dyspnea. Noteworthy, a considerable percentage of COVID-19 cases have rapidly progressed to a severe and critical condition with acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and pulmonary edema as the most common complications, resulting in a large number of pneumonia hospitalized patients requiring supplemental oxygen, mechanical ventilation, or even ECMO.

LUNG EDEMA, ENDOTHELIAL AND EPITHELIAL INJURY ARE ACCOMPANIED BY AN INFLUX OF NEUTROPHILS INTO THE INTERSTITIUM AND BRONCHEOALVEOLAR SPACE. Activation and transmigration of neutrophils are considered to play a key role in the progression of ALI and ARDS (1). Proof for the importance of neutrophils in ALI comes from clinical data and animal models. In patients with ARDS, the concentration of neutrophils in the bronchoalveolar lavage (BAL) fluid correlates with severity of ARDS and outcome (2; 3), whereas the severity of lung injury has been reduced by neutrophil depletion in mice. Furthermore, after blocking interleukin-8 (IL-8), a major chemoattractant for neutrophils, rabbits have been protected from acid aspiration-induced lung injury. A multitude of experimental and clinical data point at the causative role of neutrophils in lung injury (1-57). Although neutrophil activation is vital for the host defense, overzealous activation leads to tissue damage by release of cytotoxic and immune cell–activating agents such as proteinases, cationic polypeptides, cytokines, and reactive oxygen species.

1.2 Mechanism of action of Reparixin

NUMEROUS STUDIES HAVE CONFIRMED A KEY ROLE OF CXCR1/CXCR2 RECEPTOR AS POTENTIAL THERAPEUTIC TARGET IN ACUTE LUNG INJURY (ALI) AND ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS). Neutrophil infiltration of the lung is controlled by a complex network of chemokines that are released by a variety of cell types. Alveolar macrophages are a major source of chemokines in the alveolar space and produce IL-8, growth-regulated oncogene (GRO)-related peptides and CXCL5 (also known as epithelial neutrophil-activating protein [ENA]-78) (58; 59) (60; 61). High concentrations of IL-8 in BAL fluid from ARDS patients are associated with increased neutrophil influx into the airspace (62; 63). Recent studies have revealed that IL-8 in BAL fluid is bound to IL-8 autoantibodies (anti-IL-8:IL-8 complexes) (64; 65) and BAL fluid concentrations of these complexes correlate with development and outcome of ALI (66; 67). In particular, this complex exhibits chemotactic and proinflammatory activity (68). Moreover, intratracheal application of IL-8 induces lung injury which can be attenuated by inhibition in different models of ALI (69). In rodents, the most relevant chemokines for neutrophil recruitment into the lung are keratinocyte-derived chemokine (KC, also named CXCL1) or cytokine-induced neutrophil chemoattractant (CINC; the rat homolog to KC) and macrophage inflammatory protein-2 (MIP-2, also named CXCL2). Similar to IL-8, CXCL1, CXCL2, lipopolysaccharide-induced CXC chemokine (LIX, also named CXCL5) and lungkine (CXCL15) bind to CXCR2. Inhibition or knockout of CXCR2 receptor diminishes

neutrophil influx into the lung (70-77). In contrast to the multiple CXC chemokines only two CXC chemokines receptors, CXCR1 and CXCR2, have been shown to mediate the response to CXC chemokines in human neutrophils. Whereas human CXCR1 binds to CXCL6 and CXCL8 (IL-8) with a high affinity, human CXCR2 binds also to CXCL6 and IL-8 as well as several CXC chemokines (GRO-α,GRO-β, GRO-γ, CXCL1, CXCL2, CXCL3), ENA-78 (CXCL5) and (CXCL7) (78).

MECHANISM OF ACTION OF REPARIXINAS MODULATOR OF THE INFLAMMAYORY CASCADE. Reparixin (DF1681Y) is a specific inhibitor of CXC ligand 8 [CXCL8; formerly interleukin (IL)-8] biological activity, stemming from a program of drug design of molecules intended to modulate chemokine action. Reparixin is *in vitro* a potent and specific inhibitor of CXCL8 biological activity. *In vitro* chemotaxis experiments have shown that reparixin inhibits CXCL8-induced chemotaxis of human polymorphonuclear leukocytes (PMN) in the low nanomolar range. Studies to elucidate the mechanism of action have shown that reparixin is a non-competitive allosteric inhibitor of the CXCL8 receptors CXCR1 and CXCR2. Interaction of reparixin with CXCL8 receptors inhibits the intracellular signal transduction events activated by binding of CXCL8 to CXCR1 and CXCR2 (85, 86). *In vivo*, reparixin prevented PMN infiltration into the transplanted kidney and reduced creatinin levels in a rat model of kidney transplantation. Similarly, in a rat model of lung transplantation, reparixin improved isolated graft oxygenation, decreased pulmonary oedema, and significantly reduced neutrophil infiltration into transplanted lungs. Moreover, reparixin prevented PMN infiltration and tissue damage in other animal models of ischemia/reperfusion injury of liver, brain, intestine, heart and spinal cord. In these models, *in vivo* inhibition of PMN recruitment ranged from 40 to 90%, and inhibition of tissue damage ranged from 50 to 80%. Efficacy was seen in all models at reparixin dose of 9.90 mg/kg.
Recently, reparixin lysine salt was evaluated in different models of intrahepatic pancreatic islet transplantation in mice, which include syngeneic and allogeneic settings. Reparixin was administered by s.c. continuous infusion for 7 or 14 days starting from day -1 of islet transplantation. A dose of 5.28 mg/kg/hour was administered in all experiments. Reparixin was able to significantly improve islet engraftment, as demonstrated by its ability to increase the likelihood of and to reduce the time to gain non-fasting blood glucose levels less than 200 mg/dl (normo-glycaemia) in marginal mass syngeneic islet transplantation model. In the fully mismatched allogeneic model, reparixin not only protected islets from early graft failure, but was also able to increase the time to rejection, as shown by post-transplant prolongation of normo-glycaemia. Graft function was indefinitely prolonged in 20/30% of mice treated with reparixin and rapamycin, suggesting possible tolerance induction. In parallel, reparixin treatment reduced intrahepatic infiltration of PMNs, macrophages, T helper and dendritic cells

REPARIXIN EFFECTS ON ACUTE LUNG INJURY (ALI) MODELS. The therapeutic potential of reparixin in murine models of LPS-induced pulmonary inflammation and acid-induced ALI was studied. Reparixin (15 μg g−1) reduced neutrophil recruitment in the lung by approximately 50% in an in vivo model of LPS-induced ALI. Reparixin also reduced accumulation of neutrophils in the interstitial compartment and vascular permeability in LPS-induced ALI. Both prophylactic and therapeutic application of Reparixin improved gas exchange, and reduced neutrophil recruitment and vascular permeability in a clinically relevant model of acid-induced ALI (70). In the CDE (cat dander extract) single challenge model (SCM), administration of Reparixin (15 mg/kg) suppressed neutrophil recruitment into the lungs. In the CDE Multiple Challenge Model, Reparixin inhibited eosinophil, neutrophils, and total cell numbers in BALF, serum levels of total IgEand CDE specific IgE, airway epithelial mucin secretion, levels of Th2 inflammation-associated genes periostinand muc5ac, and the BALF levels of IL-4, IL-13, IL-33, and TSLP in BALF.

REPARIXIN SUPPRESSES ALLERGEN CHALLENGE INDUCED NEUTROPHILIC INFLAMMATION AND ALLERGIC AIRWAY INFLAMMATION. In the CDE (cat dander extract) single challenge model (SCM), administration of reparixin (15 mg/kg) suppressed neutrophil recruitment into the lungs. In the CDE Multiple Challenge Model, reparixin inhibited eosinophil, neutrophils, and total cell numbers in BALF, serum levels of total IgEand CDE specific IgE, airway epithelial mucin secretion, levels of Th2 inflammation-associated genes periostin and muc5ac, and the

BALF levels of IL-4, IL-13, IL-33, and TSLP in BALF. Pharmacological inhibition of CXCR1/2-axis by administration of reparixin inhibits allergen induced innate and allergic airway inflammation in mice (79).

REPARIXIN AMELIORATES THE INCREASED SEVERITY OF PULMONARY FIBROSIS CAUSED BY PARTICULATE MATTER

In a murine model of bleomycin-induced pulmonary fibrosis, pharmaceutical inhibition of CXCR2 with reparixin ameliorated Particulate Matter-induced increased severity of pulmonary fibrosis. Co-treatment with reparixin in mice receiving Particulate Matter and bleomycin reduced neutrophil number and neutrophil elastase concentration of day 2-BALF. Moreover, reparixin improved lung function and ameliorated pulmonary fibrosis as assayed by total collagen content and histochemical stains of fibrosis markers on day 14-lung tissues. (80)

REPARIXIN ANALOGUES RESULTED A VALID THERAPEUTIC STRATEGY FOR TREATING LUNG INFECTIONS CAUSED BY INFLUENZA A VIRUS OR STREPTOCOCCUS PNUEMONIAE.

The role of CXCR1/2 during influenza, pneumococcal, and post-influenza pneumococcal infections was investigated. Mice were infected with influenza A virus (IAV) or Streptococcus pneumoniae and then treated daily with the CXCR1/2 antagonist DF2162. To study secondary pneumococcal infection, mice were infected with a sublethal inoculum of IAV then infected with S. pneumoniae 14 days later. DF2162 was given in a therapeutic schedule from days 3 to 6 after influenza infection. Lethality, weight loss, inflammation, virus/bacteria counts, and lung injury were assessed. CXCL1 and CXCL2 were produced at high levels during IAV infection. DF2162 treatment decreased morbidity and this was associated with decreased infiltration of neutrophils in the lungs and reduced pulmonary damage and viral titers. During S. pneumoniae infection, DF2162 treatment decreased neutrophil recruitment, pulmonary damage, and lethality rates, without affecting bacteria burden. Therapeutic treatment with DF2162 during sublethal IAV infection reduced the morbidity associated with virus infection and also decreased the magnitude of inflammation, lung damage, and number of bacteria in the blood of mice subsequently infected with S. pneumoniae. These data suggested that modulation of the inflammatory response by blocking CXCR1/2 improves disease outcome during respiratory influenza and pneumococcal infections, without compromising the ability of the murine host to deal with infection (81).

DF2162, a Reparixin analogue, belongs to the same family of non competitive-allosteric inhibitors of CXCR1 and CXCR2 widely characterized in our research labs in terms of structure activity relationship and mechanism of action.

The two molecules belong to the chemical class of 2-(R)- phenyl propionamide derivatives thus sharing the same chemical moiety.

Reparixin and DF2162 exhibit similar potency in the inhibition of the target receptors CXCR1 and CXCR2 (IC50s in CXCL8 induced-chemotaxis in the range of 1 nM). The molecular mechanism of action has been deeply characterized by point-mutagenesis studies on CXCR1 and CXCR2 showing that Reparixin and DF2162 bind the receptors in the same allosteric site in the Trans-Membrane region, highly conserved in the two receptor subtypes. (83-86)

The different pharmacokinetic profile of the two molecules account for a bid (15 mg/Kg) oral administration of DF2162 as compared to a tid (15 mg/Kg) administration (on continuous infusion) for reparixin.

For this reason, DF2162 has been used to assess the role of CXCR1/2 during influenza (IAV), pneumococcal, and post-influenza pneumococcal infections in mice models. Even though the extensive characterization work was conducted with DF2162, preliminary experiments showed a similar behaviour using reparixin in the single IAV model leading to comparable results.

