CLINICAL STUDY PROTOCOL

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

Study Number: REP0321

IND/EudraCT number: 150182/ 2021-006951-32

Investigational Product: Reparixin

Phase of the study: Phase III

Protocol Version - Date: Version No. 2 – Final - June 20, 2022

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List of Abbreviations and Definitions of Terms

ABG	Arterial Blood Gas
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired ImmunoDeficiency Syndrome
ALI	Acute Lung Injury
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAL	Broncho-Alveolar Lavage
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAP	Community-Acquired Pneumonia
CBC	Complete Blood Count
CDE	Cat Dander Extract
Cmax	Maximum concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
COVID	Corona Virus Disease
CSR	Clinical Study Report
Css	Concentration, steady state
CCI	[redacted]
CV	Curriculum Vitae
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DMP	Data Management Plan
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	electronic Case Record Form
EDC	Electronic Data Capture
EQ-5D-5L	EQ-5D-5L questionnaire
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	Fraction of inspiration oxygen
GCP	Good Clinical Practice
HR	Heart Rate
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDSA/ATS	Infectious Diseases Society of America/American Thoracic Society
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
IRB	Institutional Review Board
IRS	Interactive Response System
IRT	Interactive Response Technology
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous
IAV	Influenza
KM	Kaplan-Meier
LD50	Lethal Dose 50%
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MDRD	Modification of Diet in Renal Disease study equation

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliters
NET	Neutrophils Extracellular Traps
NIAID-OS	National Institute of Allergy and Infectious Disease - Ordinal Scale
NEWS	National Early Warning Score
PaO_2	Partial pressure of oxygen (arterial)
PI	Principal Investigator
PK	Pharmacokinetic
PMN	Polymorphonuclear cell
PP	Per Protocol
RR	Respiratory Rate
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SpO_2	Peripheral Capillary Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TID	Three times a day
ULN	Upper Limit of Normal
VFDs	Ventilatory-free days
WBC	White Blood Cell

1. STUDY SYNOPSIS

CLINICAL STUDY SYNOPSIS:	
Study Number	REP0321
Title of Study	Reparixin 1200 mg three times a day as add-on therapy to standard of care to limit disease progression in hospitalised adult patients with COVID-19 and other community-acquired pneumonia. A multinational, multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase III trial (REPAVID-22)
IND/EudraCT No.	150182/ 2021-006951-32
Study Centres (Country)	US, EU
Development Phase	III
Objective	Primary objective. To evaluate the efficacy of oral reparixin versus standard care alone in limiting disease progression in adult patients hospitalised for infectious pneumonia acquired in the community (CAP), including COVID-19. Secondary objectives. To determine the effect of reparixin on several disease severity/progression measures including recovery, ventilatory free days and mortality. Safety objectives. To evaluate the safety of oral reparixin versus placebo in the specific clinical setting.
Study Design and Methodology	Multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase III trial. It will enrol 526 male and female patients ≥18 years, hospitalised for CAP (including COVID-19), assigned (1:1) to receive either oral reparixin (treatment group) or matched placebo (control group) three times a day (TID) for up to 21 days. Randomisation will be stratified according to disease severity and site. All the patients will receive the standard of care based on their clinical need, including COVID-19 and CAP medications, as per local standard therapy at the trial site and in line with international guidelines. The primary outcome will be evaluated at day 28, secondary will be evaluated from day 3 to day 180. An independent external data monitoring committee (DMC) will oversee the study and evaluate unblinded interim data for efficacy, futility, and safety.
Study procedures	The study will consist of three periods: screening, treatment (up to 21 days), and follow-up (up to 180 days). Potential study patients will be identified from those hospitalised at the participating clinical sites for disease management. Screening: screening will be performed in consented patients for assessment of eligibility and will include: • collection of demographic data, past medical history, disease-specific clinical information, and previous medications • evaluation of clinical severity scores: National Institute of Allergy and Infectious Disease - Ordinal Scale (NIAID-OS) • review of available chest imaging, • measurement of SpO_2 (and/or PaO_2) and FiO_2;

	• pregnancy test (urine dipstick), in women of childbearing potential. Positive urine test results will be confirmed with a serum pregnancy test; • blood sampling for measurement of haematology/biochemistry and derived renal and hepatic function (Safety Laboratory Tests), if not already performed during current hospitalization. Patients should not be screened if, for any reason, there is a high probability that they will be transferred during the treatment phase to another institution not belonging to the study network. Randomisation: patients meeting all inclusion and none of the exclusion criteria will be enrolled (eligibility confirmed) and randomised to start study drug administration (either reparixin or placebo) within 24 hours from screening assessments. Before the administration of the first dose of study product, the following assessments will be performed: • 12-lead ECG performed using local equipment • RT-PCR for SARS-CoV-2 from the respiratory tract • targeted examination: systolic/diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), body temperature, level of consciousness, SpO_2, and use of supplemental oxygen • clinical severity scores: NIAID-OS and Pneumonia Severity Index (PSI) (If not already available, blood urea nitrogen should be measured, and PSI calculated once all laboratory results will be available) • blood sampling for measurement of inflammatory markers (lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, D-dimer, procalcitonin (PCT)) • blood sampling for measurement of a panel of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 (at selected sites) Baseline is defined as the parameters prior to and including the date of the randomization visit. Treatment and post-treatment hospital stay up to day 28: NIAID-OS, National Early Warning Score (NEWS) and concomitant medications will be evaluated daily until day 28 (or hospital discharge). The following measurements/assessments will be performed at day 3, 7±1, 14±2, 21±2, 28±2 (or hospital discharge): • PaO_2 (or SpO_2) and FiO_2; • blood sampling for Safety Laboratory Tests; • blood sampling for measurement of inflammatory markers (LDH, CRP, ferritin, D-dimer, PCT) • vital signs (can be derived by NEWS) At the end of treatment, the following measurements/assessments will be performed: • Blood sampling for measurement of inflammatory markers • Blood sampling for measurement of a panel of pro-inflammatory cytokines (at selected sites) • ECG

	• pregnancy test (urine dipstick), in women of childbearing potential. Positive urine test results will be confirmed with a serum pregnancy test; At day 28 and hospital discharge, the following data will be collected: duration of invasive mechanical ventilation (IMV) and/or extra corporeal membrane oxygenation (ECMO), intensive care unit (ICU) admission and ICU length of stay, hospital discharge hospital length of stay. At discharge, etiologic agents (if identified as per clinical need) and EQ-5D-5L questionnaire will be collected. CCI [redacted] Serum samples for PK analysis will be obtained CCI [redacted]. At day 90±7 and 180(±14 days), the following measurements/assessments will be performed by phone: hospital re-admission, mortality, EQ-5D-5L questionnaire, occurrence of any adverse event (AE) or serious adverse event (SAE). If re-hospitalized, it should be also collected: duration of IMV and/or ECMO, ICU admission and ICU length of stay, hospital length of stay, occurrence of infections.
Number of Patients	526 patients hospitalised for CAP including COVID-19, to target 500 evaluable patients
Diagnosis and Main Criteria for Inclusion/Exclusion	<u>Inclusion criteria</u> 1. Informed consent signed 2. Male and female adults ≥18 years old 3. Patients hospitalised for clinically suspected CAP, defined as the occurrence of (within 48h from hospital admission): a) at least 1 of the following signs/symptoms: dyspnea, cough, purulent sputum, crackles (rales) and/or rhonchi b) body temperature > 38°C or <36°C (before or during admission) or leukocytosis (> local ULN) c) new/increased pulmonary infiltrate(s) by chest imaging 4. Need for non-invasive supplemental oxygen (NIAID-OS 5-6) 5. SpO_2 <92% at room air or PaO_2/FiO_2 (or SpO_2/FiO_2) <300 6. 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: a) Hormonal contraception, systemic, implantable, transdermal, or injectable contraceptives from at least 2 months before the screening visit until 30 days after the last Investigational Medicinal Product (IMP) dose b) 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 from at least 2 months before the screening visit until 30 days after the last IMP dose c) A male sexual partner who agrees to use a male condom with spermicide d) 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. Treatment with IMV or ECMO (NIAID-OS 7) 2. Hepatic dysfunction: ALT or AST > 5 ULN; history of chronic hepatic disease (defined with Child-Pugh score B or C) 3. Renal dysfunction: estimated glomerular filtration rate (eGFR; MDRD) <50 mL/min/1.73 m^2, or need for haemodialysis or hemofiltration; 4. Current use of >2 immunosuppressive medications or immunosuppression status (AIDS, aplastic anaemia, asplenia, systemic chemotherapy within the past 3 months, neutropenia (ANC < local LLN), solid organ or bone marrow transplant recipients) 5. Treatment with a prohibited medication within 5 half-lives, and inability to stop during treatment period (paragraph 5.5.2) 6. Anticipated discharge from the hospital or transfer to another hospital within 72 hours of screening 7. History of: ~~a.~~ intolerance or hypersensitivity to ibuprofen to more than one medication belonging to the class of sulfonamides, such as sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib (hypersensitivity to sulphanilamide antibiotics alone, e.g. sulfamethoxazole does not qualify for exclusion); b. lactase deficiency, galactosemia or glucose-galactose malabsorption c. gastrointestinal bleeding or perforation due to previous NSAIDs therapy or recurrent peptic ulcer/haemorrhage d. allergy to reparixin or any component of the IMP formulation 8. Active bleeding or bleeding diathesis (excluding menses), prior intracranial haemorrhage 9. Participation in other interventional clinical trials 10. Clinical condition not compatible with oral administration of the study drug 11. Pregnancy: a. positive or missing pregnancy test before first drug intake or day b. pregnant or lactating women c. 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 12. Current hospital stay >72h 13. Complicated CAP-associated conditions, such as fungal pulmonary infection, tuberculosis infection, abscess, empyema, significant bilateral pleural effusion, massive pulmonary embolism
Test Product, Dosage and Mode of Administration	Reparixin CCI [redacted], administered orally at the dose of 1200 mg TID (2 tablets TID) as add-on therapy to standard of care. IMP can be taken with a glass of water (about 250 mL) and a light meal or snack (it is preferable that reparixin is taken with food). However, if the patient is unable to eat, the study drug may still be administered without concomitant food ingestion.
Duration of Treatment	Up to 21 days (or until IMV/ECMO, if any)

Reference product, Dosage and Mode of Administration	Placebo tablets. Administered orally with the same schedule as reparixin.
Primary Efficacy Endpoint	Proportion of patients dead or requiring IMV (or ECMO)by day 28
Secondary Endpoints	Key Secondary endpoints: - All-cause mortality at day 180 - Proportion of patients alive and discharged at day 28 - Ventilatory-free days at day 28 - Occurrence of IMV (or ECMO) by day 28 - Length of primary hospital stay Other secondary efficacy endpoints: - Clinical failure (need for IMV/ECMO or vasopressor, or death) by day 3 and day 7 - 28-day ICU-free days - Days free of IMV/ECMO (number of days with NIAID-OS 1-6) at day 28 - Duration of antibiotic therapy (days) at day 28 - 28-day hospital free days - Proportion of patients recovered (downward shift from screening of ≤2 points on the NIAID-OS or live discharge from hospital) at day 3, 7±1, 14±2, 21±2, 28 ±2 or at hospital discharge - Proportion of patients worsening (upward shift from screening of at least ≥1 point of the NIAID-OS) at day 3, 7±1, 14±2, 21±2, 28 ±2 or at hospital discharge - PaO_2/FiO_2, at day 3, 7±1, 14±2, 21±2, 28±2 or at hospital discharge - All-cause mortality, at by day 28, and day 90 - Hospital re-admission by day 90 and 180 - Time to discharge or to a NEWS of ≤ 2 (for 24 hours), whichever occurs first - Change in Inflammatory markers (LDH, CRP, ferritin, D-dimer; PCT) and cytokines [at day 3, 7±1, 14±2, 21±2, 28±2 or at hospital discharge] - Change in quality of life using EQ-5D-5L [90±7 and 180±14 days] - duration of IMV and/or ECMO at 90 and 180d - ICU admission and ICU length of stay at 90 and 180d - hospital length of stay at 90 and 180d - occurrence of infections at 90 and 180d CCI [redacted] PK endpoints: - Serum concentration of reparixin (bound and free) CCI [redacted]

<table>
<tr><td>Safety Endpoint</td><td>- Incidence of Treatment Emergent AEs (TEAEs) and SAEs (TESAEs) from the beginning of study treatment to up to the end of study participation.
- Incidence of lung fungal infections by 28 days
- Haematology/biochemistry tests [baseline, day 3, 7±1, 14±2, 21±2, 28±2 at hospital discharge]
- BP and HR [baseline, day 3, 7±1, 14±2, 21±2, 28±2 or at hospital discharge]
- ECG [baseline, end of treatment]</td></tr>
<tr><td>Statistical Methods</td><td>The sample size of the study is calculated based on results from the CCI study (phase III study) with reparixin and literature on CAP. Sample size has been determined to achieve an overall power of approximately 90% to show superiority of reparixin vs placebo in terms of the primary endpoint (expected effect in favour of reparixin: CC) and controlling the overall one-sided alpha below 0.025. An interim analysis, to take place when half of the planned evaluable participants have reached their primary endpoint, will be performed to evaluate efficacy and futility.
O'Brien-Fleming's 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. P-value boundaries are reported in the following Table:
<table>
<tr><th rowspan="2">Analysis</th><th rowspan="2">Sample Size (evaluable patients)</th><th colspan="2">Boundaries for primary endpoint</th></tr>
<tr><th>Efficacy</th><th>Futility</th></tr>
<tr><td>Interim</td><td>250</td><td>p-value CCI</td><td>p-value CCI</td></tr>
<tr><td>Final</td><td>500</td><td>p-value CCI</td><td>p-value CCI</td></tr>
</table>
Assuming that 5% of patients will not be evaluable for primary analysis, the total number of patients to be enrolled will be approximately 526.
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.
The Safety (SAF) and the Full Analysis Set population will consist of all patients who will be randomised and received at least one dose of the investigational product. Safety population will be analysed according to the actual treatment received; FAS population will be analysed according to the Intention To Treat (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.</td></tr>
</table>

	The treatment policy strategy will be used for analysis of primary endpoint. Specifically, the primary estimand is defined by the following: • Population: adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study. • Variable: Patients dead or requiring IMV (or ECMO) by day 28. • Intercurrent event: The occurrence of any intercurrent event is irrelevant. All observed values will be used regardless of occurrence of these intercurrent events. • Population-level summary: Difference in proportion of patients dead or requiring IMV (or ECMO) by day 28. Primary endpoint will be analysed by means of logistic regression adjusting by pre-defined baseline factors. Missing data will be addressed by means of multiple imputation based on retrieved dropouts. Sensitivity analyses will be defined to address the robustness of results on primary endpoint versus deviations from the assumptions used in the statistical model. 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 to control the type I error at 0.025. Estimands for key secondary endpoints will be described in the Statistical Analysis Plan. Independently of the results on primary endpoints, all secondary endpoints will be analysed at each available time point by means of summary statistics and by appropriate parametric or non-parametric tests depending on the nature of the variable and its distribution. All analyses will be descriptively in nature. TEAEs and TESAEs will be presented in terms of the number and incidence of TEAEs and TESAEs. Other safety parameters will be summarised by treatment at each available time point by means of descriptive statistics. The Study Statistical Analysis Plan with more technical and detailed elaboration of the principal features of statistical analyses will be finalised before interim analysis. Any deviation from the original statistical plan will be described in the Clinical Study Report

2. SCHEDULE OF EVALUATION

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

Study procedures	**Screening day -1 or 1**	**Baseline[3] Day 1**	**Day 3**	**Day 7 (±1)**	**Day 14 (±2)**	**Day 21 (±2)[11]**	**Day 28 (±2)**	**Hospital discharge[20]**	**Day 90 (±7)**	**Day 180 (±14)**
ELIGIBILITY										
Informed Consent	X[1]									
Inclusion/Exclusion Criteria	X									
Demographics, Medical History	X									
Previous medications	X									
STUDY INTERVENTION										
Randomization		X								
Study product administration[4]		<---------- daily ---------->								
STUDY PROCEDURES										
SARS-CoV-2 RT-PCR		X[12]								
Clinical severity score (NIAID-OS)	X	<---------- daily[15] ---------->								
Physiological parameters (NEWS)[18]		<---------- daily ---------->								
PSI		X[12]								
PaO_2/FiO_2[19]	X[12]		X	X	X	X	X			
Chest imaging review	X[13]	CCI								
Adverse events evaluation		<----------								---------->
Concomitant medications	<----------									---------->
Additional Clinical Findings[10]							X	X		
EQ-5D-5L[2]								X	X	X
Follow-up[16]									X	X
SAFETY PROCEDURES										
Safety Laboratory Tests[6]	X[12]		X	X	X	X	X			
Pregnancy Test[7]	X					X				
Vital signs[14]		X	X	X	X	X	X	X		
ECG		X				X				
RESEARCH LABORATORY										
Cytokines[8]		X				X				
Inflammatory markers[9]		X[12]	X	X	X	X	X	X		
Serum PK			X[17]							

1 Informed consent must be documented before any study-specific screening procedure
2 Telephone interview version
3 Screening and baseline (pre-treatment assessment) may coincide (both as Day 1)
4 Study product will be administered TID up to 21 days
5 CCI
6 Includes Haematology (RBC count, haematocrit, haemoglobin, WBC count and differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes], platelets count) and Biochemistry (sodium, potassium, chloride, calcium, glucose, creatinine [to calculate eGFR using MDRD], albumin, AST, ALT, total and direct bilirubin).
7 For women of childbearing potential. Positive urine test results will be confirmed with a serum pregnancy test. Study drug must not be administered unless pregnancy test result is negative.
8 Such as IL-1, IL-6, IL-8 (in selected centres), to be checked prior to first IMP administration and at the end of treatment
9 LDH, ferritin, CRP, D-dimer, PCT
10 Include final evaluation of days of hospitalisation, etiologic agents (if identified), ICU admission and total days in ICU, occurrence and duration of IMV and/or ECMO, if any.
11 Or end of treatment
12 Diagnostic and Laboratory tests performed at the site during current hospitalization will be accepted for determination of eligibility and/or used as baseline data
13 Screening chest imaging, already performed per clinical needs, should be reviewed to confirm new/worsening lung infiltrate(s)
14 Systolic / diastolic blood pressure (BP; mmHg); heart rate (HR; b/min), respiratory rate (RR; n/min)
15 Every morning during hospitalization
16 Phone follow-up to assess re-hospitalization, all-cause mortality (health registry may be used). If re-hospitalized, it should be also collected: duration of IMV and/or ECMO, ICU admission and ICU length of stay, hospital discharge and hospital length of stay, occurrence of infections.
CC
18 In a scored system, NEWS includes Blood Pressure (BP), Heart Rate (HR), Respiratory Rate (RR), body temperature, level of consciousness (A, V, P, U), SpO_2 and use of supplemental oxygen (see 14.4.4)
19 If Arterial Blood Gas (ABG) analysis is not readily available, SpO_2 can be used to estimate PaO_2 (see appendix 14.4.6)
20 It can occur before or after 28d
21 If not already available, blood urea nitrogen should be measured to calculate PSI. In case the laboratory results are not readily available, and PSI calculated once all laboratory results will be available

2.1. BACKGROUND INFORMATION

Reparixin is a specific inhibitor of IL-8 (CXCL8) biological activity, stemming from a program of drug design of molecules intended to modulate chemokine action. Reparixin is the first low molecular weight blocker of IL8 biological activity in clinical development.

Based on its mechanism of action, early pre-clinical characterization of reparixin was specifically targeted to evaluate the inhibition of PMN recruitment and the prevention of Ischemia/Reperfusion injury. Original development was focused to solid organ transplantation, where reparixin was infused i.v. for up to 7 days. In this filed, reparixin has received the orphan drug designation in EU in September 2001 and in USA in January 2003 for prevention of delayed graft function after solid organ transplantation. More recently, orphan drug designation has been granted in EU (September 2011) for the "prevention of graft loss in pancreatic islet transplantation" and in the US (September 2012) for the "prevention of graft loss in islet cell transplantation".

Similarly, oncology studies in human breast cancer stem cells *in vitro* and in xenografts evidenced of the role of IL-8 in tumor metastasis and in tissue damage induced by chemotherapeutic agents and supported the clinical development of oral reparixin in breast cancer patients.

Given the prominent role played by CXCL8 and PMN in COVID19 pulmonary inflammation, oral reparixin is being studied in the indication of severe COVID-19 pneumonia.

2.2 RELEVANT NON-CLINICAL PHARMACOLOGY

Reparixin is in vitro a potent and specific inhibitor of CXCL8 biological activity. *In vitro* 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 [1-2]. In vivo, reparixin prevented PMN infiltration into the transplanted kidney and reduced creatinine 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%. CCI

In a murine model of LPS-induced ALI, reparixin (15 μg g^{-1}) reduced neutrophil recruitment in the lung by approximately 50%, the accumulation of neutrophils in the interstitial compartment and vascular permeability. 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[3].

In the cat dander extract (CDE) single challenge model, 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 BAL fluid, serum levels of total IgE and CDE specific IgE, airway epithelial mucin secretion, levels of Th2 inflammation-associated genes periostin and muc5ac, and the BAL fluid levels of IL-4, IL-13, IL-33, and TSLP. Pharmacological inhibition of CXCR1/2-axis by administration of reparixin inhibits allergen induced innate and allergic airway inflammation in mice[4].

In a murine model of bleomycin-induced pulmonary fibrosis, 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 BAL fluid. 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[5].

The role of CXCR1/2 inhibition during influenza, pneumococcal, and post-influenza pneumococcal infections was also investigated. Most experiments were conducted using DF2162, a Reparixin analogue, belonging to the same family of non-competitive allosteric inhibitors of CXCR1 and CXCR2. Reparixin and DF2162 exhibit similar potency in the inhibition of the target receptors CXCR1 and CXCR2 (IC50s in IL-8-

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, which is highly conserved in the two receptor subtypes. For this reason, DF2162 has been used to assess the role of CXCR1/2 during influenza (IAV), pneumococcal, and post-influenza pneumococcal infections in the mouse models. Mice were infected with IAV or Streptococcus pneumoniae and then treated daily with 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 count, 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 titres. 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[6]. 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 leukocyte 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. In conclusion, even though the extensive characterization work with infectious agents was conducted with DF2162, preliminary experiments showed a similar behaviour using reparixin in the single IAV model leading to comparable results.

A recent study has showed that COVID-19 neutrophils are characterized by IL-8-induced degranulation and drive a systemic prothrombotic phenotype. It also showed that therapeutic blockade of IL-8 by reparixin reduces COVID-19-associated human neutrophil activation in vitro and attenuates ARDS-related microthrombosis in vivo in the transgenic hACE2 mouse model of COVID-19 associated respiratory failure, where reparixin treatment led to decreased fibrinogen binding by intravascular neutrophils and an attenuation of pulmonary micro-thrombosis[7].

2.3. A SUMMARY OF 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 CCI [redacted] Continuous i.v. administration to dogs for 2 weeks resulted in a safe dose of CCI [redacted]. Continuous i.v. infusion of reparixin to the male and female rat at dose levels of up to CCI [redacted] 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 CCI [redacted]. 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 CCI [redacted] higher than those reached in man, as may occur during the treatment of patients receiving kidney transplantation.

In the preclinical setting, reparixin has shown an excellent safety profile as demonstrated with a very comprehensive toxicological investigation in vitro and in animal species.

2.4. PHARMACOKINETICS AND PRODUCT METABOLISM

Pharmacokinetic (PK) studies by i.v. injection revealed that reparixin is very rapidly eliminated in rats and humans CCI whereas elimination is slower in dogs CCI 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 CCI (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 rats, 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 CCI followed by CCI 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 C indicating the absence of accumulation over the dosing period. Also, $t_{1/2}$ did not change from day 1 to day C with a median value of about 2 hrs. Once absorbed, reparixin is highly bound to proteins 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 C within the observed intersubject variability. The $t_{1/2}$ of all three metabolites appeared to remain about the same from day 1 to day C

To investigate the PK/PD characteristics of reparixin, we assessed the effect of the drug in inhibiting IL-8-mediated Neutrophils Extracellular Traps (NET) release by hPMN in whole blood of healthy volunteers. Reparixin blocked IL-8-induced NET formation in a concentration dependent manner, being the inhibition (40%) statistically significant at CCI and reaching the almost complete inhibition (about 90%) at CC . This finding supports that the total blood concentration of CCI (corresponding to a free unbound concentration of CCI), as that reached at the steady state (Css) by i.v. infusion or by repeated oral administration, 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.

2.5. A SUMMARY OF CLINICAL DATA

To date, several clinical studies (from Phase I to Phase III) with a total of 627 subjects exposed to the drug, of whom 342 and 337 received oral tablets and i.v. formulation, respectively were performed.

During the Phase I studies a total of 166 subjects of whom 103 normal volunteers and 17 patients with different grade of renal impairment, 16 patients undergoing cardiopulmonary bypass and 30 patients with metastatic breast cancer were exposed to reparixin.

In Phase II and III studies, a total of 318 patients have been treated with reparixin I.V. (in phase II only) and oral tablets. For I.V. administration: 46 undergoing lung transplantation, 48 patients undergoing kidney transplant, 85 patients undergoing intrahepatic islet transplantation, 22 undergoing orthotopic liver transplantation and 4 patients with severe COVID-19 pneumonia (under compassionate use).

For oral administration: 122 patients with breast cancer, 220 patients hospitalized for COVID-19 pneumonia

were treated.

In all studies, reparixin has shown a good safety profile with both I.V. and oral administration routes.

Data with oral tablets include treatments repeated monthly cycles of 21 days continuous treatment in breast cancer patients, which exceed the duration of the treatment in the COVID-19 studies, which require a single cycle only of 21 days.

2.5.1. Efficacy in patients with Covid-19

To date three studies were performed with reparixin in COVID-19 patients. They were represented by:

a. Compassionate use with reparixin i.v. infusion,
b. Phase II open-label study CCI),
c. Phase III double-blind study CCI).

In particular:

1. In March 2020, IRCCS Ospedale San Raffaele, a reference center in Italy for COVID-19 pandemic emergency, utilized reparixin under a compassionate use application. Four patients with ARDS caused by COVID-19 pneumonia with the clinical indication for intubation and invasive mechanical ventilation (IMV) were treated with reparixin i.v. infusion CCI via high-flow central vein for 5 days. An article on these patients was published (Piemonti et al., 2020), reporting that 1 out of the 4 patients was never intubated and discharged from the hospital, and 3 were intubated: 1 in stable condition and 2 with improving lung function.
   From a haemato-chemical standpoint, there was an improvement or stabilization of the inflammatory markers [C-reactive protein (CRP), procalcitonin (PCT), and ferritin] during treatment with reparixin, as per tissue damage markers [lactate dehydrogenase (LDH), ALT, AST]. As per the last update in March 2021, 3 of the 4 patients treated were intubated, and all patients were discharged alive from hospital.
2. Phase II open-label study CCI . In 2020 Dompé concluded the Phase II segment of an adaptive Phase II/III, randomized, controlled multicenter study on the efficacy and safety of reparixin in the treatment of hospitalized patients with COVID-19 pneumonia. Fifty-six patients were randomized 2:1 to receive 1200 mg (2x 600 mg tablets) oral reparixin three times daily (37 pts) or standard of care (SOC) (19 pts) for up to 21 days. Results suggested that Reparixin may prevent the progression to severe disease, as it significantly decreased the incidence of at least one clinical event of the composite endpoint including supplemental oxygen requirement, invasive mechanical ventilation use, admission to ICU, and use of a rescue medication for any reason. Treatment with Reparixin was well tolerated in terms of treatment-emergent adverse events, laboratory tests and vital signs parameters.
3. Phase III double-blind study CCI . The Phase II study CCI results informed the design of a subsequent double-blind, placebo-controlled clinical study CCI), approved in Italy (EudraCT Number: CCI) and in the US; nonetheless, due to a late activation of the three centers in US, that coincided with a lowering incidence of new COVID-19 infections, the study enrolled only in Italy. Study CCI title was CCI ” and its objective was to evaluate efficacy and safety of oral reparixin as compared to placebo (both on top of standard treatment). A planned primary analysis on efficacy endpoint up to Day 28 was recently completed. To maintain study integrity, results were disclosed to the study Sponsor in an aggregate way, study personnel remained blinded to patient-level information, and analyses were conducted by an independent statistician. From February 2021 to June 2021, patients with RT-PCR-confirmed severe COVID-19 were randomized in a 2:1 fashion to receive oral reparixin 1200 mg (2x 600 mg tablets) three times a day (TID) or placebo for 21 days. Schedule and regimen were consistent with the previous trial. Follow-up information on the patient's clinical condition and survival are collected until day 90. Briefly, patients were considered for inclusion if they needed oxygen support with a PaO2/FiO2 between 100 and 300 (or SpO2 >95% at room air, or RR ≥24 breaths/min at room air), abnormal chest imaging, and laboratory signs of inflammation (LDH >normal range, CRP ≥100 mg/L or IL-6 ≥40 pg/mL, serum ferritin ≥900 ng/mL, XDP >20 mcg/mL). The primary efficacy outcome was the proportion of patients alive and with no respiratory failure at day 28, defined as no need for IMV, extracorporeal membrane oxygenation (ECMO), or admission to ICU due to worsening respiratory status. Among 278 randomized patients, all enrolled in Europe, 179/183 (97.8%) in the reparixin group and 88/95 (92.6%) in