To investigate the role of CXCR1/2 during influenza infection, mice were infected with 1 × 104 PFU of IAV and then treated three times a day (from day 0 - at the time of the infection - to day 5 post-infection) with reparixin at 15 mg/Kg. Similarly to DF2162, treatment with reparixin decreased morbidity, as seen by the reduction of weight loss, reduced leukocytes infiltration into the airways, including neutrophils, and the levels of the pro-inflammatory cytokines TNF-α and CXCL1 and reduced the lung injury associated with IAV infection measure by histopathological score.

1.3 Toxicology data

Reparixin was tested for toxicity in rodent and non-rodent animal species after single and repeated i.v. doses. The repeated dose administration studies were conducted by i.v. continuous infusion, according to the intended human administration route. The general toxicological profile of i.v. Reparixin, in the studies conducted to date, is characterized by a low toxicity after single or repeated dose administrations in rats (LD50 = 229.68 mg/kg i.v.; 660.00 mg/kg/day as No Observed Adverse Effect Level from 4-week studies) and mice (401.94 mg/kg i.v.). Continuous i.v. administration to dogs for 2 weeks resulted in a safe dose of 39.60 mg/kg/day. Continuous i.v. infusion of Reparixin to the male and female rat at dose levels of up to 660.00 mg/kg/day did not have any significant adverse effects on mating performance and fertility. Reparixin poses no genotoxic hazard for humans. Reparixin lysine salt, at doses in excess of those intended to be used in humans, has a safe pharmacology profile in the renal, cardiovascular and respiratory systems of rats and dogs. The local tolerability of reparixin lysine salt was assayed in the rabbit ear lateral vein. The compound was well tolerated in concentrations up to 4.95 mg/mL (1 mL/kg) infused over a minute. In order to provide evidence of the safety of DF2243Y, the main metabolite of reparixin excreted in urine in humans, safety pharmacology and toxicity studies have been performed at doses 2 to 3 times higher that those reached in man, as may occur during the treatment of patients receiving kidney transplantation.

1.4 Pharmacokinetics and product metabolism

PK studies by i.v. injection revealed that Reparixin is very rapidly eliminated in rats and humans (t1/2 0.5-3 hrs and 1.0-1.5 hrs, respectively) whereas elimination is slower in dogs (12-28 hrs). The PK of reparixin was linear in rats and in dogs but linearity was less evident in humans. Reparixin undergoes complete metabolism (oxidation + conjugation) in all the species tested. The *in vitro* human hepatic, phase I metabolism of Reparixin is catalysed by CYP2C9 and to a lesser extent by CYP2C19. DF2243Y, DF2188Y, methanesulfonamide and ibuprofen are the metabolites detected in human plasma and urine, with DF2243Y being the major metabolite. Exposure to ibuprofen after administration of Reparixin 2.77 mg/kg/h for 48 hrs (the highest dose tested in humans) was similar or lower than that obtained after a standard therapeutic single dose of ibuprofen (300mg). Preliminary PK data obtained in a few patients undergoing islet transplantation shows that plasma levels of Reparixin (total and unbound) and its major metabolite DF2243Y appears to be within the expected range according to the dose administered. Due to extensive metabolism, unchanged Reparixin was poorly or not excreted into the urine of rat, dogs and humans so that the PK profile of Reparixin is not influenced by renal impairment. *In vitro* protein binding of [14C]-reparixin showed that Reparixin is highly bound (approximately 99%) to plasma proteins in rats, dogs, rabbits, cynomolgus monkeys and humans. Albumin is likely to be the major binding protein in plasma in all species, accounting for 99.2% in humans.

In clinical trials with oral tablets Reparixin was administered for 21 consecutive days followed by 7 days of drug holyday before the next cycle. Reparixin was rapidly absorbed (median T_{max} 1 hr). Reparixin systemic exposure (C_{max} and AUC_{last}) did not change from day 1 to day 21, indicating the absence of accumulation over the dosing period. Also $t_{1/2}$ did not change from day 1 to day 21, with a median value of about 2 hrs. Once absorbed, Reparixin is highly protein bound as only <0.1% to 0.2% of total Reparixin is available as unbound (free) drug. Reparixin was rapidly metabolized to DF2243Y, DF2188Y and ibuprofen. For all three metabolites systemic exposure was similar on both day 1 and day 21 within the observed intersubject variability. The $t_{1/2}$ of all three metabolites appeared to remain about the same from day 1 to day 21.
To investigate the PK/PD characteristics of Reparixin, we assessed the effect of the drug in inhibiting IL-8-mediated hPMN NETs release in whole blood of healthy volunteers, 500 µL/sample of whole blood were pre-incubated with vehicle or different concentrations of reparixin for 15 min at 37°C and next placed onto 13-mm

polylysine coated glass circular coverslips and incubated for 30 min at 37°C in a 5% CO_2 atmosphere to allow for cell adherence. Post-incubation, samples were stimulated with vehicle or IL-8 (100 ng/mL) for 4h (37°C, 5% CO_2), after which the supernatant was removed and coverslips washed one time with HBSS. Next, samples were stained with 40 nM Sytox Green for 10 min. Finally, cells were fixed in 2% paraformaldehyde and NETs formation determined by confocal microscopy. Reparixin blocked IL-8-induced NETs formation in a concentration dependent manner being the inhibition statistically significant at 5 µg/mL (40% of inhibition) and reaching the almost complete inhibition (about 90%) at 25 µg/mL thus confirming that the total blood concentration of 25 µg/mL (corresponding to a free unbound concentration of 100 nM) that is reached at the steady state by iv infusion or by repeated oral administration (Css) is coherent with the objective to reach the drug exposure necessary to maximize the potential clinical efficacy of the compound.
Reparixin has some potential *in vitro* for a non-competitive inhibition of the human hepatic enzyme CYP3A4 that is involved in the metabolism of cyclosporine A, tacrolimus and rapamycin. However, since inhibition is evident at concentration far higher than the free plasma concentration of Reparixin at steady state in humans, it is predicted that the clinical relevance of such inhibition is remote. Indeed, reparixin does not affect to a clinically relevant extent the activity of CYP3A4 and CYP2C9 (enzyme involved in Reparixin metabolism), as revealed by an interaction study where the PK of midazolam and tolbutamide (probe substrates for these enzymes) was evaluated in healthy subjects receiving single oral doses of the probes alone or in combination with Reparixin.

1.5 Clinical development

Reparixin is the first low molecular weight blocker of CXCL8 biological activity in clinical development.
Reparixin was granted orphan drug designation for the "prevention of delayed graft function after (solid) organ transplantations" by the European Commission of Orphan Medicinal Products in September 2001 and by the Food and Drug Administration in January 2003. Recently orphan drug designation has been granted in the EU for "prevention of graft rejection in pancreatic islet transplantation". In the 4th quarter of 2011, Dompé has received Scientific Advice from the European Medicines Agency (EMA) for the development of reparixin in pancreatic islet transplantation.

REPARIXIN IMPROVED SURVIVAL AFTER LUNG TRANSPLANTATION. In a US-Canada phase 2 study CCI, 101 patients (46 on reparixin, 55 on placebo) undergoing single or bilateral lung transplant were trated with reparixin. The patients were randomized to receive 48h i.v. continuous infusion (loading: 4.488 mg/kg/h for 30 min, maintenance: 2.772 mg/kg/h for 47.5hrs) of either reparixin or placebo starting a few hours before the transplant. The study showed a statistically significant difference in patient survival at Month 12 post-transplant between the placebo (7 deaths) and reparixin (no deaths) groups (p-value = 0.0111 [Log-Rank]).

IRCCS OSPEDALE SAN RAFFAELE COORDINATED A PHASE 3 INTERNATIONAL TRIAL WITH REPARIXIN IN PANCREATIC ISLET TRANSPLANTATION. A phase 3, multicenter, randomized, double-blind, parallel-assignment study (NCT01817959) was conducted and coordinated by Ospedale San Raffaele of Milan, Italy in recipients of islet allo-transplants randomized (2:1) to reparixin or placebo in addition to immunosuppression. Patients received either reparixin at a dose of 2.772 mg/kg body weight/h or matched (flow rate/length of infusion) placebo according to their randomization number. Study drugs were administered on top of immunosuppression by continuous infusion through a high-flow vein for 7 days starting 12 h before each islet infusion. No clear differences between treatment groups were observed for rates, severity, and distribution of AEs or SAEs. Analysis of patient subsets showed a trend for a higher percentage of subjects retaining insulin independence for 1 year after a single islet infusion in patients receiving reparixin, as compared with patients receiving placebo (26.7% vs. 0%, P = 0.09) when antithymocyte globulin was used as induction immunosuppression (82).

IRCCS OSPEDALE SAN RAFFAELE IS A REFERENCE CENTER IN THE MANAGEMENT OF THE COVID-19 PANDEMIC EMERGENCY, AND HAS RECENTLY TREATED WITH REPARIXIN (UNDER A COMPASSIONATE USE APPLICATION) FOUR PATIENTS WITH SEVERE COVID-19 PNEUMONIA. Four patients with ARDS caused by COVID-19 pneumonia with the clinical indication for intubation and mechanical ventilation were treated with Reparixin IV infusion (2.772 mg/kg body weight/hour) into a high-flow central vein for 5 days at the San Raffaele Hospital of Milan, Italy. The first patient started treatment on 24 March 2020 and the last patient on 31 March 2020. All patients were discharged alive from hospital, one of them withot requiring ICU admission and intubation. Therefore, looking at these preliminary results on a limited number of patients who had an indication for intubation and mechanical ventilation in ICU care (both events being in the proposed primary endpoint of this study) before starting treatment, the improvement observed on the expected clinical outcome in 2 out of 4 patients is aligned with the assumptions we used for sample size calculations of this trial.

From a hematochemical standpoint, during treatment with Reparixin an improvement or at least stabilization of the inflammatory markers (C-reactive protein, procalcitonin, ferritin) and of the tissue damage markers (LDH, AST, ALT) was also observed during this compassionate use experience. A list of the patients' characteristics is provided below in tabular format as provided by the San Raffaele Hospital physicians

PT ID	Sex	Age	Comorbidity	Basal treatment	Symptoms before hospital admission	Treatment start	Treatment duration
Pt1	PPD				14 d, Fever-Cough	24/03/2020 12:00	5 days
Pt2					7 d, Fever-Cough- diarrea-anosmia-disgneneusia	30/03/2020 23:30	5 days
Pt3					10d, Fever	31/03/2020 19:20	5 days
Pt4					7d, Fever	31/03/2020 19:30	5 days

As of today, no other compassionate use cases for the use of Reparixin in patients with COVID-19 pneumonia have been activated at the San Raffaele Hospital or in other sites.

A PHARMACOKINETIC STUDY WITH ORAL REPARIXIN IN CANCER PATIENTS. A phase 1b pilot study to evaluate reparixin in combination with chemotherapy with weekly paclitaxel in patients with HER-2 negative metastatic breast cancer (study CCI) has provided pharmacokinetic data on human exposure to oral 1200 mg TID. At the 21st day of treatment (i.e. no paclitaxel from day 15th) the mean drug concentration at the steady state (Css) was 23,88 mcg/ml (Css = AUC/τ), which is comparable to the Css obtained by IV continuous infusion, with AUC 0-8h(τ) = 191 mcg*h/ml and τ (dose interval) = 8 hours.