the placebo group received at least one dose of investigational product and were included in the primary intention-to-treat (ITT) analysis of efficacy. All participants had a positive RT-PCR assay for SARS-CoV-2 RNA from the upper respiratory tract. At baseline, the cohort was well-balanced across the two groups: mean age 60.8 (SD 11.9) years, 73% were males, 27% had a Hispanic origin, and 30% with a BMI>30 Kg/m^2. All participants had the typical features of acute respiratory failure, such as abnormal findings at the chest imaging, need for oxygen therapy either low flow or HFNC/NIV (HFNC/NIV, 49.2% in the reparixin and 50.0% in the placebo group), with a mean PaO2/FiO2 of 200.2 (SD 67.5). The treatment was discontinued more frequently in placebo (33 patients [18.0%] vs. 21 [22.1%]), with good compliance to study medication during treatment in both arms (median 95.8% in the reparixin group and 96.5% in the placebo group). According to ITT principle, all randomized and treated patients were considered for the efficacy analysis, using retrieve dropouts' information to handle missing data at Day 28. CCI [redacted] Patients in both treatment arms received the standard supportive care based on the patient's clinical need as per local standard therapy: 85.2% of patients in the placebo group received glucocorticoids (82.7% in reparixin), 35.2% received remdesivir (29.6% in reparixin), and 2.3% received tocilizumab (3.4% in reparixin). The mortality at 28 days was CCI in the placebo group and CCI in the reparixin group (OR 0.543 [95%IC 0.185-1.592], p=0.265). Nonetheless, there was a strong signal in favour of reparixin in limiting the worsening of respiratory failure at day 28. In fact, the proportion of ICU admission due to a deterioration of respiratory failure (followed by IMV, or ECMO, or death) was lower in the treatment group, 9 (5.9%) in the reparixin group and 11 (13.8%) in the placebo group, OR 0.372 [95%IC 0.144-0.960], p=0.041. The incidence of IMV/ECMO was also lower in the treatment group: 8 patients (5.3%) in reparixin vs. 10 (12.7%) in placebo group, p = 0.048. This is also corroborated by physiological parameters, as the 28-d trajectory of PaO2/FiO2 was significantly better in patients receiving oral reparixin: PaO2/FiO2 mean change from baseline: 145.0 [SD 146.5] in reparixin vs. -27.9 [SD 130] in the control group, p=0.008. Once again, there was a strong safety signal even as the number of adverse events was steadily higher in the control group.

2.5.2. Safety

In all studies, reparixin has shown a good safety profile with both i.v. and oral administration routes.

A total of 448 subjects have been exposed to reparixin in the clinical studies completed up to the start of the phase II 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 CCI over 30min or CCI over 48h and, in pancreatic islet and liver transplantation studies CCI 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 (SAE) or Adverse Events (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 II and III 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 CCI in several patients. Most frequent Adverse Drug Reactions (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 judged probable in relation to the 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.

The most frequent (>10%) ADRs observed in studies on i.v. formulation were:

Gastrointestinal disorders (about 26% of the total number of reports), including abdominal pain lower, abdominal pain NOS, abdominal pain upper, constipation, diarrhoea, dyspepsia, flatulence, gastroesophageal reflux disease, gastrointestinal haemorrhage, intra-abdominal haemorrhage, nausea and vomiting.

Nervous system disorders (about 19%), including headache, dizziness, hypoesthesia, 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 patients 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 : 61 patients). In these studies, 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 REP0114 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.

Preliminary safety data derived from the CCI trial confirmed the tolerability of reparixin in patients with COVID-19, with treatment emergent adverse events/treatment emergent serious adverse event (TEAEs/TESAEs) profile similar in both treatment groups. A total of 161 TEAEs were reported in 71 patients (39.7%) in the reparixin group and 100 TEAEs were reported in 42 patients (47.7%) in the placebo group. Similarly, TESAEs were reported in 18 patients (10.1%) in the reparixin group (22 TEAEs) and in 12 (13.6%) in the placebo (15 TEAEs) and were related to treatment in 1 patient (1.1%) in the placebo group (1 TEAE). Eighteen TEAEs leading to discontinuation of the Investigational Medicinal Product (IMP) were reported in 15 patients (8.4%) in the reparixin group and 12 TEAEs leading to discontinuation of IMP were reported in 11 patients (12.5%) in the placebo group. One patient (0.6%) in the reparixin group discontinued the study due to a TEAE. Thirteen TEAEs leading to death were reported in 11 patients (6.1%) in the reparixin group and 9 TEAEs leading to death were reported in 7 patients (8.0%) in the placebo group.

2.6. DISEASE REVIEW AND STUDY RATIONALE

COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. WHO first learned of this new virus on 31 December 2019, following a report of a cluster of cases of "viral pneumonia" in Wuhan, People's Republic of China. The most common symptoms of COVID-19 are fever, dry cough, fatigue. Other symptoms that are less common and may affect some patients include loss of taste or smell, nasal congestion, conjunctivitis, sore throat, headache, muscle or joint pain, skin rash, nausea or vomiting, diarrhoea, dizziness. Symptoms of severe COVID-19 disease include shortness of breath, loss of appetite, confusion, persistent pain or pressure in the chest, high fever above 38 °C[8].

NIH published criteria for Therapeutic Management of Hospitalized Adults With COVID-19[9].

Noteworthy, a considerable percentage of COVID-19 cases have rapidly progressed to severe and critical type, among which acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the most common complications, resulting in a large number of pneumonia hospitalized patients requiring supplemental oxygen, mechanical ventilation, or even Extracorporeal membrane oxygenation (ECMO). Pulmonary oedema is a detrimental feature as well as a key causal factor of ALI/ARDS.

One of the most significant findings in COVID-19 patients who require admission to ICU, as compared to less severe patients, is prominent neutrophilia[10]. Excessive recruitment of neutrophils and their release of neutrophil extracellular traps (NETs) can aggravate tissue injury in several disease conditions[11]. In severe COVID-19 infection, greater neutrophilia may drive elevated pulmonary influx of neutrophils and stimulate excessive NET release, leading to signs and symptoms of ARDS. In keeping with this hypothesis, elevated NET breakdown products were found in sera of severely ill COVID-19 patients[12]. Neutrophil recruitment to the lung parenchyma requires chemoattraction. In patients with severe clinical course of COVID-19 infection, statistically significantly higher levels of IL-8 were detected as compared to non-severe patients[13]. Binding of IL-8 to its receptors on neutrophils mediates recruitment, activation and NET release. 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 (IL-6) and CXCL8 (IL-8) with a high affinity, human CXCR2 binds also to IL-6 and IL-8 as well as several CXC chemokines (GRO-α, GRO-β, GRO-γ, CXCL1, CXCL2, CXCL3), ENA-78 (CXCL5) and CXCL7[14]. Thus, inhibition of IL-8 receptors (CXCR1 and CXCR2) is being pursued as a therapeutic strategy for severe COVID-19 infections.

To a similar extent, there is a strong rationale to reduce the inflammatory response in all infectious pneumonia, as a dysregulation inflammatory response may contribute to morbidity and mortality in CAP.[23] Pathogenic organisms other than SARS-CoV-2 may similarly contribute to pneumonia pathogenesis and progression, as neutrophils play a significant role in its development and progression. IL-8 primarily mediates neutrophil activation, migration, and NETosis. A dysregulated IL-8 axis may trigger a prothrombotic neutrophil phenotype, excessive degranulation, NET formation, cytotoxic effect, microvascular occlusion, and fibrosis.[20] Indeed, in some patients, the initial systemic inflammatory response can become dysregulated, leading to tissue injury and organ dysfunction which may result in clinical manifestations such as acute respiratory distress syndrome (ARDS), sepsis, and multiple organ dysfunction syndrome.[21] Nonetheless, available trails have been mainly focused on glucocorticoids, and constitute insufficient evidence to recommend their routine use in CAP (ATS/IDSA guidelines).[22] This critical unmet clinical need may represent a key benefit of reparixin in patients suffering from an acute lung infection, which still constitutes a leading cause of morbidity and mortality worldwide. Thus, inhibition of IL-8 receptors (CXCR1 and CXCR2) is being pursued as a therapeutic strategy for CAP.

Since the beginning of 2021, when vaccination plan started, the in-hospital fatality rate in Europe has declined over the pandemic, mainly due to improvement in clinical knowledge, patient management, and treatments[15-16]. Changes in respiratory support and steroids have played a crucial role, accounting for 22.2% in-hospital mortality risk reduction (OR 0.95 [95%CI 0.94–0.95], p<0·0001)[17]. However, there are still limited approved and adequate medications to prevent disease progression. The healthcare resource allocation for respiratory failure, IMV and ICU is still challenged in some geographic areas, and the low vaccination rate in some EU countries and the uncertainty on SARS-Cov-2 variants spread still represent a high level of risk for pandemic management. Interventions for reducing respiratory failure, the need for IMV and access to ICU would significantly improve patients' care and healthcare resource allocation. To a similar extent, community-acquired pneumonia (CAP), including all acute pneumonia acquired outside the hospital, still represents a leading cause of morbidity and mortality worldwide. Despite advancements in clinical and therapeutic management, CAP is the second most common cause of hospitalization and the most common infectious cause of death, representing a pressing unmet clinical need.[23]

In preclinical studies, CXCR1/2 inhibition improves disease outcomes during respiratory influenza and pneumococcal infections, two primary pathogens of CAP.[24] Of foremost importance, the ability of the murine host to deal with the infection was not impaired.[24] Clinical data obtained in the compassionate use, as well as in the phase II and III trials in COVID-19 patients support the potential clinical efficacy of reparixin in limiting the progression of the disease in patients with established COVID-19. These findings, coupled with the safety shown in phase I to III clinical trials, provide strong rationale supporting further testing of reparixin in CAP including COVID-19, and the conduct of this new phase III clinical study.

The comparable pathophysiologic mechanism of acute lung infection, the preclinical data on reparixin in infectious diseases, the continuity of target populations and the prominent clinical needs support the extension of the current disease target to a broader umbrella of acute infection of the pulmonary parenchyma acquired outside of the hospital, including COVID-19 among the CAP infections.

2.6.1. Alternative treatments

There are pharmacologic treatments approved for COVID-19 and other infectious pneumonia, other than supportive and invasive care management. The current trial will not interfere with the usual management of the patients, as reparixin/placebo will be used as an add-on therapy. The evaluation, the assessment, and management of the patients (such as decisions on anti-infective medications, adjunctive therapy, supportive therapy, and site and level of care) will not be determined or influenced by study procedures, and will be entirely under the control of the treating physicians as all patients, regardless of group allocation or study participation, will receive the standard of optimal care.

2.6.2. Risk – benefit evaluation

2.6.2.1. Risk related to reparixin

Results from preclinical and clinical studies support the level of drug exposure planned in this study.

The safety was confirmed in the phase II trial using the same schedule; indeed, no safety concerns were raised in COVID-19 patients. As immunomodulator, there is possible risk of higher secondary infection. Nonetheless, recent clinical and preclinical data suggest that reparixin do not increase the risk of secondary infection. Moreover, to minimize the risk in CAP, patients with fungal infections and immunosuppression will not be included in the trial.

Any possible risk derived from the continuous administration of reparixin in the specific population involved in this study will be minimized by integrated monitoring which include laboratory tests and daily clinical observations.

Even if reparixin in vitro marginally inhibits the enzyme CYP2C9 (IC50 79 µM) and slightly inhibits CYP3A4 (IC50 8 µM), it does not affect to a clinically relevant extent the activity of CYP3A4 and CYP2C9 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 (Reparixin Investigator's Brochure, 2021).

2.6.2.2. Blood sampling

Participation in the study might require additional blood samplings other than the routine ones. In particular:

- blood samples (about [redacted] mL) will be obtained to evaluate haematology and clinical chemistry (Safety Laboratory Tests, baseline, day 3, 7±1, 14±2, 21±2, 28±2 or hospital discharge)
- blood samples for inflammatory markers (about [redacted] mL) will be taken baseline, day 3, 7±1, 14±2, 21±2, 28±2 or hospital discharge
- in selected centers, blood samples for cytokines (about [redacted] mL) at baseline and at the end of treatment, and PK [redacted]

These samplings might be at risk of minor pain, bruising, inflammation or excessive bleeding at the venipuncture site and faintness and/or swelling, pain, redness, or infection (infection rarely happens) at the site where the needle is inserted. Rare risks include hematoma, infection, arterial sampling. The volume of blood above is an amount that the body can safely replace. Also, multiple punctures might be required to identify the veins.

For the arterial blood gas (ABG) analysis, a small syringe and small needle (topic 1% lidocaine, if available) will be utilized to withdraw at least 1-2 mL of blood from an artery (preferably radial).

Time of IMP administration and actual sampling times for each patient will be recorded in the individual eCRF.