The oral dose of 1200 mg TID has been identified as the dose for phase 2 trials.

1.6 Safety data

A total of 448 subjects have been exposed to reparixin in the clinical studies completed up to the start of the phase 2 in COVID-19. Of these, 337 and 112 received i.v. formulation and oral tablets, respectively. The patient

population exposed to i.v. formulation includes 103 adult healthy subjects (100M/3F), 17 patients with different grades of renal impairment (12M/5F), 16 patients undergoing cardiopulmonary by pass (10M/6F), 46 patients undergoing lung transplantation (23M/23F), 48 patients undergoing kidney transplant (31M/17F), 22 undergoing liver transplant (18M/4F) and 85 receiving intrahepatic pancreatic islet infusion (32M/53F), with 22 patients in this group receiving reparixin twice. Exposure included short or prolonged i.v. infusion up to 10.6 mg/kg over 30min or 133 mg/kg over 48h and, in pancreatic islet and liver transplantation studies, 2.772 mg/kg body weight/hour i.v. continuous infusion for 7 days. Overall, reparixin was safe and well tolerated in both healthy subjects and critically ill patients. In phase 1 studies, no deaths, Serious Adverse Events (SAEs) or Adverse Event (AE)-related withdrawals were reported. The majority of AEs reported were of mild intensity. All subjects had recovered completely or had ongoing adverse events of mild intensity when they were discharged. The safety of reparixin was confirmed also in patients with different grades of renal impairment. In the interaction study no safety concerns were raised during co-administration of midazolam/tolbutamide with reparixin. During phase 2 and 3 studies, AE and SAE profile was similar for both placebo and reparixin groups and no particular safety concerns were raised. Data obtained in the trials in islet transplantation further support the safety profile of the proposed dose, even after a 7-day administration, repeated twice in several patients. Most frequent ADRs were nausea, headache, and vomiting; great majority of these were mild to moderate in nature and none required discontinuation of the Investigational Product. Tachycardia occurred in one patient from Days 5 to 38 after 1st islet infusion was judjed probable in relation to Investigational Product. Vomiting, nausea and headache on Day 5 and 6 after 2nd islet infusion in one patient and erythema, nausea and headache on Days 2 to 6 after 1st islet infusion in another patient were judged highly probable in relation to the Investigational Product. Nausea, vomiting and severe gastrointestinal bleeding associated with anaemia developed in a female patient early after the beginning of reparixin infusion because the patient received a dose of reparixin 3 times as high as that foreseen in the protocol (medical error). These events were assessed as serious by the investigator and by the Sponsor.
Overall, the most frequent (>10%) ADRs observed in the phase 1 to phase 3 I.V. studies were: Gastrointestinal disorders (about 26% of the total number of reports), including abdominal pain lower, abdominal pain NOS, abdominal pain upper, constipation, diarrhea, dyspepsia, flatulence, gastroesophageal reflux disease, gastrointestinal haemorrhage, intra-abdominal haemorrhage, nausea and vomiting.
Nervous system disorders (about 19%), including headache, dizziness, hypoaesthesia, somnolence.
General disorders and administration site conditions (about 16%), including cannula site reaction, fatigue, implant site haemorrhage, injection site thrombosis, infusion site oedema, lethargy, malaise, oedema, oedema peripheral, and pyrexia
The patient population exposed to reparixin oral tablets consists of 111 female subjects receiving either single agent reparixin CCI , operable breast cancer: 20 patients) or the combination of reparixin and weekly paclitaxel in metastatic breast cancer CCI : 30 patients; CCI randomized CCI 61 patients).

In the studies completed so far, reparixin was generally well tolerated at all doses studied. Overall, 505 ADRs were reported in 78 patients in the safety population.

70.9% of the ADRs were grade 1 (mild), 22.9% were grade 2 (moderate) and 4.3% were grade 3 (severe). One grade 4 ADR was reported overall (CCI). In addition, one patient in clinical trial CCI experienced serious ADRs including grade 4 peritonitis and grade 5 intestinal perforation.

The most frequent (>10%) ADRs observed in the three studies were:

Gastrointestinal disorders (31.8%), including nausea, vomiting, abdominal pain, discomfort or distension, dyspepsia, flatulence, constipation.
General disorders and administration site conditions (16.4%), including fatigue and peripheral oedema.

Further data can be found in the Investigator's Brochure (Appendix 1)

1.7 Phase 2 study

An open-label, phase 2 study was conducted to assess the efficacy and tolerability of Reparixin in comparison with standard of care. The study included patients with severe COVID-19 requiring supplemental oxygen, or non-invasive mechanical ventilation. 51 patients were randomized overall, 34 in the Reparixin group and 17 in the standard of care group (2:1 randomization ratio). The primary end-point was the first occurrence of a composite endpoint (supplemental oxygen requirement, invasive mechanical ventilation use, admission to ICU, use of a rescue medication for any reason). The treatment with reparixin was associated with a statistically significant improvement in the time to the composite endpoint (defined as the occurrence of at least one of the following: supplemental oxygen requirement, mechanical ventilation use, admission to ICU, use of a rescue medication for any reason), with fewer days of oxygen use and shorter duration of mechanical ventilation. The results of the study suggest that the treatment with reparixin may have prevented the progression to more severe respiratory disease. One death occurred in the Reparixin group and three in the control arm. No adverse events were related to Reparixin.
The analysis of the phase 2 data has allowed establishing proof-of-concept, endpoint selection, and sample size planning along with review of Data Monitoring Committee (DMC) recommendations.

1.8 Phase 3 study

This phase 3 study has been designed as a double-blind study comparing Reparixin vs placebo on top of the standard therapy in the same patient population as that enrolled in the phase 2. Hospitalized patient with severe COVID-19 pneumonia requiring supplemental oxygen will be randomized. The reference group with placebo is justified by the current unavailability of an effective therapy for COVID-19 after having various compounds been tested, e.g. remdesivir, hydroxychloroquine, protease inhibitors, tyrosine kinase inhibitors, convalescent plasma or intravenous immunoglobulins. The use of any of these treatments is allowed in the study provided that it is started as background treatment in all patients characterized by a similar level of disease severity, at a site level.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

Efficacy and safety of Reparixin treatment as compared to placebo (both on top of standard treatment) in adult patients with severe COVID-19 pneumonia.

2.2 Primary Endpoint

- Proportion of patients alive and free of respiratory failure at Day 28, i.e. with no need of invasive mechanical ventilation or ECMO or admission to ICU linked to worsening of respiratory parameters compared to baseline.

2.3 Key Secondary Endpoints

- Proportion of patients alive and free of respiratory failure (as described for the primary endpoint) at Day 60,
- Mortality rates up to Day 28,
- Incidence of ICU admission until Day 28,

- Time to recovery (category 1 - 2 - 3 of the 7-point WHO Ordinal Scale of clinical improvement (WHO-OS) until Day 28.

2.4 Additional Secondary Endpoints

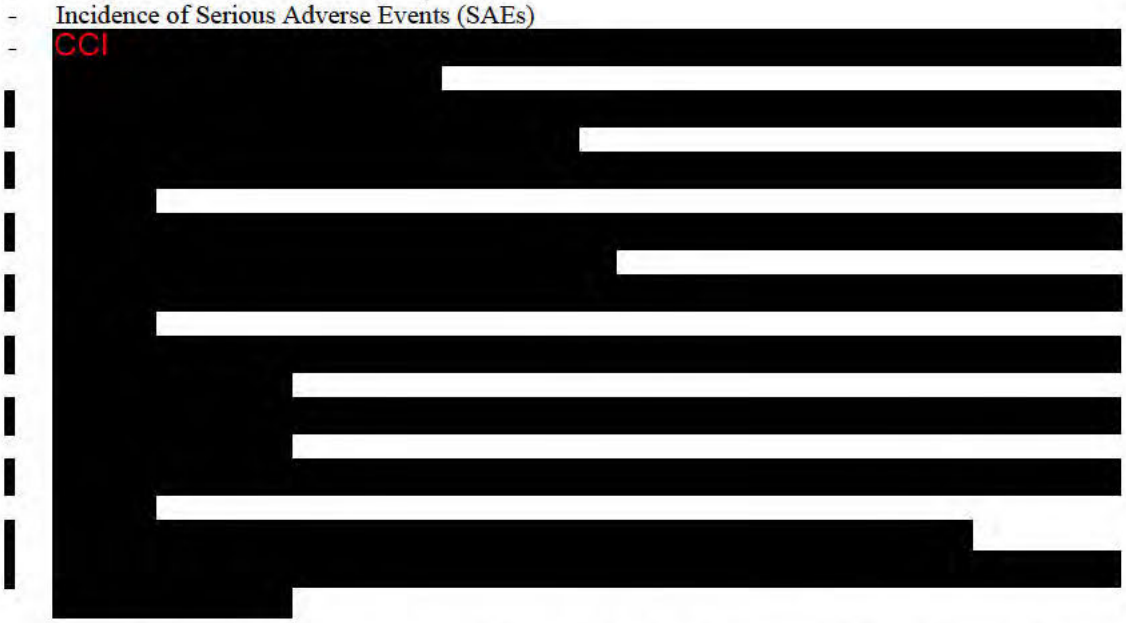
- Proportion of patients alive and free of respiratory failure (as described for the primary endpoint) at fixed time-points: days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) -60(±2) after randomization (*randomization = day 1*),
- Mean changes in clinical severity score based on the 7-point WHO-OS,
- Time to clinical improvement 1 (decline of 1 category in the 7-point WHO-OS) up to Day 28,
- Time to clinical improvement 2 (decline of 2 categories in the 7-point WHO-OS) up to Day 28,
- Time to discharge from hospital (up to day 28),
- Clinical status at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) - 90 (±2) either in hospital or at home (7-point WHO-OS). When patient is at home, his/her clinical status can be assessed by phone,
- Dyspnea severity (Likert scale and VAS scale) at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Duration of supplemental oxygen treatment (days) up to Day 28,
- Incidence of invasive mechanical ventilation use, or ECMO up to Day60,
- Duration of invasive mechanical ventilation, or ECMO (days) up to Day60,
- Duration of non-invasive mechanical ventilation (days) up to Day 28,
- Duration of ICU admission (days) up to Day60,
- Duration of hospitalization since randomization (days) up to Day 28,
- Partial pressure of oxygen (PaO_2): change from baseline to the firstly available daily value at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO_2) at days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- P/F ratio [partial arteriolar oxygen pressure (PaO_2) to fraction of inspiration O_2 (FiO_2) ratio] from baseline to days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge,
- Hs-CRP: change from baseline to days 3 - 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) or until discharge (alternatively, CRP),
- Mortality rates up to Day 60 and Day 90,
- Freedom from (time to) death or respiratory failure (as described for the primary end-point).

2.5 Exploratory Endpoints

- CCI

2.6 Safety Endpoints

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



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

3. STUDY DESIGN AND METHODOLOGY

3.1 Study design

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

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

5.2: Other treatments). Follow-up information on the patient's clinical condition (new hospitalization, need of supplemental oxygen, adverse events) and survival will be collected until day90.
An interim analysis for efficacy and futility is planned when half of the planned patients has reached the primary endpoint.

3.2 Study population

Hospitalized adult patients with rt-PCR-confirmed severe COVID-19 pneumonia. Patients are considered to have severe disease in the presence of respiratory distress and requiring supplemental oxygen.
No gender and/or ethnicity restrictions will apply.