2.6.2.3. Potential benefit

The rationale for treating patients with CAP including COVID-19 is to reduce the inflammatory response to pneumonia, which may contribute to its morbidity and mortality. Nonetheless, available trails in CAP have

been mainly focused on glucocorticoids, and constitute insufficient evidence to recommend their routine use (ATS/IDSA guidelines). This critical unmet clinical need may represent a key benefit of reparixin in patients suffering from an acute lung infection, which still constitutes a leading cause of morbidity and mortality worldwide.

In summary, given the cumulative knowledge for the safety profile of reparixin in patients with COVID-19, and the significant unmet need for a treatment to prevent the progression in lung infections, the benefit/risk balance for this study is assessed to be favourable.

To the patients: half of the patients will be assigned to the placebo arm and will therefore obtain no benefit. Patients receiving reparixin treatment may possibly benefit, but this is to be ascertained.

To society: This study may identify a useful medication that may help limiting disease progression in severe COVID-19 and CAP adult patients.

2.6.3. Description of the Investigational Products

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

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

The 1200 mg TID dosage is supported by both preclinical studies and efficacy/safety results from phase I and phase II clinical studies already conducted. The resulting average steady state plasma concentration of the reparixin unbound fraction should ensure full inhibition of PMN migration, considering that the in vitro IC_{50} is in the range of 1 ng/mL.

The toxicity studies conducted to date support the dose and the dose regimen proposed for this study, a treatment schedule already used for the previous phase II and phase III trials in COVID-19 adult patients.

3. OVERALL STUDY DESIGN AND INVESTIGATIONAL PLAN

3.1. STUDY OBJECTIVES

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

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

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

3.2. STUDY ADMINISTRATIVE STRUCTURES, STAFF AND RESPONSIBILITY

This study will be performed at designated clinical spaces available for clinical studies, under the supervision and responsibility of the Principal Investigator (PI). The PI will be responsible for ensuring that the investigation is conducted according to the signed Investigator agreement, the protocol, Good Clinical practice (GCP) guidelines, institutional, federal, state and local regulations.

The PI will be responsible for the management of the study, which will consist of maintaining the study file and the patient records, reporting SAEs within required timelines, completing the electronic case report form (eCRF) and any other study document. PI should also correspond with the Institutional Review Board (IRB).

The PI is responsible for supervising any individual or party to whom (s)he delegates trial related duties and functions conducted at the trial site. The PI/institution should ensure that any individual or party that performs trial related duties and functions is qualified to perform those trial related duties and functions and should implement procedures to ensure the integrity of the trial related duties and functions performed and any data generated. Similarly, it is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

The PI will maintain a list of delegated responsibility detailing the various study tasks to be performed by each member of his/her study staff. Each staff member should sign the delegation of authority/activity log for their performing each of the tasks delegated to them on the list. Where reference is made in this protocol to the PI, either the PI and/or one or more delegated members of his/her staff are meant, according to the list of delegated responsibility.

3.3. OVERALL STUDY DESIGN

The study is a multinational, multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase III trial.

It will enrol approximately 526 adult patients hospitalized for CAP (including severe COVID-19) that meet the entry criteria (sections 4.1 and 4.2), randomly assigned at 1:1 ratio to receive either oral reparixin 1200 mg (treatment group) or matched placebo (control group) TID for up to 21 days. All patients must receive standard and supportive care according to their clinical status and local guidelines during the whole study period.

Each patient will be involved in the study for up to 180 days. This period consists of informed consent acquisition and screening, randomization and baseline assessments, and a post-randomization study period of up to 28 days from the first IMP dose (or hospital discharge). Subjects will be assessed daily while hospitalized up to 28 days from first IMP administration (or hospital discharge). Detailed evaluations and their timing are presented in sections 2 and section 6.1. Follow-up information on the patient's clinical condition and survival will be collected until day 180, regardless of hospitalization.

An interim analysis for efficacy and futility is planned when half of the planned patients is evaluable for the primary endpoint. The end of this study is defined as the date of the last patient's last visit.

3.3.1. Rationale for Selection of dose, control group and treatment schedule in the study

The dose and dose regimen have been selected according to the rationale reported in Section 2.6.3.

A double-blind, randomized study design is being adopted as the gold standard to minimize systematic bias and increase baseline comparability between treatment groups. So, the study will include a control group receiving a placebo. Despite significant unmet needs for the selected study population, the standard and supportive care in severe COVID-19 includes dose corticosteroids and, depending on local guidelines, additional immunomodulators or anti-viral agents. The use of corticosteroids in other form of CAP, although less recognized, will not be prohibited and it will be decided by the treating physicians. Thus, in this rapidly evolving scenario, this study should involve patients treated with the current standard care plus placebo.

3.4. STUDY TIME-TABLE.

Overall planned study timelines are reported below

Study period First Patient First Visit: April 4, 2022

Last Patient First Visit: Sep 2023

Last Patient Last Visit: March2024

Detailed assessments and schedule are presented in sections 2 and section 6.1.

4. SELECTION OF STUDY POPULATION

Number of patients: approximately 526 adult patients hospitalized for suspected CAP (including established COVID-19) will be enrolled to target 500 evaluable patients. A patient is considered enrolled if, after signature of consent and screening, (s)he provides that (s)he fully meets all the Inclusion Criteria and none of the Exclusion Criteria described in Sections 4.1. and 4.2. below.

4.1. INCLUSION CRITERIA

To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria:

1. Informed consent signed
2. Male and female ≥18 years old;
3. Patients hospitalized for clinically suspected CAP, defined as the occurrence of (within 48h from hospital admission):
    a. at least 1 of the following signs/symptoms: dyspnea, cough, purulent sputum, crackles (rales) and/or rhonchi
    b. body temperature > 38°C or <36°C (before or during admission) or leucocytosis (> local ULN)
    c. new/increased pulmonary infiltrate(s) by chest imaging
4. Need for non-invasive supplemental oxygen (NIAID-OS 5-6; Appendix 14.4.1);
5. SpO_2 <92% at room air, or PaO_2/FiO_2 (or SpO_2/FiO_2) <300;
6. 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:
    a. Hormonal contraception, systemic, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit until 30 days after the last IMP dose
    b. 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 the last IMP dose
    c. A male sexual partner who agrees to use a male condom with spermicide
    d. 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. EXCLUSION CRITERIA

Patients who meet any of the following criteria are NOT eligible for inclusion in the study:

1. Treatment with IMV or ECMO (NIAID-OS 7);
2. Hepatic dysfunction: ALT or AST > 5 ULN; history of chronic hepatic disease (defined with Child-Pugh score B or C);
3. Renal dysfunction: estimated glomerular filtration rate (eGFR, MDRD) <50 mL/min/1.73 m^2, or need for haemodialysis or hemofiltration;
4. Current use of >2 immunosuppressive medications or immunosuppression status (AIDS, aplastic anaemia, asplenia, systemic chemotherapy within the past 3 months, neutropenia (ANC < local LLN), solid organ or bone marrow transplant recipients)
5. Treatment with prohibited medication within 5 half-lives, and inability to stop during treatment period (see section 5.5.2);
6. Anticipated discharge from the hospital or transfer to another hospital within 72 hours of screening
7. History of:
    a. intolerance or hypersensitivity to ibuprofen to more than one medication belonging to the class of sulfonamides, such as sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib (hypersensitivity to sulphanilamide antibiotics alone, e.g. sulfamethoxazole does not qualify for exclusion)
    b. lactase deficiency, galactosemia or glucose-galactose malabsorption

c. gastrointestinal bleeding or perforation due to previous NSAIDs therapy or recurrent peptic ulcer/haemorrhage
d. allergy to reparixin or any component of the IMP formulation

8. Active bleeding or bleeding diathesis (excluding menses), prior intracranial haemorrhage
9. Participation in other interventional clinical trials
10. Clinical condition not compatible with oral administration of the study drug
11. 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

12. Current hospital stay >72h
13. Complicated CAP-associated conditions, such as fungal pulmonary infection, tuberculosis infection, abscess, empyema, significant bilateral pleural effusion, massive pulmonary embolism

4.3. ASSIGNMENT OF PATIENT NUMBER

At screening, each patient will be assigned a unique sequential screening number. If the patient is randomized, the randomization number will be assigned in a sequential manner. This numbers will be used for identification throughout the study and will not be used for any other participant.

If a patient is dropped from the study for any reason, the patient's randomization number will not be reassigned.

5. STUDY MEDICATION

5.1. PRESENTATION, PACKAGING AND LABELING, SUPPLY, AND STORAGE OF THE INVESTIGATIONAL MEDICINAL PRODUCT

5.1.1. Presentation of the Investigational Medicinal Product

In this study the IMP will be either reparixin OR matched placebo, which will be provided in the form of tablets for oral administration.

A tablet of reparixin has the following composition:

Composition for each unit reparixin (tablet)

Ingredient	Amount per tablet (mg)	Function	Quality standard
Reparixin CCI	CCI		In-house specification
		CCI	

Placebo tablets are identical in appearance to the active formulation.

Batch release certificate will be provided together with the IMP.

5.1.2. Manufacturing, Packaging and Labelling of IMP

Tablets will be manufactured by either CCI or CCI Primary packaging will be performed by either CCI or CCI Secondary packaging and labelling will be performed by CCI or alternatively, might be performed by CCI

The study medication will be provided as a **Patient Kit**, containing CCI with C tablets each, for a total of C tablets, an amount slightly in excess of that required for a week treatment course (42 tablets).

All labels will be prepared to meet local regulatory requirements. Details of packaging and labelling are reported in **Appendix 14.3**.

5.1.3. Supply, Storage and Handling of IMP

An appropriate number of packages will be initially sent to the site as soon as all essential documents and regulatory/ethics approvals have been obtained. IMP re-supply will be planned on demand, according to enrolment rate.

The IMP must be kept at a temperature not exceeding 30°C and must not be frozen.

A temperature probe will accompany the drug on shipment. Temperature range reached during shipment will be verified on receipt at site, so that potential stability concerns during shipment can be investigated and appropriate action taken.

Once received at the site, the Pharmacist (or designee) will check the package for accurate delivery and acknowledge receipt; any deviations from expected package content (inconsistency, damages) should be immediately reported to Dompé (or appointed CRO) and the use of the drug suspended until authorization for its continued use has been given by Dompé (or appointed CRO).

The IMP must be stored at site in a secure location, in a temperature-controlled room. Temperature records must be available for the clinical research associate (CRA) to review at monitoring visits; any deviations

from the recommended storage conditions should be immediately reported to Dompé (or appointed CRO) and the use of the drug suspended until authorization for its continued use has been given by Dompé (or appointed CRO).

5.1.4. Blinding

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

For each randomized subject, individual code breaks will be accessible in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. Only the responsible investigator, or authorized delegates, can break the code via the Interactive Response Technology (IRT).

Investigators will be allowed to unblind study medication directly through the IRT system; any emergency unblinding must be notified to the CRO's medical monitor. Training is provided to investigators prior to authorization to use the IRT system and the unblinding function is outlined in the study specific user guide.

The sponsor's personnel from the Pharmacovigilance Department of Dompé may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case requires expedited regulatory reporting.

With the exception of the above-mentioned episodes, the identity of the treatments will remain unknown to the subject, Investigator, site staff, CRO and Dompé's personnel until the study completion and formal unmasking. Only the DMC will have access to group-unblinded and/or fully unblinded DMC reports.

For analysis purposes, the randomization codes will be broken when the last enrolled patient has completed therapy, and once the database has been locked.

5.2. DOSE, ROUTE AND SCHEDULE OF IMP ADMINISTRATION

Reparixin will be administered orally at the dose of 1200 mg (2 x 600 mg tablets) TID (6 tablets daily) for up to 21 days. Placebo will be administered with the same treatment schedule.

The three daily doses will be administered maintaining an interval between doses of about CCI . It is advisable to take the 2 tablets with a glass of water to facilitate swallowing.

IMP can be taken with a glass of water (about 250 mL) and a light meal or snack, as it is preferable that reparixin is taken with food. However, if the patient is unable to eat, the study drug may still be administered without concomitant food ingestion.

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.

5.3. CRITERIA FOR SCHEDULE ADJUSTMENT/DOSE-MODIFICATION OR DISCONTINUATION OF THE IMP

5.3.1. Criteria for schedule adjustment/dose-modification

No schedule adjustment and/or dose modification is foreseen, except for discontinuation of IMP as detailed below.

5.3.2. Criteria for discontinuation of the IMP

The IMP must be discontinued in the case:

- The patient develops renal (eGFR < 50 mL/min) or hepatic (increased ALT/AST > 5 x ULN) dysfunction;
- The patient is discharged from the hospital ;
- The patient develops clinical condition not compatible with oral administration of the study drug, or IMV/ECMO;
- Pregnancy occurs
- Any medical condition may threaten the safety of the patient if they continue to receive study treatment (as per investigator or Sponsor evaluation)
- Initiation of a prohibited medication (paragraph 5.5.2)
- CAP diagnosis ruled out, and/or any complicated CAP-associated conditions such as fungal pulmonary infection, abscess, tuberculosis infection, empyema, significant bilateral pleural effusion, massive pulmonary embolism (as in exclusion criterion n13)

Occurrence of renal or hepatic disfunction will be specifically monitored through safety laboratory tests obtained at day 3, 7±1, 14±2, 21±2 during treatment, and at 28±2 or hospital discharge. The other criteria that qualify the patient to treatment discontinuation will be monitored daily.

In addition, the IMP will be immediately discontinued in the event of any other possibly drug related occurrences that the study physician believes might compromise patient's safety.

If the IMP administration is prematurely discontinued, the primary reason for discontinuation must be recorded in the eCRF. Patients who discontinue the treatment with the IMP 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.

5.4. ACCOUNTABILITY OF THE IMP

All supplies will be maintained under adequate security by the designated member of site staff, until they are dispensed to the patients. The Investigator will ensure that study treatment is only dispensed by designated staff within the centre.

When the IMP is received at the site, designated member of site staff will check for accurate delivery and acknowledge receipt by signing and dating the documentation provided by or on behalf of Dompé and returning it to Dompé or to the appointed CRO. A copy will be retained for the Investigator/Pharmacy file.

The dispensing of the IMP will be carefully recorded on the eCRF and appropriate drug accountability forms; an accurate accounting will be available for verification by the CRA at each monitoring visit.