3.3 Study duration

The overall study duration is 90 days, including follow-up, but with a variable treatment period.
The investigational treatment will last up to a maximum of 21 days (depending the Investigator's decision based on the patient's condition, or patient decision to withdraw), with a follow-up period lasting up to 90 days since baseline.
The treatment is not foreseen to be continued at home.

3.4 Description of the study

The study will consist of three study periods: screening, treatment period (up to a maximum of 21 days), follow-up (up to 90 days).
During the course of the study, visits and assessments will be performed as defined in the Schedule of Assessments.

Screening period
Patients are included in the study after a variable period at home with initial symptoms of the COVID-19 infection; during this period, the patient had supposedly been treated by the family doctor. In case of worsening of his/her general and pulmonary condition eventually requiring oxygen supplementation in a hospital environment, the patient will start the screening phase for the confirmation of the selection criteria.
Before any study related procedures, at study entry all patients must have given a written informed consent for the study and will be assigned a screening number.
Patient meeting all of the inclusion criteria and none of the exclusion criteria will be randomized (see section 4.2).
No time limit has been posed for the time from the onset of symptoms and hospitalization. No time limit has been posed for the duration of the screening period until the treatment start as well. The time between onset of symptoms at home and the initiation of the investigational treatment, as well as the time between hospitalization and initiation of the investigational treatmentwill have to be recorded.
If a subject fails screening, the subject may be rescreened once (immediately or later) if deemed appropriate by the investigator. In that case, the subject must be re-consented. A new rescreening period will start and all screening procedures must be repeated.

Randomization and treatment
In order to request randomization to the study, all the pre-treatment evaluations must be completed and all the inclusion and exclusion criteria satisfied.
Consecutive randomisation numbers will be given to the subjects upon their confirmed eligibility for randomization . Subjects will be assigned to their treatment according to their randomisation number. Patients will

be randomized in a 2:1 fashion between Reparixin and placebo using a computer-generated randomization list generated in the study.
Randomization will be performed through Interactive Response Technology (IRT). Investigators will have to remain blind throughout the whole study duration; sealed envelopes containing information on the actual study treatment to which the patient was randomized (active or placebo) will be provided for emergency use only. Information for unblinding is provided in section 5.1.

Baseline is the day of randomization (study Day 1) and should possibly be coincident with the start of the investigational treatment. End of Treatment (EoT) is the last day of treatment administration.
The treatment is allowed up to 21 days but it will be interrupted earlier for the following reasons:

- Investigator's decision based on clinical judgment of clinical improvement, even if the patient is still hospitalized but no longer requiring supplemental oxygen or significant medical care;
- occurrence of adverse events;
- patient's withdrawal of consent to the treatment.

During the treatment period assessment visits will be performed at study days 3 - 7 (±1) - 14 (±2) - 21 (±2), or until early treatment interruption for any reason.
An additional visit will be performed on the day of discharge from hospital (or maximum at Day 28 ±2) for post-treatment collection of clinical and laboratory data.

Follow-up period
After discharge from hospital, subjects will be contacted for a follow-up check on their health status at Day 60 and Day 90 (preferably in person at the Center, or by interview via a telephone call), unless the patient also withdraws the consent to the follow-up.
For subjects discharged home before the completion of the 21-day treatment period, follow-up visits will be held at days 7 (±1) - 14 (±2) - 21 (±2) - 28 (±2) - 60 (±2) and/or 90 (±2) depending on the discharge time point.
End of Study (EoS) is defined as the last day the last patient completes the last study assessment (including the follow-up assessments), or withdraws the consent to participate in the study, including follow-up. Subjects with EoS before Day 28 should undergo a full evaluation (as required on Day 28). Subjects with EoS after Day 28 but earlier than Day 90 should undergo evaluation as required on Day90.

4. STUDY POPULATION

4.1 Number of patients

A total number of 312 subjects will be randomized with a 2:1 randomization ratio (208 in the reparixin group; 104 in the placebo group). No significant drop-out rate is foreseen which could impact on the number of the study population
Enrollment can be interrupted at the interim analysys for futility or early efficacy (superiority) of Reparixin over placebo.

4.2 Inclusion/exclusion criteria

4.2.1 Inclusion Criteria:

1. Age 18 to 90, male and female subject of any race
2. Reverse transcriptase Polymerase Chain Reaction (rt-PCR)-confirmed COVID-19 infection based on a nasal / oropharyngeal swab within 10 days before randomization
3. At least one of the following: 1) Respiratory distress with tachypnea (RR ≥ 24 breaths/min without oxygen); 2) Partial arterial oxygen pressure (PaO_2) / Fraction of inspiration O_2 (FiO_2), P/F >100 and <300 mmHg (1mmHg = 0.133kPa), 3) $SpO_2 \leq 94\%$ while breathing ambient air.
   Calculation through validated Sat/FiO2 scales is allowed.
   P/F value of reference if the last available before the signature of consent.
4. Need of supplemental oxygen (i.e. new use of supplemental oxygen, or increased oxygen requirement if on chronic oxygen) requiring low- or high-flow oxygen or non-invasive mechanical ventilation (7-point WHO-OS category 4 or 5)
5. Radiological chest imaging (X-rays, CT scan) confirms lung involvement and inflammation (presence of ground-glass opacities, and/or inter/intra lobular septal thickening, and/or consolidations in a patchy distribution).
6. Inflammatory status as documented by at least one of the following: Lactate dehydrogenase (LDH) > normal range, C-reactive protein (CRP) ≥ 100 mg/L, IL-6 ≥ 40 pg/mL, serum ferritin ≥ 900 ng/mL, XDP > 20 mcg/mL.

7 Females of child-bearing potential and with an active sexual life must not wish to get pregnant within 30 days after the end of the study and must be using at least one of the following reliable methods of contraception:

v) Hormonal contraception, systemic, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit until 30 days after final visit
vi) A non-hormonal intrauterine device [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit until 30 days after final visit
vii) A male sexual partner who agrees to use a male condom with spermicide
viii) A sterile sexual partner

Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted. For all female subjects, with child-bearing potential, pregnancy test result must be negative before first drug intake.

4.2.2 Exclusion Criteria:

1. Cannot obtain informed consent.
2. hepatic dysfunction with Child Pugh score B or C, or ALT or AST> 5 times the upper limit;
3. renal dysfunction with estimated glomerular filtration rate (MDRD) < 50 mL/min/1.73 m^2 or patient receiving continuous renal replacement therapy, hemodialysis, or peritoneal dialysis.
4. Bacterial sepsis (besides COVID-19 sepsis)
5. Positive test for influenza virus, if tested during the current illness (note: influenza testing is not required by protocol)
6. Known congenital or acquired immune deficiency,
7. Patients with hypersensitivity to ibuprofen or to more than one non-steroidal anti-inflammatory drug or to more than one medication belonging to the class of sulfonamides (e.g. sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib).
   Hypersensitivity to sulphanilamide antibiotics, e.g. sulfamethoxazole, does not qualify for exclusion.

Know allergy to any medication (either investigational or non-investigational) which is planned at study entry for use during the study.

8. Patients receiving other not allowed medications (*see Section: Not allowed medications*)
9. Severe, active bleeding such as hemoptysis, gastrointestinal bleeding, central nervous system bleeding, and nosebleeds within 1 month before enrollment.
10. Evidence of COVID-19 disease progression during previously initiated treatment with remdesivir (alone on in any combination with other antiviral treatments), protease inhibitors (e.g. ritonavir, lopinavir, darunavir – atazanavir), tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib), convalescent plasma or intravenous immunoglobulin for COVID-19, or investigational treatments
11. More than three infusions of remdesivir, including the loading dose, prior to randomization
12. Subject participating in other interventional clinical trials. Subject having received investigational therapy in the previous 3 days, or at least 5 half-lives.
13. At the time of enrollment, patients not in a clinical condition compatible with the oral administration of the study drug.
14. P/F < 100 mmHg
15. Pregnancy:
    i) positive or missing pregnancy test before first drug intake or day 1;
    ii) pregnant or lactating women;
    Women of childbearing potential and fertile men who do not agree to use at least one primary form of contraception for the duration of the study.

5. TREATMENTS

5.1 Investigational products

5.1.1 Dose regimen and administration

Patients who satisfy the predefined inclusion and exclusion criteria for this trial will be randomized at a 2:1 ratio to one of the following treatment groups:

- Group 1: Reparixin oral tablets, 1200 mg three times daily (TID) (2 tablets 600 mg each, TID) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care.

- Group 2 (control): placebo, 2 tablets TID (identical to Reparixin tablets) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care.

No dose modifications are allowed. In case of significant adverse events which are supposed to be possibly / probably related to Reparixin, the study drug may be temporarily interrupted (and eventually resumed at the standard dose / schedule, if considered safe for the patient), or definitively withdrawn.
Because the blinded condition does not allow the Investigator to know the actual treatment in a given patient, any decision will be made assuming that the concerned treatment is Reparixin.

For each administration, two tablets of Reparixin (600 mg each) or placebo will be taken, for the total of three daily administrations (6 tablets daily). It is advisable to take the tablets with a glass of water to facilitate swallowing.
For patients who are unwilling or unable, in the opinion of the investigator, to comply with the oral tablet treatment, is possible to continue the regular administration of the study drug by administering the medicine through a naso-gastric tube, following this procedure: for each administration, disperse two Reparixin 600 mg tablets in 25 mL of

drinking water in a suitable container (e.g. conical tubes for 50 mL Falcon centrifuge). Disgregate the tablets (shaking manually or with the aid of a planetary shaker or a rocker) until obtaining a homogeneous milky suspension (time required 7 - 10 minutes). Keep the prepared suspension at room temperature and protected from light for up to 24 hours. Immediately before administration, manually shake the suspension again until complete and homogeneous resuspension, withdraw using a 50 mL needle-free syringe and administer to the patient using a naso-gastric tube. After administration, run 25 ml of drinking water through the gastric tube.

The use of the study drug not in accordance with this protocol could constitute a protocol violation.
The use of the study drug outside this protocol is not allowed.

5.1.2 Randomization

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

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

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

5.1.3 Unblinding

For each randomized subject, individual code breaks will be accessible in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. Only the responsible investigator, or authorized delegates, can break the code via the IRT or by opening the sealed envelopes with indication of the actual treatment.
Describe unblinding procedure-to be modified based on study specific process.
(Paper envelope unblinding) Individual treatment codes will be provided as a tamper-resistant system (either a sealed envelope or a scratch card) to:

- the Investigator for emergency procedures;
- the Dompé Drug Safety for safety procedures.

Individual treatment codes must be kept in a secure location accessible only to designated staff in order to prevent dissemination of the treatment to personnel involved in study conduct who must remain blind.
During the study the integrity of the envelopes will be regularly checked by [CRO] Monitor during the visits at site. At the end of the study all the individual envelopes must be returned to Dompé. A copy of the Individual envelopes identified with the subject assignment number will be also sent to the Dompé Pharmacovigilance Responsible.
Any breaking of the treatment code by the investigational staff must be reported immediately to the Sponsor and must include an explanation for breaking the code. The sponsor should be contacted to discuss the case, if possible, prior to unblinding.
A general rule is that breaking the code is only allowed if the knowledge of the actual treatment is necessary for an appropriate decision on actions / treatments for the safety of the patient.
The DMC will have access to group-unblinded and/or fully unblinded DMC reports.

The sponsor's personnel from the Pharmacovigilance Department of Dompè 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.
Pharmacists will be provided with the 'Instructions to the Pharmacy'.

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

Unblinding can only occur in case of emergency, when knowledge of the treatment identity is essential for treating the subject.
If the treatment code needs to be broken in the interest of patient safety for a medical emergency, the Investigator is allowed to break the treatment code for the specific patient, even before informing the Sponsor. The Investigator must always notify the Sponsor, so that the reason for any premature unmasking can be documented, by means of a communication to CRO/Dompé Pharmacovigilance to the contact details in the section "Contact Information" and to Dompé Medical Expert.
The Investigator will inform the Dompé representative (Dompé Medical Expert) if an emergency unmasking was performed without revealing the treatment identity, but only referring to the kit number involved in the unmasking in order to avoid a dissemination of unmasked information.
Dompé Pharmacovigilance will unmask patient treatment only for safety reason and will document envelope opening or unblinding through the IRT system.
Additionally, Dompé Pharmacovigilance may need to unmask the patient's treatment if a reported SAE meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements. Unmasked information shall not be disclosed to Investigators.
The identity of the treatments will remain unknown to the subject, Investigator, site staff, CRO and Dompé's Development personnel until the study completion and formal unmasking.

5.1.4 Compliance to Treatment

The actual doses of the study drugs received by each patient during the trial will be recorded. A reconciliation will be made by the study monitor between expected and actual administrations over the time between baseline and EoT. Discrepancies will have to be documented and justified.

5.2 Other treatments

5.2.1 Additional therapy

Any additional therapy must be considered as local standard of care treatment, and it must be able to be administered to all patients enrolled in the study. Investigators are allowed to provide any medications having received final or conditional approval for the treatment of the COVID-19 infection, or used off-label at the Investigator's discretion and justified by scientific evidence of effectiveness against the COVID-19 infection without to stop study treatment.

5.2.3 Concomitant and not allowed medications

No specific wash-out is required for treatments (symptomatic treatment for COVID-19, or any therapy for concomitant diseases) which are ongoing at screening, unless decided by the Investigator.
During hospitalization, patient will receive the standard supportive care based on the patient's clinical need, eventually including anticoagulants, corticosteroids, antibiotics, among others, as per local standard therapy and in line with international guidelines. Optimal oxygenation can be considered an SpO_2 between 92% and 96%; however, no specific oxygen target is required by the protocol.
The Investigator's intention to adopt a supportive use of other specific COVID-19 treatments, available off-label or under conditional or final approval [*for example: remdesivir (± baricitinib), hydroxychloroquine, protease inhibitors (e.g. lopinavir / ritonavir, darunavir – atazanavir), tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib), convalescent plasma or intravenous immunoglobulin*] should be discussed with the Sponsor's Clinical Operations. This preventive measure may be allowed only if that medication is routinely used at the site as a local standard of therapy, there is guarantee that it will be available during the whole duration of the study and it will be uniformly applied to all the study patients to be enrolled at that Center in this protocol characterized by a similar level of disease severity, at a site level.

Any concomitant medication that the participant will be receiving during the participation in this study will be recorded in the CRF with annotation of whether the medication is considered a specific "standard of care" for the treatment of the COVID-19. Dose, schedule of administration, start and end date, and reason of use will be collected. In case of complex schedules of administrations or variable intraday dosing (as those possibly in use in the ICU) an estimated, consistent, average dose can be reported, if also recorded in the source documents.

There is no contraindication to the use of concomitant supportive and prophylactic care medications as deemed necessary by the treating physicians, unless a significant drug-drug interaction leading to metabolic alterations and potential harm to the patient is suspected based on the respective metabolic pathways. Reparixin is catalysed by CYP2C9 and to a lesser extent by CYP2C19. Reparixin has some potential *in-vitro* for a non-competitive inhibition of the human hepatic enzyme CYP3A4.
However, at the present time, clinically significant untoward pharmacological interactions are not known for reparixin.
A list of medications known to act as inhibitor or inducer of CYP2C9 is provided hereafter:

- CYP2C9 Inducers: rifampin, carbamezapine, aprepitant, bosentan, phenobarbital, St. John's Wort;
- CYP2C9 Inhibitors: amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast.

For remdesivir (*recently receiving conditional approval for the treatment of COVID-19; June 2020*) no clinical interaction studies have been performed and the overall potential of this drug for interactions is currently unknown. However, reparixin is not a substrate of the microsomal enzymes of which remdesivir is an *in-vitro* inhibitor (CYP3A4, OATP1B1, OATP1B3) or inducer (CYP1A2, CYP3A).
Reparixin was found to slightly inhibit human CYP3A4 but only at very high unbound drug concentration of (IC50 8 μM), concentration significantly higher than the concentration of unbound drug reachable with the proposed administration regimen.
Furthermore, recent expert reports suggest remdesivir exposures unlikely to be substantially affected by CYP3A4, 2C8, or 2D6 isoenzymes or by P-gp or OATP drug transporters and the drug may be administered with weak to moderate inducers or with strong inhibitors of these CYP isoenzymes or drug transporters. However, because strong inducers may modestly reduce remdesivir exposures and clinical relevance of lower exposures is unknown, experts state that concomitant use with drugs that are strong inducers (e.g., rifampin) not recommended (reference attached.

Patients should remain under close observation during the days of remdesivir administration if given concomitantly with reparixin.

Concomitant medications will be used as available on the market and as provided by the local pharmacy, without specific overlabelling for the study.

5.3 Preparation, Handling, Storage and Accountability of the study drugs

5.3.1 Reparixin

The investigational product is in the form of oral immediate release 600 mg tablets containing the active ingredient reparixin. Reparixin 600 mg immediate release tablets are white oblong tablets.

Refer to the following table for Reparixin tablets Description and Composition.

NAMES OF INGREDIENTS	AMOUNT PER TABLET	FUNCTION OF INGREDIENT	REFERENCE TO QUALITY STANDARDS
Reparixin (DF 1681Y)	600.0 mg	Drug substance	Internal monograph
CCI [redacted]	[redacted]	[redacted]	[redacted]
Total	CCI	-	-

5.3.2 Placebo

Tablets are identical in appearance to the active formulation.

5.3.3 Management, Packaging and Labelling of Investigational Products

Reparixin and placebo tablets will be packaged according to the randomization schema in white PVDC/PE/PVC/Aluminum blisters provided without evidence of their content in the form of patient kits numbered to maintain blinding.

The study drug should be stored at temperature not higher than 30°C.

The study drug is manufactured according to current Good Manufacturing Practice requirements.

Medication labels will comply with the Competent Authority requirements and will be printed in a multilanguage format where needed. Refer to the Appendix 2 for reparixin packaging and labeling details.

The study drug will be sent to the hospital pharmacy and distributed by the pharmacist to the Investigator, unless differently required by local reagulations. The Investigator and the pharmacist are responsible for receipt, locked and secure storage and proper usage of study drug during the time of their specific competence. They will also

keep a cumulative inventory and records of dispensing, use or loss of study drug. A reconciliation will be done between delivery and used / returned medication. Any discrepancies must be accounted for and documented.

At the end of the study and after drug accountability has been conducted by the Sponsor or representative, partially used or unused study drug should be disposed for desctruction operated by the local inestigational site according to their procedures (documentation of destruction provided to Dompé farmaceutici), or returned to Dompé farmaceutici, as agreed between the parts.
Drug returns have to be performed before the drug's expiry date.

6. DISCONTINUATIONS

End of treatment (EOT) definition: EOT is defined as the last treatment day in a randomized patient. EOT occurs upon completion of the scheduled treatment period (up to 21 days) for clinical judgment of improvement, or at the time of discharge from hospital, or at any time the treatment is terminated early for any reason (e.g. for adverse events, ineffectiveness, withdrawal of consent for treatment). Patients randomized but with no actual treatment ever initiated, will have their EOT and EoS on the date of randomization.
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.

End of study (EOS) definition: EOS is defined as the last day the last patient completes the last study assessment (including the follow-up assessments), or withdraws the consent to participate in the study including refusal to undergo follow-up, or is deceased or otherwise lost to follow-up.

Discontinuation and withdrawal
A patient has the right to withdraw from this clinical trial at any time and for any reason, without any repercussion. Investigators also have the right to withdraw a patient from the study at any time if in their opinion it is no longer in the best interest of the patient to remain in the study.
The patient has no obligation to give a justification for his decision to withdraw from the study, however, the Investigator should investigate the reason, as far as possible, and record it in the CRF. The primary, actual, reason of withdrawal should be recorded, especially if there is supect of withdrawal due to adverse events ("withdrawal of consent" is a definition to be used if the patient does not give reasons). Notifications will be made to the regulatory authorities of study withdrawals for safety reasons and for any DMC decision to pause enrollment or terminate the study, according to the local country regulations.
Participants who withdraw from the study cannot be re-randomized and are not replaced by another subject.
All discontinuations must be recorded by the investigators; they should be promptly reported to the Sponsor if due to serious adverse events. In case of treatment discontinuation, an EoT visit should be conducted and data recorded; in case of withdrawal from the study, an EoT and/or EoS visit should be conducted.
Patients will be followed-up according to the study procedures set forth in this clinical trial protocol and until the scheduled last day of follow-up (day90). The only exception will be the collection and reporting of AEs that have occurred during the clinical trial and have not resolved by the time of the end of follow-up: in this case AEs will be followed until resolution or stabilization.

Stopping criteria for individual subjects
Subjects should be prematurely discontinued from study treatment for any of the following reasons:

- subject no longer consents to participate in the treatment phase of the study, yet consenting for the continuation of the collection of information in the follow-up phase of the study (specific consent to be signed).
  Patient may eventually decide to withdraw the consent for the study continuation including the collection of information in the follow-up phase,
- physician decision that it is in the best interest of the subject to be discontinued from study treatment,
- physician decision because of poor efficacy or poor tolerability of the investigational treatment,
- the treatment will be interrupted in case of significant worsening of the renal function with eGFR (MDRD) falling to below 30 ml/min/1.75m^2 or an increase of serum creatinine by more than 50% since randomization, either due to the study drug (or other concomitant drugs) or to the progression of the underlying disease,
- severe protocol deviations, e.g. in relation to the inclusion / exclusion criteria, major treatment uncompliance (> 3 days of unjustified missed treatment), major procedural uncompliance (notably, the missed collection of information for the determination of the study primary end-point).

All study subjects, including treatment discontinuations for any reason, will have to be followed up until the End of Study, unless the patient withdraws his/her consent to the study continuation including the follow-up.

Stopping criteria for the clinical trial:
The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns.
The recommendations of the Data Monitoring Committee will be taken into consideration in this regard.
If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7. ASSESSMENTS AND PROCEDURES

7.1 Procedures

Potential study patients with confirmed COVID-19 diagnosis will be identified from those referring to the participating clinical sites for diagnosis and/or management. Screening will be performed and completed in consented patients and any suitable study patients will be treated. All subjects signing the informed consent form and screened for the present study will be coded with “unique subject identifiers” (see section 11.6).
Each patient will be involved in the study for the entire duration of the hospital treatment and for a maximum of 90 days since randomization and including the follow-up.
Patient should not be screened if, for any reason, there is a high probability that he/she will be transferred during the treatment phase to another institution (administratively separated from the investigational site) not belonging to this study network. Should this occur, the patient will be withdrawn from the study. If the randomized patient is transferred to another already opened study center, the responsibility for the patient treatment and management will be assumed by the new Principal Investigator. Agreements will have to be made with the Sponsor for the provision of the study material for that patient.