Drug accountability records will include:

1. the confirmation of receipt of the IMP at the trial site,
2. the dispensing of the IMP to the patient,
3. the disposition of unused product(s),
4. accounts of any IMP accidentally or deliberately destroyed,

They should include dates, quantities, batch numbers, expiration dates (if applicable), and any unique code numbers assigned to the IMP and/or patients. Investigators should maintain records which document adequately that:

1. the patients were provided the doses specified by the protocol/amendment(s),
2. the IMP provided was fully reconciled at the site.

The administration of the IMP (date/time for each administration) will be recorded by the site staff in the eCRF. The CRA will review the drug accountability forms/eCRF and check all IMP (both unused and used) prior to deciding for their disposal.

IMP which has been dispensed to a patient and was not used will not be re-dispensed to a different patient. Unused IMP (tablets) must remain in the Patient Kit and must not be discarded or used for any purpose. Any

remaining test material at the end of the trial will be returned to Dompé or disposed of, as determined by Dompé.

5.4.1. Assessment of compliance

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 the start and the end of treatment. Discrepancies will be documented and justified.

Compliance with the study product dosing schedule will be verified by the investigator and confirmed/checked by the delegated monitoring personnel of the study during on-site monitoring visits, as per records in the specific study eCRF and actual tables remaining in the Patient Kits. Compliance, calculated on the TID regimen, will be assessed based on the actual duration of treatment (up to 21 days).

5.5. PRIOR AND CONCOMITANT MEDICATION

5.5.1. Reporting of prior and concomitant medication

Prior and concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines) used by a patient in addition to the IMP from 7 days before the screening to Day 28 / end of study visit. All such medications will be reported in the appropriate section of the eCRF. Anticoagulants, as per local standard dose, are recommended for all the patients without major contraindications.

All the details as per the eCRF fields (sequential number, drug name, indication, starting dose, start/stop date, route of administration) will be recorded. Change in dose will be tracked.

5.5.2 Prohibited 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. Patients should remain under close observation during the days of administration of drugs with similar metabolic pathway if given concomitantly with reparixin.

The following medications **should not be used** from within 5 half-lives from screening to day 28:

1) Treatment with any not authorized investigational agent (except for off-label use of anti-COVID-19 agents, with approval of Medical Monitor)

2) T cell or B cell-targeted therapies, interferon, or convalescent plasma

3) CYP2C9 inducers (rifampin, carbamezapine, aprepitant, bosentan, phenobarbital, St. John's Wort) or CYP2C9 inhibitors (amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast).

6. STUDY PROCEDURE AND ASSESSMENT

During the course of the study, visits and assessments will be performed as defined in the Schedule of Assessments (Section 2).

For all measurements, the actual date and time of assessment, including date of sampling, will be recorded in the Source Document and in the eCRFs.

6.1. STUDY VISITS AND STUDY EVENTS/PROCEDURES DETAILS

The study will consist of three study periods: screening, treatment (up to 21 days), and follow-up (up to 180 days). Potential participants will be identified from those hospitalized at the participating clinical sites to manage CAP including COVID-19. Patients under evaluation at the Emergency Department with an expected admission to the ward will be considered hospitalized for study purposes.

6.1.1 Screening Procedures

Written informed consent must be documented before any study-specific screening procedure. Patients should not be screened if, for any reason, there is a high probability that they will be transferred during the treatment phase to another institution not belonging to the study network.

Procedures included in the screening will include:

- collection of demographic data, past medical history, disease-specific clinical information, and previous medications
- evaluation of NIAID-OS
- review of available chest imaging
- measurement of SpO_2, PaO_2, and FiO_2 (if ABG is not readily available, SpO_2 can be used to estimate PaO_2, see appendix 14.4.6);
- pregnancy test (urine dipstick), in women of childbearing potential. Positive urine test results will be confirmed with a serum pregnancy test;
- blood sampling for measurement of hematology/biochemistry and derived renal and hepatic function (Safety Laboratory Tests), , if not already performed during current hospitalization.;

The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. 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.

6.1.2 Randomization and Baseline (Day 1) assessment

Patients meeting all inclusion and none of the exclusion criteria will be enrolled (eligibility confirmed) and randomized (see sections 4.1 and 4.2). No time limit has been posed for the time from the onset of symptoms and hospitalization. Consecutive randomization 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 1:1 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. Information for unblinding is provided in section 5.1.

The following additional baseline assessments, to be completed within 24 hours from screening, should be performed before the first administration of the study drug (Day 1):

- 12-lead ECG performed using local equipment
- systolic/diastolic Blood Pressure (BP), Heart Rate (HR), Respiratory Rate (RR), body temperature, level of consciousness (A, V, P, U), SpO_2, and use of supplemental oxygen (utilized as physiological parameters using NEWS and vital signs)
- RT-PCR for SARS-CoV-2 from the respiratory tract (if not already performed during the current hospitalization)
- Clinical severity score (NIAID-OS) and Pneumonia Severity Index (PSI)

  - If not already available, blood urea nitrogen should be measured to calculate PSI. In case the laboratory results are not readily available, PSI can be calculated later on (once all laboratory results are available) to do not stop recruitment
- blood sampling for measurement of inflammatory markers (lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, D-dimer, procalcitonin (PCT))
- blood sampling for measurement of cytokines

6.1.3 Treatment and post-treatment hospital stay up to day 28 (or discharge)

NIAID-OS, NEWS and concomitant medications will be evaluated daily up to day 28 (or discharge).

The following measurements/assessments will be performed at day 3, 7±1, 14±2, 21±2, 28±2 (or hospital discharge):

- PaO_2 and FiO_2 (if ABG is not readily available, SpO_2 can be collected and used to estimate PaO_2, see appendix 14.4.6);
- blood sampling for Safety Laboratory Tests;
- blood sampling for measurement of inflammatory markers: LDH, CRP, ferritin, D-dimer, PCT
- vital signs (can be derived by NEWS)

At the end of treatment, the following measurements/assessments will be performed:

- Blood sampling for measurement of inflammatory markers and cytokines
- ECG
- Pregnancy test

At day 28 and hospital discharge, the following data will be collected: duration of IMV and/or ECMO, ICU admission and ICU length of stay, hospital discharge and hospital length of stay. At discharge, etiologic agents (if identified), and EQ-5D-5L questionnaire will be collected/performed. CCI [redacted]

In selected centres, serum samples for PK analysis will be obtained CCI [redacted].

In case of treatment termination will occur <21 days (Section 5.3.2), patient will undergo the assessment planned as per day 21.

If hospital discharge will occur before day 28, in-person visits will be planned at day 14±2 and 28±2 (depending on the discharge time point), as the preferred modality to obtain both safety laboratory tests and clinical data (NEWS and NIAID-OS). However, restrictions during the pandemic may limit outpatient visits due to hospital restrictions and travel limitations. If so, phone visit will be performed also at day 14±2 and 28±2 to assess NIAID-OS only.

6.1.4 90-day and 180-d follow-up

After discharge from hospital, subjects will be contacted for a follow-up check on their health status at Day 90 and day 180 by interview via a telephone call (or other telecommunication networks), unless the patient also withdraws the consent to the follow-up. In some cases, health registry may be also used.

The following measurements/assessments will be performed by phone at day 90±7 and 180 ±14 days:

- EQ-5D-5L questionnaire
- re-hospitalization, all-cause mortality. If re-hospitalization, duration of IMV and/or ECMO, ICU admission and ICU length of stay, hospital discharge and hospital length of stay
- Occurrence of any AE or SAE

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

6.2. EARLY PATIENT WITHDRAWAL

6.2.1. Withdrawal criteria

Patients will be informed that they have the right to withdraw from the study at any time (withdrawal of consent), without prejudice to their medical care, and are not obliged to state their reasons.

The primary, actual, reason of withdrawal should be recorded, especially if there is suspect of withdrawal due to adverse events ("withdrawal of consent" is a definition to be used if the patient does not give reasons). Safety laboratory tests should be performed whenever possible at patient withdrawal.

Patients who discontinue the treatment with the IMP (Section 5.3.2) will not be withdrawn from the study but will be asked to complete observations as per the protocol, unless otherwise they withdraw their consent. It is important that any randomized patient remains in the study and is followed for both efficacy and safety outcomes, regardless he/she has completed or discontinued the study treatment.

Investigators will be trained about the importance of patient retention through the duration of the trial.

In case of pregnancy, the patient will be withdrawn from the study, but she will be monitored for safety and pregnancy outcomes, unless she withdraws her consent.

Any withdrawals must be fully documented in the eCRF.

6.2.2. Replacement procedures

There are no plans to replace discontinued subjects.

6.3. END OF STUDY

For the purpose of this trial, the End of Study is defined as the date of the last assessment of the last patient.

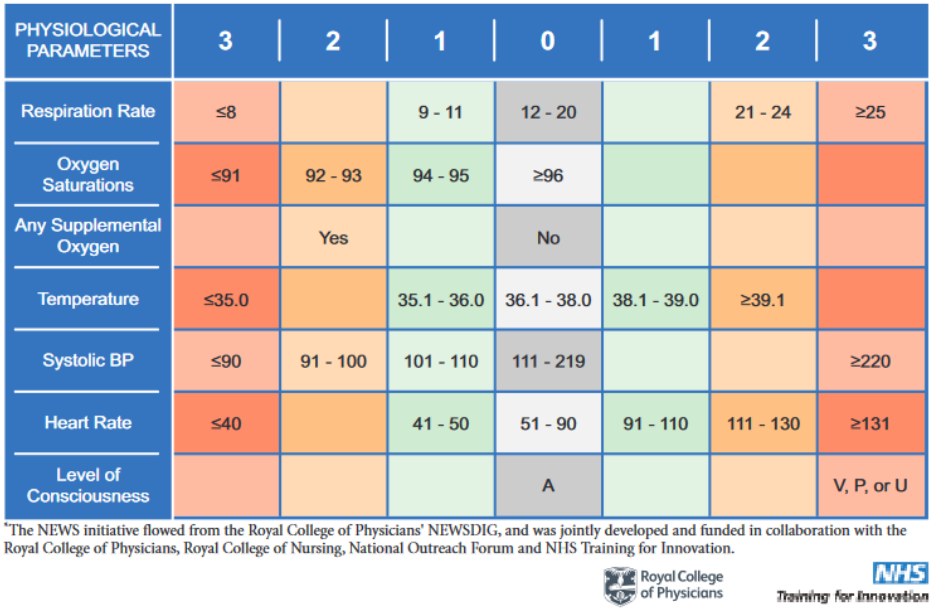
6.4. PATIENT MANAGEMENT AFTER STUDY COMPLETION OR TERMINATION

After completion of the 180-day assessment or at study termination (for any other reason), patients will receive post-study care as prescribed by their non-study health care provider. No post-study or post study-termination treatment will be provided by the study team or Dompé.

6.5 Assessments and clinical definitions

Assessment type	Parameters to be analyzed (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); - self-reported race/ethnicity (Black / African American, White, Asian, Hispanic / Latino, multiple / other) - height (cm), also self-reported; - body weight (kg)
Medical history	- all relevant past and ongoing diseases and surgeries - allergy, with a particular focus on IMP-related allergy/intolerance - past (no / yes) or current tobacco use (no / yes, < or ≥ 10 cigarettes daily) - past (no / yes) or current alcohol consumption (no / yes, < or ≥ one litre of wine daily, or equivalent) - recent test for influenza (no / yes, positive / negative) - vaccination for COVID-19 (no / yes: number of doses) - vaccination for influenza (no / yes: number of doses) - date of onset of COVID-19/CAP signs and symptoms

<table>
<tr><td></td><td>- date of hospital/ED admission
- disease specific clinical information (including elements of inclusion criterion 3)</td></tr>
<tr><td>Chest imaging</td><td>Chest X-ray/CCI lung US will be reviewed
Findings to be recorded (multiple answers allowed):
• consolidation
• ground-glass opacities
• Air bronchograms
• Pleural and Interlobular septal thickening
• Other finding(s):_____</td></tr>
<tr><td>NIAID-OS</td><td>
<table>
<tr><th>Score</th><th>Patient State Descriptor</th></tr>
<tr><td>OS 1</td><td>Not hospitalized, no limitations on activities</td></tr>
<tr><td>OS 2</td><td>Not hospitalized, limitation on activities and/or requiring home oxygen</td></tr>
<tr><td>OS 3</td><td>Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care</td></tr>
<tr><td>OS 4</td><td>Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care</td></tr>
<tr><td>OS 5</td><td>Hospitalized, requiring supplemental oxygen</td></tr>
<tr><td>OS 6</td><td>Hospitalized, on non-invasive ventilation or high-flow oxygen devices</td></tr>
<tr><td>OS 7</td><td>Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)</td></tr>
<tr><td>OS 8</td><td>Death</td></tr>
</table>
NIAID-OS=National Institute of Allergy and Infectious Disease Ordinal Scale.
Lancet Respir Med. 2021 Dec; 9(12): 1407–1418
</td></tr>
<tr><td>PSI</td><td>
<table>
<tr><th>Patient Characteristics</th><th>Points</th></tr>
<tr><td>Demographics</td><td></td></tr>
<tr><td>Age(years): Male: age</td><td>—</td></tr>
<tr><td>Female: age</td><td>—</td></tr>
<tr><td>Nursing home resident</td><td>+10</td></tr>
<tr><td>Co-morbidities</td><td></td></tr>
<tr><td>Neoplastic disease</td><td>+30</td></tr>
<tr><td>Liver disease</td><td>+20</td></tr>
<tr><td>Congestive heart failure</td><td>+10</td></tr>
<tr><td>Cerebrovascular disease</td><td>+10</td></tr>
<tr><td>Renal disease</td><td>+10</td></tr>
<tr><td>Examination findings</td><td></td></tr>
<tr><td>Altered mental status</td><td>+20</td></tr>
<tr><td>Respiratory rate ³30/minute</td><td>+20</td></tr>
<tr><td>Systolic blood pressure <90 mmHg</td><td>+20</td></tr>
<tr><td>Temperature <35°C or ³40°C</td><td>+15</td></tr>
<tr><td>Pulse ³125/minute</td><td>+10</td></tr>
<tr><td>Laboratory findings</td><td></td></tr>
<tr><td>pH <7.35 (do ABG only if hypoxic or COPD)</td><td>+30</td></tr>
<tr><td>BUN >10.7 mmol/ L</td><td>+20</td></tr>
<tr><td>Sodium <130 mEq/L</td><td>+20</td></tr>
<tr><td>Glucose ³13.9 mmol/L</td><td>+10</td></tr>
<tr><td>Hematocrit <0.30</td><td>+10</td></tr>
<tr><td>PaO_2 <60mmHg or oxygen saturation <90%</td><td>+10</td></tr>
<tr><td>Pleural effusion</td><td>+30</td></tr>
</table>
</td></tr>
<tr><td>NEWS</td><td>National Early Warning Score (NEWS)</td></tr>
</table>

	 *Royal College of Physicians. National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS. Report of a working party. London: RCP, 2012*
Safety Laboratory Tests	Hematology • RBC count (n x10^6/µL), haematocrit (%), haemoglobin (g/dL) • WBC count and differential count: neutrophils, eosinophils, basophils, monocytes, lymphocytes (n x10^3/µL) • platelets count (n x10^3/µL) Biochemistry • albumin (mmol/L or g/dL) • AST (nkat/L or U/L) • ALT (nkat/L or U/L) • total and direct bilirubin (e.g., nkat/L or U/L) • creatinine (µmol/L or mg/dL) • estimated Glomerular Filtration Rate (eGFR; MDRD formula, ml/min/1.73m^2) GFR (MDRD) = 175 × Serum Cr $^{-1.154}$ × age$^{-0.203}$ × (0.742, if female) × (1.212, if black) • INR (units) • serum glucose (mmol/L or mg/dL); specify if fasting or fed • sodium (mmol/L or mEq/L), potassium (mmol/L or mEq/L), chloride (mmol/L or mEq/L), calcium (mmol/L or mg/dL) • albumin (mmol/L or g/dL) (units may change as per local lab standard)
Inflammatory markers	• C-reactive protein (hs-CRP or CRP; nmol/L or mg/L), • ferritin (nmol/L or ng/mL) • D-dimer • LDH (nkat/L or U/L) • PCT
Prior and 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.