During the study, the results of all required clinical, laboratory, instrumental examination will have to be reported in the eCRF (date of the test, outcome, units). Original data have to be kept in the patient’s hospital files and made available to the clinical monitor of the study for quality checks.
Clinical examinations will be performed by the Principal Investigator or authorized sub-Investigator or nurse.

CCI [redacted] Blood samples can be stored on ice and centrifuged within 4 h. After centrifugation and separation of the serum / plasma, samples will be stored freezed at the study site at the temperature of -80 °C until transfer to a dedicated laboratory. Samples will be labelled with indication of the test, study and subject number, date and time of collection.
Determination of Reparixin and its metabolites serum concentration is planned to be performed in a subset of patients in US considering the feasibility in all of sites that will be activated in the country. Due to the Covid-19 emergency scenario, the protocol should not overload the Covid-19 clinical practice. At the same time, the sites should guarantee the efforts to be compliant to the protocol procedures.
Any procedure deviation will be managed properly.
CCI [redacted]

When the decision is made by the Investigator to discharge the patient, the study treatment is not foreseen to be continued at home. It is possible that the patient will still be kept in hospital for some days (without study treatment and supposedly without requiring significant clinical / therapeutical intervention) before the actual release of the patient. The actual date of patient's discharge will be recorded.
Upon discharge,anappointment will be fixed for afollow-up visit (in person, or via a telephone call, if consented by the patient) at Day 90 (±2). The patient will be encouraged to keep records of any untoward medical occurrence at home, and to call the investigator in case of relevant adverse events or hospitalization.
In case the patient is lost to the follow-up at Day90, the investigator will make any reasonable effort to investigate the reason for the patient's missed visit (by way of repeated phone calls, letters, or the search for a life certificate issued by the municipality where the patient has his/her domicile).

7.2 Screening and Baseline assessments

In addition to the verification of the inclusion / exclusion criteria, the following information will be collected at Screening and/or at Baseline, as summarized in the Schedule of Assessments (page 20) CCI [redacted]

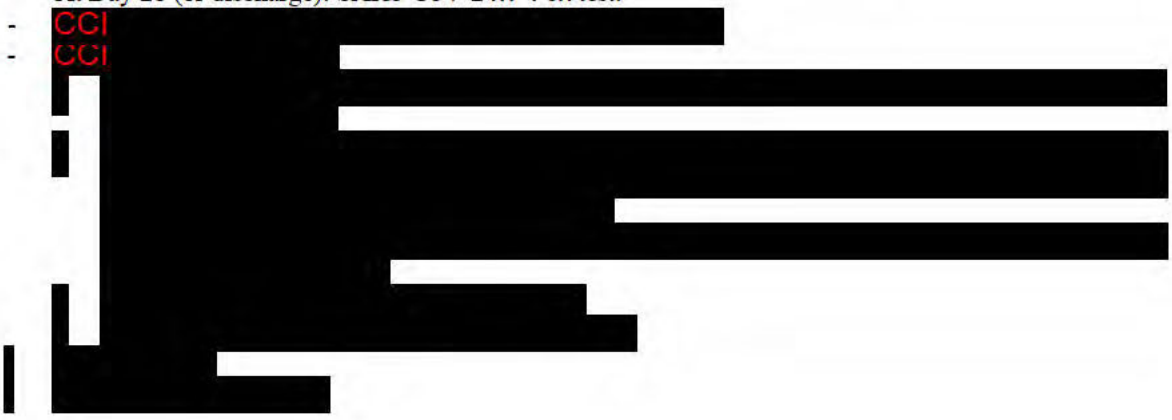
- Demographic data
- Medical history (possibly report diagnoses, not just signs / symptoms)
- Previous and concomitant medications: name, indication, total daily dose, dose unit, route, start and end dates to be recorded.
  Specific information on the preventive off-label use of other anti-COVID-19 medications [*for example: remdesivir (± baricitinib), hydroxychloroquine, protease inhibitors (e.g. lopinavir / ritonavir, darunavir – atazanavir), tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib), convalescent plasma or intravenous immunoglobulin*];
- Diagnosis and clinical information related to the COVID-19 disease: start date of symptoms possibly referred to COVID-19; SARS-CoV-2 RT-PCR test; chest imaging; clinical severity score (7-point WHO-OS); lung function (SpO_2, PaO_2, FiO_2, P/F ratio); severity of dyspnea (VAS scale); need and extent of supplemental oxygen; specifications on non-invasive oxygenation / ventilation.
- CCI [redacted]

- dverse Events recording

7.3 On-treatment assessments

The following information will be collected during the treatment period until discharge from hospital, as summarized in the Schedule of Assessments (page 20) CCI (see section 7.4):

- Study drug administration (days of administration; confirmation that no change in dose has been made)
- Concomitant medications: change of already recorded, or new concomitant medications. Name, indication, total daily dose, dose unit, route, start and end dates to be recorded.
  Specific information on the preventive off-label use of other anti-COVID-19 medications.
- Clinical information related to the COVID-19 disease: clinical severity score (7-point WHO-OS); lung function (SpO_2, PaO_2, FiO_2, P/F ratio); severity of dyspnea (Likert scale; VAS scale); need and extent of supplemental oxygen; specifications on non-invasive oxygenation / ventilation; need of invasive mechanical ventilation or ECMO; ICU admission; total days of hospitalization
  Chest imaging when deemed appropriate by the investigator.
  At Day 28 (or discharge): SARS-CoV-2 RT-PCR test.
- CCI
- CCI



7.4 Follow-up

A follow-up visits will be done at Day 60 and Day 90. This can be with the patient presenting in person at the clinic or via a phone call (main elements of the conversation to be reported in a a signed note to be filed in the patient's documentation). Information will be collected on the general patient's condition (in particular, if the patient is still alive), the occurrence of clinically important adverse events since hospital discharge, or new hospitalizations, regardless of whether supposedly related to the study drug, the COVID-disease, or other reasons. For this purpose, the clinical rating based on the 7-point WHO-OS can be recorded:

- clinical severity score (7-point WHO-OS)

- Adverse Events recording

PPD

Table 1. Clinical PPD parameters

Assessment type	Parameters to be analysed (units)
Demographic data	- age (years); - date of birth (or only year of birth if full date of birth cannot be recorded, for local regulations); - sex (M/F); - race (white, black or african american, asian, other; hispanic or latino ethnicity), - height (cm); - body weight (kg).
Medical history	- all relevant past (no longer present) and ongoing conditions, including a past COVID-19 disease - past (no / yes) or current tobacco use (no / yes, < or ≥ 10 sigarettes daily) - past (no / yes) or current alcohol consumption (no / yes, < or ≥ one liter of wine daily, or equivalent) - recent test for influenza (no / yes, positive / negative) - vaccination for COVID-19
Concomitant medications	At screening: recording of drug name, indication, total daily dose, dose unit, route, start and end dates. During study: recording of any change of already recorded, or new concomitant medications. Also, specific information on the preventive off-label use of other anti-COVID-19 medications [*for example: remdesivir (± baricitinib), hydroxychloroquine, protease inhibitors (e.g. lopinavir / ritonavir, darunavir – atazanavir), tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib), convalescent plasma or intravenous immunoglobulin*]
Vital signs	- systolic / diastolic blood pressure (SBP / DBP; mmHg); - pulse rate (HR; b/min) - respiratory rate (RR; n/min) - temperature (°C) Blood pressure and heart rate measurements to be done with an electronic automated device, with the patient resting for at least 5 minutes.
Information related to the COVID-19 disease	- start date of symptoms possibly referred to COVID-19 (fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorders, diarrhea, other)

	- SARS-CoV-2 Reverse transcriptase polymerase chain reaction (rt-PCR) test (positive / negative) - chest imaging (positive / negative for lung involvement. Presence of: monolateral / bilateral findings, peripheral lung alterations, consolidations, ground-glass appearance, pleural effusion, thoracic lymphadenopathy, other abnormalities)
CCI	
CCI	
Clinical severity score	- 7-point WHO-OS 1) not hospitalized, with resumption of normal activities; 2) not hospitalized, but unable to resume normal activities; 3) hospitalized, not requiring supplemental oxygen; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6) hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7) death
Lung function	- peripheral arterial oxygen saturation (SpO_2; %) - partial pressure of oxygen (PaO_2; mmHg) - fraction of inspiration O_2 (FiO_2; 0.21 to 1) - P/F ratio (PaO_2/FiO_2; mmHg)
CCI	

	- IL-8 (pg/mL)
Severity of dyspnea	- Likert scale: grading the current experience of breathing discomfort compared to baseline (randomization) status (from -3 to 3). -1 = minimally worse, -2 = moderately worse, -3 = markedly worse 0 = no change, 1 = minimally better, 2 = moderately better, 3 = markedly better, - VAS scale: grading from 0 to 100 on a horizontal line to show the degree of how the patient feels about breathing. "0" = worst breathing; "100" = best
Supplemental oxygen	- requirement (no / yes) - if yes, < 6 L/min, 6 - 10 L/min, >10 L/min (daily average) - Liters per day
Non-invasive supplemental oxygen	- low-flow (via e.g. nasal cannula, simple mask, partial rebreathing mask; other) - high-flow (via e.g. high-flow nasal cannula, HFNC; other) - non-invasive ventilation (via e.g. non-invasive positive pressure ventilation, NIPPV, such as CPAP or BiPAP; other) Duration of any non-invasive supplemental oxygen to be recorded (days) PEEP (no / yes; for how long daily)
Invasive mechanical ventilation or ECMO	- endotracheal intubation - tracheostomy tube - Extracorporeal Membrane Oxygenation (ECMO) Duration of any invasive mechanical ventilation or ECMO to be recorded (days)
CCI	CCI

8. EVALUATION OF ADVERSE EVENTS AND SAFETY INFORMATION

8.1 Definitions

Adverse Event

An **Adverse Event** (**AE**) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory

finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Drug Reaction

An **Adverse Drug Reaction (ADR)** is defined as an adverse experience which is reasonably likely to have been caused by the drug. Adverse events are to be considered unsuspected if the relationship to the study drug as described in the table in section 7.3.4 is none or unlikely; whereas any AE reported in the study having a possible, probable or highly probable relationship to study drug will be considered as an ADR. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Serious Adverse Event

A **Serious Adverse Event** (**SAE**) is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,

  NOTE: In general, hospitalization means that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.
- results in persistent or significant disability/incapacity,

  NOTE: This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- is a congenital anomaly/birth defect,
- is medically significant or important medical condition, i.e. an important medical event that based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

  An important medical condition is an event that may not result in death, be life-threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Death shall always be reported as SAE: anyway, death due to progression of disease would not have a causal relationship to the product, based on Investigator's assessment. The investigator should report the event immediately to the sponsor, but the sponsor will not report the event as expedited to regulatory authority. Cause of death shall always be specified when known.

Unexpected Adverse Events

An AE or ADR is considered unexpected if it is not listed in the Investigator Brochure (Reference Safety Information section) or in the applicable authorised Summary of Product Characteristics. An event is unexpected also when it is not listed at the specificity or severity that has been observed and listed in the Investigator Brochure.

Events that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

The determination of expectedness shall be made on the basis of the IB Reference Safety Information (RSI) section.

Suspected Serious Unexpected Adverse Reaction (SUSAR)

A suspected serious unexpected adverse reaction is defined as an adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Reaction.

8.2 Monitoring for adverse events

During the study, the subject shall have the opportunity to spontaneously mention any problems and anyway the Investigator or appropriate designee should inquire about AEs by asking the standard questions:

• "Have you had any health problems since your last study visit?"

• "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant condition(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health, regardless of causality. Changes in any protocol-specific systemic parameter evaluated during the study are to be reviewed by the Investigator.

8.3 Recording of adverse events

AEs will be collected and recorded for any untoward event that occurs in a patient from the time he or she signs the Informed Consent for the trial until the end of the follow up period. Thus, any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment, in treatment, or post treatment period are to be considered AEs and/or SAEs, and consequently recorded and reported as such. Should a non-serious AE become serious, the Investigator will then follow the same reporting procedures as for SAEs.

Each AE will be described by:

- Its duration (start and stop dates).
- Its seriousness.
- Its relationship to the study drug (suspected/unsuspected).
- Action(s) taken.
- Outcome.

Medical conditions/diseases and related signs/symptoms present before starting study treatment shall be documented in the medical history section of the CRF; these conditions are considered AEs only if they increase either in frequency or severity once informed consent has been signed.

8.4 Relationship and severity of AEs to the Investigational product

The Investigator will assess the possible relationship between the AE and the investigational medication, according to the criteria in Table below:

Relationship of the Adverse Event to the IMP

None (Intercurrent Event)	An event that is not and cannot be related to the Investigational Product, e.g. patient is a passenger in a road traffic accident.
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide more plausible explanations
Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause
Probable	Relationship is likely, the AE abates upon discontinuation of Investigational Product and cannot be due to the patient's condition
Highly Probable	Strong relationship, the event abates upon discontinuation of Investigational Product and, if applicable, re-appears upon repeat exposure

The Investigator will grade the severity of any AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) toxicity grading scale, version 5.0, as per definitions in the Table below. For each episode, the highest severity grade attained should be reported.

Grading scale of the Adverse Event

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

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

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

8.5 Follow-up of patients with adverse events

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. All AEs should be followed-up to determine outcome of the reaction. The Investigator should follow up the event until resolution or

stabilization of the condition. It is the Investigator's responsibility to ensure that the subjects experiencing AEs receive definite treatment for any AE, if required.
If subject was hospitalized due to a SAE, a copy of the discharge summary is to be forwarded to the Sponsor as soon as it becomes available.
In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests also may be requested. Further, depending upon the nature of the SAE, Dompé may request copies of applicable segments of the patient's medical records. In case of death, a copy of the autopsy report, if performed, should also be provided.
The Investigator shall inform the Sponsor with an appropriate written communication, whenever he becomes aware of new available information regarding the SAE, once the condition is resolved or stabilized and when no more information about the event is expected. Follow-up SAE information should be processed as initial SAE notification (see Par. 7.3.6).
For pharmacovigilance purposes, all SAEs should be followed-up in order to clarify as completely as possible their nature and/or causality and until all queries have been resolved. All SAEs will be followed up until the events resolve or the events or sequelae stabilize, or it is unlikely that any additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e. subject or Investigator is unable to provide additional information, or the subject is lost to follow up), unless subject has withdrawn his/her consent.

8.6 Serious adverse events reporting

Reporting Procedure for Investigators

The Investigator must report all SAEs, regardless of presumed causal relationship, to Dompé Pharmacovigilance Department, Dompé Clinical Operations Department and CRO Monitor preferably by e-mail, (to farmacovigilanza@dompe.com, PPD . CRO Monitor's details will be provide to the clinical centre accordingly to the Monitor in charge for the specific centre" within 24 hours of learning of the event. Contact details for SAE reporting are provided in the section "Contact Information".
The investigator should also report information on SAEs that continue after patient has completed his/her participation in the study (whether study completion or withdrawal) unless patient has withdrawn his/her consent. Information on SAEs will be recorded on the SAE form (Appendix 3). Follow-up reports (as many as required) should be completed and e-mailed /faxed following the same procedure above, marking the SAE form as "follow up Number XX".
Whenever more than one SAE is observed, the Investigator should identify which is the primary adverse event, i.e. the most relevant one. If other events are listed in the same report, the Investigator, along with their relatedness to the Investigational Product, should identify which adverse events are serious and which are non-serious. In any case, the Investigator is requested to record his/her opinion about the relatedness of the observed event(s) with the investigational medication.
In line with CT3 Detailed Guidance and ICH E2A provisions, although the Investigator does not usually need to actively monitor patients for AEs once the trial has ended, if the Investigator becomes aware of a SAE occurring to a patient after that patient has ended his/her participation in the study (whether study completion or withdrawal), the SAE should be reported by the Investigator to Dompé Pharmacovigilance. Such "post-study cases" should be regarded for expedited reporting purposes by Dompé, as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

Conditions that should not be reported as Seriou Adverse Events

The condition listed below, that may require hospitalization of a patient, is not considered to be SAE and shall not be reported as such, but only need to be recorded in the CRF:

• Abnormal CCI values or test results that do not induce clinical signs and/or symptoms and require intervention/therapy, i.e. are clinically significant.

Adverse Events Exemption

Not applicable. There is no event to be considered routinely associated to any clinical study procedure, therefore requiring neither recording nor reporting.

Reporting procedure of safety information

SUSAR expedited reporting to Regulatory Authorities and ECs

The Investigator shall report all serious adverse events immediately to Dompé Pharmacovigilance and Clinical Operations and to the CRO contact, as described in Section 7.3.6 .
The Investigator shall notify SAE to his/her EC as applicable; in addition, for reported deaths of a subject, the Investigator shall supply Dompé Pharmacovigilance and Clinical Operations /CRO Monitorand the Ethics Committee with any additional information requested. Copies of all correspondence relating to reporting of any SAEs to the EC should be maintained in the Investigator's Files.

Dompé Pharmacovigilance shall submit any serious unexpected ADR (SUSAR) to the concerned EC and Regulatory Authority (via Eudravigilance Clinical Trial module) which approved the study, as soon as possible and in no event later than:

- seven calendar days after becoming aware of the information if the event is fatal or life threatening; to be followed by any relevant information within eight days.
- fifteen calendar days after becoming aware of the information if the serious event is neither fatal nor life threatening.

Dompé Pharmacovigilance shall report any relevant updated follow-up safety information as soon as available.
If the results of an investigation show that an ADR not initially determined to be reportable is reclassified as reportable, Dompé Pharmacovigilance shall report such reaction in a written safety report as soon as possible, within the timeframes defined by current law requirements.
Treatment will be unblinded by Dompé Pharmacovigilance prior to regulatory submission of a SUSAR to Regulatory Authorities and ECs and only cases referred to active treatment will be considered expeditable for regulatory reporting, in line with law requirements.

Periodical Reporting to Regulatory Authorities, ECs and Investigators
Dompé shall be responsible to prepare and submit annual safety reports (Development Safety Update Report – DSUR) to relevant Regulatory Authorities, as applicable. In addition, Investigator will receive from Dompé Pharmacovigilance appropriate periodic safety updates, as per applicable local requirements and regulations.

8.7 Exposure to investigational product during pregnancy

Any pregnancy detected at screening leads to the immediate exclusion from the trial.

8.8 Adverse events causing treatment discontinuation

If a patient is withdrawn from the study as a consequence of an AE, this must be recorded and reasoned in the CRF, and the patient must be followed up until the resolution of the AE or as instructed by the medical monitor.

8.9 Overdose

Cases of overdose (accidental or intentional) which may or may not result in serious adverse reactions are to be reported to Dompé Pharmacovigilance and Clinical Operations /CRO Monitor , following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. The Medical Expert should be contacted to discuss corrective treatment, if necessary.
An overdose of the study drug is defined as:

- Tablets: The administration of 3 or more additional tablets on any given treatment day
- IV formulation: The administration of more than 50% of the daily dose.

Overdose includes reports related to drug intake through different routes (e.g. ingestion) or with suicidal intentions and consequent drug overdose.
The Investigator shall provide in the SAE form information about symptoms, corrective treatment and outcome of overdose.

9. DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be appointed with the responsibility of safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the clinical trial. These tasks will be accomplished on an ongoing basis throughout the trial. The DMC will provide recommendations about stopping or continuing the trial. In order to contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC will be advisory to the clinical trial leadership group (the Scientific Committee of the study). The Scientific Committee will be comprised of the sponsor's study team and lead study investigators, who jointly will have responsibility for the design, conduct and analysis of the clinical trial. The Scientific Committee will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in the study conduct are required.

10. STATISTICAL CONSIDERATIONS

10.1 Sample size

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

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

Sample size has been adjusted in order to take into consideration an interim analysis during the study. Details on interim analysis are provided in section 10.4. 1. No additional multiplicity correction of alpha is required.

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

10.2 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 evaluable patients has reached the primary endpoints at Day 28 (details in section 10.4. 1);
- Key first efficacy analysis: this analysis will be conducted by an independent statistician when all enrolled patients are evaluable for the primary analysis at 28 days and the database has been interim locked (details in section 10.4.2);
- Final analysis: this analysis will be conducted when all enrolled subjects have completed the study and the study database has been unblinded and locked;
- Analyses for the Data Monitoring Committee: these analyses will be produced periodically according to the DMC charter.

10.3 Analysis Population

The following population will be defined:

- The Safety (SAF) population will consist of all randomized patients who received at least one dose of the investigational product. Safety population will be analyzed according to the actual treatment received. The SAF population will be used to present results on safety data.
- The Full Analysis Set (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 ITT principle, i.e. by treatment allocation. The FAS population will be used for the primary analyses of the study and to present results on efficacy data.
- The Per Protocol (PP) population will consist of all randomized patients who received at least one dose of the investigational product and do not have Major Protocol Deviations. The PP population will be used for sensitivity analyses.

10.4 Inter mediate analyses

10.4.1 Interim analysis

An interim analysis is planned when half of the planned evaluable patients has reached the primary endpoints at Day 28 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 are reported in Table 2.

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

Analysis	Sample Size (evaluable patients)	Boundaries for primary endpoint	
		Efficacy	Futility
Interim #1	132	p-value <0.00258	p-value ≥0.32561
Final	264	p-value <0.02400	p-value ≥0.02400

The interim analysis will be conducted by an independent statistician who will share the results on primary endpoint (full list of interim outputs are detailed in the SAP) with the DMC. On the basis of the interim results, DMC will communicate to the Sponsor the consequent decision on the continuation of the study. The following scenarios may emerge:

1. The communication will be "Not enough evidence for demonstrate superiority of reparixin". In this case, since results are not considered enough to draw conclusions on primary endpoints, the enrolment will continue up to the final analysis step, and treatments and follow-ups will proceed without modifications. When all subjects complete the follow-up and database is close, final analysis is performed and clinical study report will be released.
2. The communication will be "Superiority of reparixin is shown". In this case, enrollment of subjects is stopped and considered completed. Already-enrolled subjects continue their residual treatment and follow-up as planned. When all enrolled subjects complete the follow-up and database is close, final analysis is performed and clinical study report will be released.
3. The communication will be "Superiority of reparixin is excluded". In this case, 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. When database is close, final analysis is performed and clinical study report will be released.

10.4.2 Key first efficacy analysis

The aim of this key first analysis is to provide efficacy results on primary endpoint to populate an intermediate clinical study report. It will be performed when all patients are evaluable for the primary analysis at 28 days. This analysis will be conducted by an independent statistician after data base interim lock.
To maintain the unblinding, results will be disclosed to the Sponsor in an aggregate way. The entire study personnel will remain blinded to patient-level information.