	Specific anti-COVID-19 and anti-CAP therapy may include anti-infective medications, and authorized or off-label medications, such as glucocorticoids, baricitinib and JAK inhibitors, remdesivir, tocilizumab, other interleukin inhibitors.
Vital signs	- systolic / diastolic blood pressure (BP; mmHg); - heart rate (HR; b/min) - respiratory rate (RR; n/min) - BP and HR measurements to be done with an electronic automated device, with the patient resting for at least 5 minutes
Lung function	- peripheral arterial oxygen saturation (SpO_2; %) - arterial partial pressure of oxygen (PaO_2; mmHg) - fraction of inspiration O_2 (FiO_2; 0.21 to 1) - PaO_2/FiO_2 (mmHg), SpO2 may be used in place of FiO2 if ABG not available , (see appendix 14.4.6)
Cytokines	Panel of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 (in selected centers)
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)
IMV/ECMO	- endotracheal intubation - tracheostomy tube - Extracorporeal Membrane Oxygenation (ECMO) Duration of any invasive mechanical ventilation or ECMO to be recorded (days)
ECG	ECG after the subject has been lying quietly for 5 minutes. The following to be recorded: - overall assessment for the presence of alterations (no / yes), - presence of: arrhythmia, conduction abnormalities; ST-segment elevation / depression; T-wave alterations; - HR (b/min) - PQ interval (msec); - QT/QTc (Bazett formula; msec) Clinically significant abnormalities should be marked in the ECG-CRF (no / yes, specify) and also reported as an AE

7. STUDY ENDPOINTS

7.1. EFFICACY ENDPOINTS

Primary endpoint: The primary study endpoint is the proportion of patients dead or requiring IMV (or ECMO) by day 28.

Key secondary endpoints:

The following key secondary endpoints will be considered:

1. All-cause mortality at day 180
2. Proportion of patients alive and discharged at day 28
3. Ventilatory-free days (VFD) at day 28
    - Number of days from Day 0 to Day 28 when the patient will alive and free of invasive ventilation. In case of multiple periods of IMV during the first 28 days, the total duration of ventilation considered all periods of ventilation during the index admission. Patients who will die within 28 days or will be still on invasive ventilation after 28 days will score zero VFDs[18].
4. Occurrence of IMV (or ECMO) by day 28
5. Length of primary hospital stay

Other secondary endpoints:

In addition, the following secondary endpoints will be assessed:

- Clinical failure by day 3 and day 7
    - Clinical failure will be defined as the occurrence of IMV/ECMO or vasopressor, or death
- 28-day ICU-free days
- Days free of IMV/ECMO (number of days with NIAID-OS 1-6) at day 28
- Duration of antibiotic therapy (days) at day 28
- Hospital free days [timeframe: day 28]
- Proportion of patients recovered (downward shift from screening of ≤2 points on the NIAID-OS or live discharge from hospital) [timeframe: day 3, 7±1, 14±2, 21±2, 28 ±2 or at hospital discharge]
- Proportion of patients worsening (upward shift from screening of at least ≥1 point of the NIAID-OS) [timeframe: day 3, 7±1, 14±2, 21±2, 28 ±2 or at hospital discharge]
- PO_2/FiO_2 [timeframe: day 3, 7±1, 14±2, 21±2, 28 ±2 or at hospital discharge]
- All-cause mortality [day 28, and 90]
- Hospital re-admission by day 90 and 180
- Time to discharge or to a NEWS of ≤ 2 (for 24 hours), whichever occurs first [timeframe: day 28]
- Change in inflammatory markers (LDH, CRP, ferritin; D-dimer, PCT) and cytokines [at day 3, 7±1, 14±2, 21±2, 28±2 or at hospital discharge]
- Change in quality of life using EQ-5D-5L [90±7 and 180±14 days]
- duration of IMV and/or ECMO at 90 and 180d
- ICU admission and ICU length of stay at 90 and 180d
- hospital length of stay at 90 and 180d
- occurrence of infections at 90 and 180d

CC [redacted]

[redacted]

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

7.3. SAFETY ENDPOINTS

- BP and HR [timeframe: baseline and day 3, 7±1, 14±2, 21±2, 28±2 or at hospital discharge]
- Haematology (RBC, haematocrit, haemoglobin, WBC, neutrophils and lymphocytes absolute count, platelets count) and biochemistry (sodium, potassium, chloride, calcium, glucose, creatinine, eGFR albumin, AST, ALT, total and direct bilirubin) [Timeframe: day 3, 7±1, 14±2, 21±2, 28±2 or at hospital discharge];
- ECG [baseline - end of treatment]
- Incidence of lung bacterial and/or fungal infections (that does not appear to be incubating at the time of inclusion, confirmed microbiologically) by day 28
- Incidence of TEAEs and Treatment Emergent Serious Adverse Events (TESAEs) [Timeframe: from the beginning of IMP administration up to the end of study participation]

7.4 PHARMACOKINETIC ENDPOINT

Serum concentration of reparixin (bind and free) CCI [redacted]

8. ADVERSE EVENTS

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 unfavorable 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 event, which is reasonably likely to have been caused by the IMP. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. For the purposes of IND safety reporting in the U.S., "reasonable possibility" means there are facts (evidence) or arguments to suggest a causal relationship between the drug and the adverse event.

Serious Adverse Event/Reaction

A Serious Adverse Event **(**SAE**)**/Reaction 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, diarrhoea, influenza, or accidental trauma (e.g., sprained ankle, back pain) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- is a congenital anomaly/birth defect
- is a 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.

NOTE: 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.

Pre-planned hospitalization or hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition are not considered to be serious events. These events must be recorded in the AE section (except for hospitalization for study procedures) of the eCRF where a variable will be ticked to indicate that they are not SAEs.

Death shall always be reported as SAE, and 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). 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.

According to the Investigator Brochure (Reference to Safety Information, section 6.4), for the purpose of this study, considering that current early clinical development status in the indication investigated, where each adverse event has to be carefully evaluated, no Serious Adverse Reaction will be considered expected by the sponsor for the purpose of expedited reporting of SUSARs and the identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the DSUR for the IMP.

Suspected serious unexpected adverse reaction

A suspected serious unexpected adverse reaction (SUSAR) 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

Following study informed consent form signature, after the patient has had the opportunity to spontaneously mention any problem, the Investigator or appropriate designee should inquire/monitor daily about the occurrence of an AEs.

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 patient's medical health. Changes in any protocol-specific systemic parameter evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

8.3. RECORDING OF ADVERSE EVENTS

All AEs (serious and non-serious) which occur from signature of the informed consent through patient participation in the study (last planned visit or early withdrawal date) will be collected and recorded in the eCRF. It is important that the AE dedicated section of the eCRF includes the duration of the AE (onset/resolution dates), the relationship to the drug, the severity, the outcome, the action(s) taken and relevant concomitant treatments dispensed. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event.

All AEs should be followed-up to determine the 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 assure that the patients experiencing an AE receive definite treatment for any AE, if required.

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

Worsening of an already recorded Adverse Event shall be reported as a new AE, filling in the relevant AE page in the CRF, with the new information, including the onset date and action taken.

8.3.1. Follow-up of patients with AEs

The Investigator is responsible for adequate and safe medical care of patients 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 assure that the patients experiencing AEs receive definite treatment for any AE, if required.

If patient's conditions worsen due to a SAE, the Investigator will provide supporting documentation, as well as results of any relevant laboratory tests and redacted section of medical records may be provided to the Sponsor and/or delegate, if relevant for the SAE. 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 Sections 8.4, 8.5).

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. patient or Investigator is unable to provide additional information, or the patient is lost to follow up), unless patient has withdrawn his/her consent.

8.3.2. Relationship of AEs to the Investigational Medicinal Product

The Investigator will assess the causal relationship between the AE and the IMP (either reparixin or placebo), according to the criteria in the Table below:

Relationship of the AEs to the IMP

None (Intercurrent Event)	An event that is not and cannot be related to the Investigational Product, e.g. a surgical intervention for nevus removal performed during the study, but planned before patient enrolment into the study
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

Any AE reported in the study having a possible, probable or highly probable relationship to the study drug will be considered as an ADR. On the other hand, AEs marked with relationship none or unlikely, will not be considered as ADR.

8.3.3. Severity of adverse events

The Investigator will grade the severity of any AE using the definitions in the Table below. For each episode, the highest severity grade attained should be reported.

Severity of the Adverse Event

Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

8.4. SERIOUS ADVERSE EVENT REPORTING

8.4.1. Reporting Procedure for the Investigator to Dompé/CRO

The Principal Investigator must report all SAEs occurring during patient participation in the study, regardless of presumed causal relationship, to the appropriate Sponsor/CRO Pharmacovigilance contact by e-mail (preferred) or fax **within 24 hours** of learning of the event. Contact details for SAE reporting by the Investigator are provided in the section "Contact Information" (See Page 2 of this Protocol).

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.

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 of withdrawal), the SAE should be reported by the Investigator to the appropriate Pharmacovigilance or directly to the Dompé Global Pharmacovigilance, Safety and Surveillance Department, should the whole study have been ended. Such "post-study cases" should be regarded for expedited reporting purposes 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.

Information on SAEs will be recorded on a specific SAE form. Both electronic and blank paper copies will be included in the Investigator's Site File. Follow-up reports (as many as required) should be completed and e-mailed/faxed following the same procedure above.

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.

8.4.2. Conditions that should not be reported as serious adverse events

- Not applicable.

8.4.3. 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.

8.4.4. Reporting Procedure to IEC and to Regulatory Authorities in the European Union

Reporting of Suspected Unexpected Serious Adverse Reaction

The Investigator must report all SAEs to the Sponsor/CRO immediately, within 24 hours (see Section 8.4.1).

Dompé Global Pharmacovigilance, Safety and Surveillance Department, with the support of the CRO as appropriate, shall report any SUSAR to the concerned IEC which approved the protocol and the Regulatory Authority (via the Eudravigilance Clinical Trial module) 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 event is neither fatal nor life threatening.

Treatment will be unblinded by Dompé Global Pharmacovigilance, Safety and Surveillance Department prior to regulatory submission of a SUSAR to Regulatory Authorities and IEC, and only cases referred to active treatment will be considered expeditable for regulatory reporting, in line with law requirements.

If the results of an investigation show that an AE not initially determined to be reportable is reclassified as reportable, Dompé shall notify such SUSAR in a written safety report as soon as possible, but in no event later than 7/15 calendar days after the determination is made.

Copies of all correspondence relating to reporting of any SAEs to the IEC should be maintained in the Investigator's Files.

Periodical Reporting to EU Regulatory Authorities and Investigators

Dompé Global Pharmacovigilance, Safety and Surveillance Department will prepare and submit (via the CRO as applicable) to Investigators appropriate periodical safety updates as per applicable EU and local requirements and regulations. Dompé Global Pharmacovigilance, Safety and Surveillance Department shall also be responsible to prepare and submit annual safety reports (Development Safety Update Report – DSUR) to relevant Regulatory Authorities and to IECs

8.4.5. Reporting Procedures to IRB and to the FDA in the United States

Reporting of Suspected Unexpected Serious Adverse Reaction

The Investigator must report all SAEs to the Sponsor/CRO immediately, within 24 hours (see Section 8.4.1).

In line with provisions set forth in 21CFR312, Dompé Global Pharmacovigilance, Safety and Surveillance Department, with the support of the CRO as appropriate, shall notify the Investigators and the FDA in an IND safety report of any SUSAR and of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case 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 event is neither fatal nor life threatening.

The Investigators in turn shall notify their IRB. Investigators are required to promptly report "to the IRB all unanticipated problems involving risk to human patients or others," including adverse events that should be considered unanticipated problems (21 CFR 312.66).

Treatment will be unblinded by Dompé Global Pharmacovigilance, Safety and Surveillance Department prior to regulatory submission of a SUSAR to FDA and IRB and only cases referred to active treatment will be considered expeditable for regulatory reporting, in line with law requirements.

The blind should ordinarily be broken for IND safety reports submitted to FDA and all participating investigators. If the results of an investigation show that an AE not initially determined to be reportable is reclassified as reportable, Dompé Global Pharmacovigilance, Safety and Surveillance Department shall notify such SUSAR in a written safety report as soon as possible, but in no event later than 7/15 calendar days after the determination is made.

Copies of all correspondence relating to reporting of any SAEs to the IRB should be maintained in the Investigator's Files.

Potential serious risks arising from clinical trials or any other source, to be reported to FDA and to the Investigators, include:

- any SUSAR. Dompé must report an adverse event as a suspected adverse reaction only if there is evidence to suggest to the Sponsor a causal relationship between the drug and the adverse event.
- findings from other studies that suggest a significant risk in humans exposed to the drug. Such a finding would result in a safety-related change in the overall conduct of the clinical investigation.

- findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- increased rate of occurrence of serious suspected adverse reactions.

Periodical Reporting to US Regulatory Authorities

Based on the specific Investigator's site requirements, Dompé Global Pharmacovigilance, Safety and Surveillance Department (via the CRO as applicable) will submit to IRBs and Investigators periodical safety updates, as per applicable local requirements and regulations.

Dompé Global Pharmacovigilance, Safety and Surveillance Department (via the CRO as applicable) shall also be responsible to prepare and submit annual safety reports (Development Safety Update Report – DSUR) to FDA and IRBs, as applicable.

8.5. EXPOSURE TO IMP DURING PREGNANCY

Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Prior to enrolment in the clinical trial, female patients of childbearing potential and their partners must be advised of the importance of avoiding pregnancy during the entire course of the study treatment and for the 30 days after the end of IMP administration and of the potential risks associated with an unintentional pregnancy. During the trial (treatment period or follow up period), female patients are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. In the same way, male patients who become aware that the partner might be pregnant, are to be instructed to contact the Investigator immediately.

The Investigator must report every pregnancy on a pregnancy report form as soon as possible (within 24 hours of learning of the pregnancy to the Pharmacovigilance Contacts specified in the section "Contact Information", even if no AE has occurred, and follow it to term. If, however, the pregnancy is associated with an SAE (e g, if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be filed as described in Section 8.6, with the appropriate serious criterion indicated on the SAE report form. Miscarriage, stillbirth and any malformation/disease must be reported as a SAE.

Any pregnancy leads to the immediate withdrawal of the study patient from the trial.

8.6. 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 eCRF, and the patient must be followed up until the resolution of the AE or as instructed by the medical expert.

8.7. OVERDOSE

Accidental or intentional overdose, which may or may not result in serious adverse reactions, is to be reported to CRO Pharmacovigilance, Dompé Global Pharmacovigilance, Safety and Surveillance Department and to Dompé Medical Expert, following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. This includes reports related to drug intake through different routes (e.g. ingestion) or with suicidal intentions and consequent drug overdose.

An overdose of reparixin is defined as the administration of 3 or more additional tablets on any given treatment day.

The Investigator shall provide in the SAE form information about symptoms, corrective treatment, and outcome of overdose. The Medical Expert should be contacted to discuss corrective treatment, if necessary.

9. STATISTICAL CONSIDERATIONS

9.1. SAMPLE SIZE

The sample size of the study is calculated based on results from the phase III randomized controlled trial CCI and literature on CAP. Considering a randomization ratio 1:1 (reparixin:placebo) and a one-sided alpha of 0.025, a total of 500 evaluable patients will allow to achieve an overall power of 90% to detect a group difference CCI in proportion of patients dead or requiring IMV (or ECMO) by day 28 in favour of reparixin, assuming that the proportion of patients dead or requiring IMV (or ECMO) in the placebo group by day 28 will be approximately CCI.

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 9.4. No additional multiplicity correction of alpha is required.

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

9.2. RANDOMIZATION

Enrolled patients will be randomized in a 1:1 ratio to either reparixin or placebo according to the stratified randomization list. Dropouts after randomization will not be replaced.

Randomization list will be stratified by disease severity (NIAID-OS 5 vs. NIAID-OS 6) and site to ensure balanced assignment across treatment groups. The stratified permuted block randomization list will be generated with a computer procedure by a CRO independent statistician not involved in the conduct of the study and will be provided to Dompé in a sealed envelope to prevent unblinding. The facility responsible of IMP packaging/labelling will also receive appropriate randomization codes for the purpose of IMP preparation.

Randomization will be performed through IRS. Each Patient Kit number will be randomly associated with a treatment group. Access to individual patient treatment code will be allowed only in the event of a medical emergency where the knowledge of patient treatment is required to provide the patient with appropriate care. The investigator and Dompé Pharmacovigilance will have access to the randomization code for a specific patient in case of a medical emergency or for safety reasons. Unblinding events will be recorded and reported in the Clinical Study Report (CSR). The treatment assignment information will be kept confidential and will not be disclosed to any other.

Once the study has been completed and the database has been locked, the treatment assignment information will be accessible to the study biostatistician(s) who will perform the statistical analyses and will generate reports.

9.3. OVERVIEW OF PLANNED STATISTICAL ANALYSIS

The study plans for the following statistical analyses:

- Interim analysis for efficacy or futility: this analysis will be conducted by an independent statistician when half of the planned evaluable patients has reached Day 28 or IMV/ECMO or an intercurrent event;
- 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.

9.4. INTERIM ANALYSIS

An interim analysis is planned when half of the planned evaluable patients has reached the primary endpoints at Day 28 (i.e., first 250 randomized patients who meet the FAS definition reaching Day 28 or primary endpoint definition) for identification of early superiority of reparixin (efficacy) or for early stop of the trial for futility.

O'Brien-Fleming's 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 the next table:

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

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

- Scenario 1: 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 shell continue up to the final analysis step, and treatments and follow-ups will proceed without modifications. Key first efficacy analysis and final analysis will be performed according to the rules described in section 9.3.
- Scenario 2: The communication will be "Superiority of Reparixin is shown". In this case, enrolment of subjects shell be stopped and considered completed. Already-enrolled subjects continue their residual treatment and follow-up as planned. Key first efficacy analysis and final analysis will be performed according to the rules described in section 9.3.
- Scenario 3: The communication will be "Superiority of Reparixin is excluded". In this case, the enrolment (if still ongoing) shell be stopped and all subjects will discontinue the treatment and will be followed-up until the next scheduled visit where they will be notified of the termination of the study. When database is closed, final analysis will be performed and the clinical study report will be written and released.

9.5. ANALYSIS POPULATION

The following populations will be defined:

- The Safety (SAF) population will consist of all randomized patients who received at least one dose of the IMP. SAF population will be analysed 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 IMP. FAS population will be analyzed according to the intention-to-treat (ITT) principle, i.e. by treatment allocation. The FAS population will be used for the primary analysis of the study and to present results on efficacy data.
- 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.

9.6. ESTIMANDS

9.6.1. Primary estimand

The primary estimand is defined by the following:

- *Population*: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- *Variable*: Patients dead or requiring IMV (or ECMO) by day 28.

- *Intercurrent event*: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of an intercurrent event. Retrieved dropouts will be used for data imputation of missing data.
- *Population-level summary*: Difference in proportion of patients dead or requiring IMV (or ECMO) by day 28.

9.6.2. Key secondary estimands

- Key secondary endpoint #1 (see section 7.1) will be analyzed according to the following estimand:

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

- Key secondary endpoint #2 (see section 7.1) will be analyzed according to the following estimand:

- *Population*: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- *Variable*: Patients alive and discharged at day 28.
- *Intercurrent event*: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of an intercurrent event. Retrieved dropouts will be used for data imputation of missing data.
- *Population-level summary*: Difference in proportion of patients alive and discharged at day 28.

- Key secondary endpoint #3 (see section 7.1) will be analyzed according to the following estimand:

- *Population*: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- *Variable*: Ventilatory free days up to day 28.
- *Intercurrent event*: The occurrence of an intercurrent event is irrelevant (Ventilatory free days definition already include death occurrence). All observed values will be used regardless of occurrence of an intercurrent event. Retrieved dropouts will be used for data imputation of missing data.
- *Population-level summary*: Difference in means of Ventilatory free days up to day 28.

- Key secondary endpoint #4 (see section 7.1) will be analyzed according to the following estimand:

- *Population*: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- *Variable*: Patients requiring IMV (or ECMO) by day 28.
- *Intercurrent event*: In case of death before day 28, an unfavorable value will be imputed to the secondary endpoint. Instead, the occurrence of other intercurrent events is irrelevant: all observed values will be used regardless of occurrence of these intercurrent events (retrieved dropouts will be used for data imputation of missing data).
- *Population-level summary*: Difference in proportion of patients requiring IMV (or ECMO) by day 28.

- Key secondary endpoint #5 (see section 7.1) will be analyzed according to the following estimand:

- *Population*: Adult patients hospitalized for CAP, as defined by the inclusion-exclusion criteria of the study.
- *Variable*: Length of hospital stay.

- *Intercurrent event*: In case of death before hospital discharge, an unfavorable value will be imputed to the secondary endpoint (hospital stay will be set as 28 days or date of death if later than 28 days). Instead, the occurrence of other intercurrent events is irrelevant: all observed values will be used regardless of occurrence of these intercurrent events (retrieved dropouts will be used for data imputation of missing data).
- *Population-level summary*: Difference in means of length of hospital stay (days).

9.7. STATISTICAL METHODOLOGY

Statistical analysis will be performed by the CRO appointed by Dompé.

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 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 (KM) 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. KM 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.

The significance level used for primary and key secondary analysis will be 0.025 one-sided. Unless otherwise specified, the significance level used for other 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 (SAP) 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.

9.7.1. Analysis of efficacy variables

9.7.1.1. Primary analysis

The following null hypothesis is defined: the proportion of patients dead or requiring Invasive Mechanical Ventilation (or ECMO) by day 28 in reparixin group is higher or equal than control:

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

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

where $T_{REPARIXIN}$ and $T_{CONTROL}$ are the proportions of patients dead or requiring Invasive Mechanical Ventilation (or ECMO) by day 28 for reparixin and control groups, respectively. The null hypothesis H_0 will be rejected, and superiority of reparixin declared if primary analysis p-value will be lower than pre-specified thresholds reported in section 9.4, depending at which analysis (interim or final) the test is performed.

Primary endpoint will be analyzed by means of logistic regression adjusting by pre-defined baseline factors (stratification factors, gender and presence of concomitant disease (yes, no)) 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 due to intercurrent events will be addressed by using multiple imputation based on retrieved dropouts information. Retrieved dropout patients are defined as patients who discontinue study treatment and decide to remain in the study by following the schedule of assessments and continuing to adhere to protocol requirements.

If not enough data was retrieved after study treatment discontinuation for assure the convergence of the MI-RD regression model (the final decision will be done at the time of the analysis and reported in the CSR), the same multiple imputation model will be fit using data from subjects of control group, washing-out the effect of treatment. This approach does not assume benefits for reparixin in case of discontinuation and limits a post-discontinuation clinical effect to that of placebo.

9.7.1.2. Sensitivity analysis

The following sensitivity analyses are defined to assess the robustness of results on primary endpoint versus assumptions used in the statistical model for the main estimator (additional analyses may be added in the SAP):

- The comparison between treatment and control will be performed in the FAS population by means of MI under MAR assumption instead of missing not at random (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-RD (or MI under wash-out approach), where the imputed values for the reparixin arm are shifted at a constant Δ to represent a worse effect in each iteration. The tipping points are the smallest Δs at which no statistical significance is shown ($p \geq 0.025$).

In addition, for supportive purposes the primary analysis described in previous section will be performed:

- by considering complete cases only (i.e. without considering patients with missing primary endpoint);
- on the PP set instead of FAS;
- by including in the logistic regression model further clinical relevant variables such as PSI, etiology, or other factors that may result imbalanced at baseline (for example specific comorbidities).

Details on sensitivity and supportive analyses will be provided in the SAP.

9.7.1.3. Secondary analyses

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 (see section 7.1).

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 #4 will be analyzed by means of a logistic regression model, while key secondary endpoints #3 and #5 by means of an ANOVA model. All models will include the covariates described in section 9.7.1.1.

In case of futility at interim analysis or in case of not rejection of null hypothesis, the above testing 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) may also be summarized for all post-baseline visits.

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[redacted]

9.7.3. Analysis of safety variables

TEAEs and TESAEs will be presented by treatment arms in terms of number of TEAEs and TESAEs and incidence by System Organ Class and Preferred Term using MedDRA. Analyses will be provided also by severity and relationship to the study drug.

Vital signs, laboratory, eGFR and ECG parameters will be summarised by treatment at each available timepoint by means of descriptive statistics.

9.7.4. Intermediate analyses for the DMC

Safety data will be reviewed on an ongoing basis by a Data Monitoring Committee (DMC). Full details of the activities and responsibilities of the DMC are provided in the study DMC Charter (see additional details in Section 12.5).

The DMC will give careful consideration to the appropriateness of trial continuation if there is emerging evidence that reparixin is harmful. Except for interim analysis (it will be involved in the evaluation of the interim analysis results and in the consequent decision on the continuation of the study), the DMC does not monitor primary endpoint for early efficacy termination, so no Type I error adjustment is necessary. Anyhow, access to unblinded information on the primary endpoint is allowed to balance patient safety risk against a possible gain in efficacy.

9.7.5. Specification of subgroups for analysis

In the presence of congruous numbers, subgroup analyses of primary and key secondary endpoints will be performed on the following subgroups defined by baseline characteristics:

- Age class (<40 yrs, 40 - 64 yrs, ≥ 65 yrs),
- Race,
- Ethnicity.

Statistical tests for interaction (between subgroup variable and treatment arm) will be performed before investigating further subgroups: analyses will be performed if interaction tests between treatment and variable is statistically significant at 15% nominal level. Variables that may be evaluated after test for interaction are:

- Region (EU, US, other),
- Clinical severity score (NIAID-OD 5 vs. NIAID-OD 6),
- Concomitant medication.

Statistical details and potential new subgroups definitions will be reported in the SAP.

9.7.6. 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 patient's participation for the full duration of the trial.

Details on how missing data will be handled in the primary analysis are reported in section 9.7.1.1.

10. ETHICAL CONSIDERATIONS

10.1. INDEPENDENT ETHICS COMMITTEE (IEC) / INSTITUTIONAL REVIEW BOARD (IRB)

It is the responsibility of the CRO appointed by Dompé or of the Study PI to obtain approval of the trial protocol/amendments from the appropriate IEC/IRB.