10.5 Statistical Methodology

10.5.1 General Considerations

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 and range (minimum and maximum) will be presented. For qualitative data, frequency distributions and percentages per category will be presented. If appropriate, confidence intervals around the mean or the proportions will be presented. The number of subjects with missing data will be presented under the "Missing" category. Missing values will not 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.

For time-to-event variables, cumulative freedom from event will be evaluated using Kaplan-Meier method. The degree of uncertainty will be expressed with 95% confidence limits (calculated per the method proposed by Greenwood). Comparison of curves among arms will be performed with the log-rank test. Kaplan-Meier graphs will be presented along with the number of patient-at-risk at exact time points. Subjects who are free from event at the time of DB lock will be censored at the DB lock date. Reasons for discontinuation will be incorporated into the analysis for determining censoring and failure status. Specifically, study discontinuation for Adverse Event, Death, Lost to follow-up or other negative outcomes will be considered as failure events. Subjects who have discontinued for other reasons without an event will be censored at the date of discontinuation.

Unless otherwise specified, the significance level used for statistical testing will be 0.05 and two-sided tests will be used. All patient data collected on the CRF will be listed by patient and centre.

The Statistical Analysis Plan will be issued before the interim analysis and database lock with more technical and detailed elaboration of the principal features of statistical analyses. Additional post-hoc analysis may be produced to further allow comparison between treatment and control, according to the results obtained. Any deviations from the original statistical plan (including unplanned analyses) will be documented in the Clinical Study Report.

10.5.2 Analysis of efficacy variables

10.5.2.1 Primary analysis

The following null hypothesis is defined: the proportion of patients alive and free of respiratory failure at Day 28 (see section 2.2 for details) 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 proportions of patients alive and free of respiratory failure at Day 28 for reparixin and control groups, respectively.The null hypothesis H_0 will be rejected, and superiority of reparixin is declared if primary analysis p-value will be lower than pre-specified threshold, depending at which analysis (interim or final) the test is performed. Thresholds are calculated according to O'Brien-Fleming spending function boundaries and are reported in Table 2.

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

Since patients who discontinue the IMP will not be withdrawn from the study but will be asked to complete safety and efficacy assessments as per the protocol, missing data will be addressed by modeling patients with missing data after retrieved drop-outs, assuming that missing data would have been like retrieved drop-outs if they were assessed. If there are no enough retrieved dropouts, a "wash-out" analysis instead of retrieved drop-out analysis will be performed: the missing primary endpoint at Day 28 will be imputed by wash-out the effect of treatment using placebo completers; this approach does not assume benefits for reparixin in case of discontinuation and limits a post-discontinuation clinical effect to that of placebo.

10.5.2.2 Sensitivity analyses

The following sensitivity analyses are defined to assess the robustness of results on primary endpoint versus adherence to protocol and presence of missing data (details will be provided in the SAP):

- The comparison between treatment and control will be performed in the PP population instead of FAS;
- The comparison between treatment and control will be performed in the FAS population considering complete cases only (i.e. without considering patients with missing primary endpoints at Day 28) instead of MI under MNAR. This analysis will assess the robustness of results to the method of handling missing data.
- The comparison between treatment and control will be performed in the FAS population by means of MI under missing at random (MAR) assumption instead of MNAR.
- A tipping point strategy will be used as a sensitivity analysis for missing data for assessment of superiority (if shown) of reparixin. Tipping point, will assess how departures from MI under MNAR assumptions must be in order to overturn conclusions from the primary superiority analysis. Tipping point will be based on iterative application of MI.

Additional sensitivity analyses may be added in the SAP.

10.5.2.3 Secondary Analyses

In case analysis of the primary endpoint leads 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 according to the following ranking:

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

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

Key secondary endpoints #1 , #2 and #3 will be analyzed by means of a logistic regression model; key secondary endpoint #4 will be analyzed as detailed in section 10.5.1.

In case of futility at interim analysis or in case of not rejection of null hypothesis, the above test strategy will not be performed. Instead, independently of results on primary endpoint, descriptive in nature analyses will be

performed on all secondary endpoints at each available timepoints by means of descriptive statistics and by appropriate parametric tests depending on the nature of the variable and its distribution. Data transformation might be used in order to satisfy the assumption of normality requested by parametric statistical tests. In case such assumptions are not met, non-parametric counterpart tests will be used. Details will be provided in the SAP. Change from baseline value (for continuous variables) and shift tables versus baseline (for categorical variables) will also be summarized for all post-baseline visits.

10.5.3 Safety Analysis

Treatment-Emergent Adverse Events (TEAEs), Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs) will be presented by treatment arm in terms of number of AEs and their incidence by System Organ Class (SOC) and Preferred Terms (PT) using MedDRA. Analyses will be provided also by severity and relationship to the treatment.

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10.5.5 Intermediate analyses for DMC

Safety data will be reviewed on an ongoing basis by a DMC. Full details of the activities and responsibilities of the DMC will be provided in the study DMC Charter. Access to unblinded information on the efficiacy analyses is allowed on DMC request in order to balance patient safety risk against a possible gain in efficacy.

The DMC will give careful consideration to the appropriateness of trial continuation if there is emerging evidence that reparixin is harmful. Since DMC does not monitor primary endpoints for early efficacy termination, 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.

10.5.6 Specification of subgroups for analysis

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 based on the following variables: age group, gender, presence of concomitant disease. Subgroup analysis will be performed if interaction tests are statistically significant at 15% nominal level. Statistical details and potential new subgroups definitions will be reported in the SAP.

10.5.7 Missing 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. However, in order to minimize missing data, if a patient cannot refer to the site for a planned follow-up visit, the Investigator will try to obtain any relevant information from the patients, including documents/laboratory results available from local medical care.

11 STUDY ORGANIZATION

11.1 Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the source documents and in all required reports.
The investigator must keep source documents for each subject in the study.
The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).
These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of Ethics Committee (EC), raw data of subjects, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent forms, confidential subjects identification code.
The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.
Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP, national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

11.2 Ethical considerations, quality assurance and monitoring

The procedures outlined in this clinical trial protocol are designed to ensure that the Sponsor and the Investigators from the Clinical Sites perform their activities throughout the set-up, conduct, evaluation, documentation and analysis of the study, in accordance to the principles of the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH) and the Declaration of Helsinki. The study will be carried out adhering to local legal requirements and the applicable national laws, whichever represents the greater protection for the individuals.
Study protocol, patient information and informed consent will be submitted to the appropriate Ethics Committee (EC) / Institutional Review Board (IRB) for approval. The Sponsor will be responsible to inform in a timely manner the appropriate Ethics Committee about any changes in the study protocol which could interfere with the patient's safety.
Due to the constrains and risks of the ongoing COVID-19 pandemia, no on-site monitoring activities will be carried out. Remote monitoring will be available periodically or at the investigators' request via web or phone communications with the adequate Sponsor personnel or their approved representatives.

REGULATORY BODY APPROVAL
Dompé or the CRO or other consultant appointed by Dompé will obtain the necessary approval from the Competent Authorities, as needed, prior to initiation of the study. The study will not be started until written approval from the relevant Competent Authorities (or no objection within the timeframe set by the local regulation, as applicable) has been received by Dompé.

11.3 Informed consent

The investigators or sub-investigators involved in this clinical trial who are responsible for treating the hospitalized patient for COVID-19 are responsible for providing all necessary information about the participation in the study to their patients, and consequently to obtain the written Informed Consent.

The same procedure applies to the information of the patient and providing of consent to the processing of personal data according to the European Regulation n. 679/2016 on the Protection of Personal Data, the Personal Data Protection Code (Legislative Decree 196/03) and subsequent amendments and additions, and to the provisions, guidelines and general authorizations of the National Guarantor for personal Data Protection.
Information to the study participant is provided with a study-specific Information Sheet. The patient will eventually sign the Informed Consent Form for consenting to the study. A sample Informed Consent Form is reported in Apppendix 5.

11.4 Data collection

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the subject's source documents detailing the unique identification number and the date and time of the study procedures performed. Any correction to the source data entries must be carried out by the investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections have to be dated and initialled. The investigator must provide a reasonable explanation for all missing data. The source documents will be completed, signed by the investigator, the sensitive data will be obscured (i.e. only randomization number will be clearly legible) and the source document will be made available to the Sponsor for data management procedures. Data Management will identify and implement the most effective data acquisition and management strategy for the clinical trial protocol and deliver datasets which support the protocol objectives. Subject data will be entered into a defined CRFs and combined with data provided from other sources where applicable in a validated data system. Subject initials will not be transmitted for inclusion in the datasets. Clinical data management will be performed in accordance with applicable standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events and concomitant medications terms will be coded using validated dictionaries.

11.5 Confidentiality and data protection

By signing this protocol, the investigator agrees to keep all the information provided by the sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the sponsor (protocols, randomization list and other materials) will be stored appropriately to ensure confidentiality. The information provided by the sponsor to the investigator cannot be disclosed to others without direct written authorisation from the sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Data on subjects collected in the source documents during the study will be transferred to the Sponsor in an anonymized way. If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the sponsor and the investigator will be bound to keep this information confidential.

11.6 Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers". The unique subject identifier consists of the sponsor study code (i.e. REPAVID-19), the 3-digit site

number (i.e. 001), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit subject randomisation number (e.g. 001, 002, etc.).
Study code, site number, screening number and subject randomisation number are separated by slashes ("/").

11.7 Database management

This study will use an electronic CRF (eCRF). It will be a web-based clinical trials data management system that provides investigational sites a standardised and validated, remote, electronic data capture system for the collection of clinical trial data. Activities performed using the eCRF include data entry, modification, review and validation. Each activity performed carries a unique user identification code and a date-time stamp.

An electronic audit trail of all changes made to the eCRF will be kept within the eCRF. This audit trail identified the user making the change by userid, and date and time of change.

Pre-defined data validation checks will be run within the eCRF as the data were entered and submitted by authorised site staff. The resulting data queries will then resolved. Additional queries will generated within the eCRF by authorized staff as a result of data review (e.g., source document review, external data reconciliation etc).

11.8 Coding dictionaries

Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™). Previous and concomitant medications will be coded using the WHO Drug Dictionary Global, B3 format. The version of the coding dictionaries will be stated in the study report.

11.9 Publication policy

Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.
The sponsor agrees that the study results may be published by the investigator, and the investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the sponsor before any public disclosure.
This will be done in order to ensure that clinical study results are reported in an objective, accurate and balanced manner. The sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30-90 days in relation with the complexity of the work).
The investigator will also be provided by the sponsor with the clinical study report and the results of any additional analysis, tables, figures, etc. undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s). On an exceptional basis, the sponsor may temporarily delay registration of certain data elements (e.g. compound, name, outcome, measures, etc.) to seek necessary intellectual property protection. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

11.10 Administrative aspects

The investigational medicinal products required for the conduct of this study will be provided free of charge by the Sponsor to the participating clinical sites.
Coverage for any damage resulting from the participation of the subjects in the clinical trial is warrented. In addition to the general insurance of the individual participating clinical centers, an insurance cover will be issued in favour of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

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13 APPENDICES

Appendix 1. Investigator's Brochure (IB)
Please refer to dedicated document

Appendix 2. Investigational Drug Labels
Please refer to dedicated document

Appendix 3. Severe Adverse Event (SAE) reporting form and completion guideline
Please refer to dedicated document

Appendix 4. Pregnancy reporting form and completion guideline
Please refer to dedicated document

Appendix 5. Informed consent form
Please refer to dedicated document