Prior to the initiation of the study, the followings will be submitted to the IEC/IRB for approval:

- the study protocol,
- the Informed Consent Form (ICF),
- the current version of the Investigator's Brochure,
- Investigator's current curriculum vitae (CV) as well as the current CVs of all key study personnel,
- Insurance certificate,
- any other IEC/IRB requested document(s).

A copy of the IRB approval will be sent to Dompé along with relevant correspondence with the IEC/IRB, a roster of IEC/IRB members or the US Department of Health and Human Services (DHHS) general assurance number.

The study will not be started until full written approval has been obtained from the appropriate IEC/IRB. The letter of approval should be dated, and should specify the type (e.g. protocol number) and the date of the documents which were reviewed and approved.

The CRO appointed by Dompé or the PI will submit any future amendment to the protocol to the IEC/IRB which granted the original approval. Any amendment will be implemented only when full approval has been obtained from the appropriate IEC/IRB, except for those amendments which involve only logistical or administrative aspects of the study.

The CRO appointed by Dompé or the PI will send to the IEC/IRB any updated Investigator's Brochure.

The CRO appointed by Dompé or the PI will also submit to the IEC/IRB which approved the protocol, at least annually, any required progress reports and study update, and will inform theIEC/ IRB of the termination of the study.

The CRO appointed by Dompé or the PI will report to the IEC/IRB any serious ADRs, life-threatening problems or deaths occurred at other sites participating to this clinical trial and/or in other clinical studies conducted with reparixin.

10.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with the protocol and current GCP, adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements (ICH E6, 45CFR46, and FDA 21CFR sections 11, 50, 56, 312).

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the IEC/IRB. Any amendments to the protocol or consent materials must also be approved before they are implemented.

10.3. PATIENT INFORMATION AND CONSENT

No study-related procedures (including non-invasive and diagnostic procedures) will be undertaken prior to completion of the consenting process.

Each potentially eligible patient will be informed of the study's objectives and overall requirements. The Investigator or delegate personnel according to site procedures, will explain the study fully to him/her using the ICF. Although patients will be informed that they can withdraw consent at any time, the Investigator will also emphasize that missing data diminish the scientific value of all patients' contributions. Similarly, patients will be informed that safety data might have to be collected after their participation in the study has been

completed. If the patient is willing to participate in the study, (s)he will be requested to give written informed consent after being given sufficient time to consider his/her participation and the opportunity to ask for further details.

The ICF will be signed and personally dated by **both** the patient and the Investigator or delegate personnel according to site procedures. A copy of the signed form will be provided to the patient, and the original signed ICF will be retained and filed in the Investigator Site File. Patient consent will be documented in the hospital records.

Individual (i.e. site specific; local language) ICFs will be provided to the site once approved by the IEC/IRB. Any changes requested by the */IEC/*IRB must be approved by Dompé prior to the documents being used.

10.4. CONFIDENTIALITY

All information obtained during the conduct of the study will be regarded as confidential. An agreement for disclosure will be obtained in writing by the patient and will be included in the ICF. Patient's data collected during (or after completion of) the study will be handled in accordance with applicable USA data protection laws, HIPAA regulations, and European data protection Regulation (EU) No. 679/2016 of the European Parliament and of the European Council regarding the protection of natural person's personal data and the free circulation of said data (hereinafter GDPR EU No. 679/2016) and according the standards of Good Clinical Practice.

On the eCRF patients will be identified ONLY by the assigned patient number. If patient names are included on copies of documents submitted to Dompé or the CRO appointed by Dompé, the names will be obliterated or masked and the assigned patient number added to the document.

The Investigator should keep a separate identification log for patients screened in the trial.

10.5. COMPENSATION FOR MEDICINE-INDUCED INJURY AND INDEMNIFICATION

Before the trial formally starts, Dompé will take out a study-specific insurance covering the amount requested by the respective national laws for patients/Investigators/Institutions participating in the clinical trial.

In case of questions about medical care, cost for medical care or insurance, patients can talk to their Investigator. Contact details will be given in the ICF.

Insurance and any updates will be provided to the Investigator before trial commencement for filing into the Investigator Site File.

11. DATA HANDLING AND RECORD-KEEPING

11.1. CASE REPORT FORM (CRF)

All data relating to the study will be recorded on Electronic CRFs (eCRF) to be provided by the CRO, through the EDC system. eCRF should not be made available in any form to third parties, except for authorized Dompé' designee or representatives of appropriate Health/Regulatory Authorities, without written permission from Dompé.

An eCRF is required and should be completed for each consented patient, regardless of actual enrolment. All entries must be written in English. Source documents should be available to support all the data recorded in the eCRF; location of source documents will be specified and listed at the centre Initiation Visit.

The eCRF must be available for review to designated Dompé's representatives at each scheduled monitoring/audit visit. The PI is responsible for verifying that all data entries in the eCRFs are accurate and correct. The PI must sign the completed eCRF before database lock and its submission to the Sponsor.

11.2. DATA MANAGEMENT

Data management will be performed by the CRO appointed by Dompé. Main Data Management activities and procedures will be accurately described in the DMP, created by the CRO and approved by Dompé.

Data collection will involve the use of an EDC system, to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by Sponsor/CRO Monitors, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol (following the Data Validation Plan). As a result of this monitoring and these checks, queries may be electronically issued to the study centers and electronically closed by those study centers. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the PI's approval of all changes performed on his or her patients' data, will be collected. Reconciliation of study data and SAEs between Clinical and Drug Safety database will be performed in ongoing basis and the before database lock. Procedure will be detailed in the DMP.

Encoding of specific data will be carried out. For this trial, Medical History, Adverse Events and Concomitant Medication will be coded; Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organisation (WHO)-DRUG Enhanced dictionaries will be used, version number of each dictionary will be documented in the DMP. Dictionary version numbers will not be changed during the study.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidances for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to Competent Authority and ICH requirements. All study records must be available for audit by Dompé, its authorized representatives, and Regulatory Inspection by Regulatory Authority.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary via an audit trail.

11.3. DOCUMENTATION REQUIRED PRIOR TO INITIATION OF, AND DURING THE STUDY

The following documents will be required from the Investigator prior to the initiation visit (and during the course of the study in case of any update):

- Current, signed and dated Curriculum Vitae of the PI any Sub-Investigators/coworkers. Updates should be provided at least every two years.
- Confidential disclosure agreement Form in accordance also with European data protection Regulation (EU) No. 679/2016 (GDPR)

- Normal ranges of all laboratory tests to be performed at the study site and a recent certification or accreditation of established quality control (or other documentation of established quality control or external quality assessment or other validation). Updates should be provided as soon as any reference value has changed.
- A signed page of the final clinical protocol and any amendments.
- IEC/IRB approval documentation, IEC/IRB-approved ICFs and study materials. Documentation of continuing IEC/IRB review and annual renewals.
- A signed copy of the study Financial Agreement/Clinical Study Agreement with Dompé (or CRO appointed by Dompé), including all study specific costs.
- List and any updates of delegated responsibility (Study Team Signature List / Delegation of Responsibilities form).
- FDA Form 1572 and financial disclosure form 3455 from all the persons listed on the 1572. If applicable, the PI will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study.

11.4 ESSENTIAL DOCUMENT RETENTION

The Investigator will retain copies of all the essential documents (as defined by ICH-GCP) until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by the applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these documents.

The essential documents include, but are not limited to: the signed protocol, copies of the completed eCRF, and Diary, signed Patient Informed Consent Forms from all patients who consented, hospital records and other source documents, and all other documentation included in the Investigator Site File and Pharmacy/Dispensing File.

The Investigator will inform Dompé (or designee) of the storage location of these essential documents and must contact Dompé before disposing of any. If the Investigator wishes to assign the files to someone else or to remove them to another location, he/she should consult with Dompé about this change.

Dompé will inform the Investigator in writing when these documents no longer need to be retained.

12 STUDY MANAGEMENT

The study will be performed in accordance with the protocol, the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, October 2013) and ICH Harmonised Tripartite Guideline for Good Clinical Practice (*ICH-GCP*) and any local regulations.

12.1 REGULATORY BODY OF APPROVAL

The CRO appointed by Dompé will obtain the necessary approval from the Competent Authorities, as needed, prior to initiation of the study. In the US, Dompé or other consultant appointed by Dompé will submit to the FDA this protocol as "new protocol" under IND 150182, according to 21 CFR Part 312.30.

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.

12.2 MONITORING

Monitoring will be carried out by the monitor of the designated CRO.

The purpose of the monitoring is to verify that the rights and the wellbeing of the patient are protected, that the reported data are accurate, complete and verifiable from source documents and that the conduct of the trial complies with the currently approved protocol and any amendments, with ICH GCP, and with regulatory requirements.

Prior to study start, the Investigator will be informed of the anticipated frequency of the monitoring visits. (S)He will also receive a notification prior to each monitoring visit during the study. It is expected that the PI and/or his/her Sub-Investigator(s) and other appropriate staff will be available on the day of the visit to discuss study conduct and to cooperate with the sponsor representative to ensure that any problems detected during these monitoring visits are resolved.

12.3 ACCESS TO RECORD

The Investigator will allow designated Dompé representatives, including staff from the appointed CRO, and Regulatory/Ethics Bodies, to have direct access to the source documents to verify the data reported in the eCRF. Source documents are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary, via an audit trail.

All study records must be available for audit by Dompé, its authorized representatives, and Regulatory Inspection by Regulatory Authority.

12.4 AUDIT AND INSPECTION

In addition to the institutional IEC/IRB(s), audit activities will be performed by the Dompé Quality Assurance Unit or any other third party delegated by Dompé, as appropriate.

12.5 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established and will be responsible for safeguarding the interests of trial participants, and for enhancing the integrity and credibility of the trial. The DMC will assess the safety of the interventions during the trial and will monitor the overall conduct of the clinical trial. The DMC will provide recommendations to Dompé about stopping or continuing the trial on safety basis. The DMC will be involved in the evaluation of the interim analysis efficacy results and in the consequent decision on the continuation of the study.

The DMC will operate independently of Dompé, and its members will not have connections to Dompé except for the compensation to DMC members related to their activities.

The DMC will comprise at least three members. They will be a multidisciplinary group that will include:

- At least two Clinicians, expert in respiratory diseases, e.g. pulmonologists and/or intensivists and/or internal medicine physician, with extensive experience in the diagnosis and management of patients with COVID-19, mainly with a severe disease presentation to require hospitalization;
- A Biostatistician with substantial experience in the DMC process.

The DMC:

- Will review unblinded data. To this purpose, an Independent Statistician will liaise with the CRO statistician and will have access to those components of the database necessary to generate the reports to the DMC.
- Will be responsible for the ongoing review of safety data throughout the trial. Primary among the safety data that will be reviewed are Serious AEs.
- Will have also access to unblinded information on the primary analysis to enable the assessment of the acceptability of safety in the context of emerging evidence about efficacy.
- Will be advisory to Dompé and make recommendations to Dompé regarding the continuation of the trial and potential modifications to the design and conduct of the trial. These recommendations will be made in a manner to maintain confidentiality of emerging information about efficacy and safety, unless access to certain data is needed to enable Dompé to make decisions about the DMC recommendations. Dompé 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

All details of the conduct and responsibilities of the DMC will comply with Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees and will be described in the 'DMC Charter' to be finalized during the set-up phase of the study and prior to the initiation of treatment.

12.6 PROTOCOL AMENDMENTS

Changes to the Study Protocol will be implemented only when written amendments have been signed by all individuals who signed the Protocol.

Any amendment will be sent to the IEC/IRB and Competent Authority / FDA, as appropriate. No deviations from or changes to the protocol will be implemented without documented approval of an amendment from the IEC/IRB which granted the original approval, except where necessary to eliminate an immediate hazard(s) to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. The deviations from or changes to the protocol implemented to eliminate an immediate hazard to the trial patient and the proposed amendment, if appropriate, should be submitted to the IEC/IRB for review and approval as soon as possible.

Any other deviation from the protocol that has not been approved by Dompé and the IEC/IRB could result in a discontinuation from the study at the centre involved.

Any written amendment will be sent to all recipients of the protocol.

12.7. DISCONTINUATION OF THE STUDY

Dompé reserves the right to stop the study at any time on the basis of new information regarding safety or efficacy, or if study progress is unsatisfactory, or for other valid administrative reasons.

After such a decision is made, the Investigator must inform all relevant persons e.g. study staff, patients etc. within 2 weeks. All delivered study materials must be collected and all eCRF completed to the extent possible.

Study discontinuation will be notified to the IEC and Competent Authority/FDA within 15 days from decision. The Investigator will inform his/her IRB within the same timeframe.

12.8. PUBLICATIONS

As this study is part of a multicentre trial, publications derived from this study will be planned and agreed with the participating Study Investigators. Publications will include input from the Investigators, his/her colleagues, other investigators in this trial and Dompé personnel. Such input will be reflected in publication authorship. Criteria for selection of authors will be agreed. After the initial publication or one year after completion of the study, whichever occurs first, an Investigator and/or his/her colleagues may publish the results of Investigator's part of the study independently.

Any manuscript, abstract or other publication or presentation of results or information arising in connection with the study must be prepared in conjunction with Dompé and must be submitted to the Dompé for review and comment at least 45 days prior to submission for publication or presentation. The Sponsor reviews proposed manuscripts prior to submission within a reasonable period (30-90 business days in relation with the complexity of the work). If such draft contains confidential patentable information, the Investigator will refrain from publishing any such information for a period not exceeding 180 days, to enable Dompé to file for the protection of any intellectual or proprietary property interest.

The Sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the Investigator publishing in peer reviewed journals; presenting results at scientific congresses; and posting information and results on internet-based public registers and databases.

In any case, study results will be communicated in full to the Competent/authority/FDA by the submission of a complete CSR.

The Investigator(s) will also be provided by the Sponsor with the CSR 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 a data could, in some circumstances, prevents or negatively impacts patentability.

13. REFERENCES

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14. APPENDICES

14.1. APPENDIX 1 - SPONSOR APPROVAL PAGE

Medical Expert: PPD

Clinical Operation Manager: PPD

Development Director PPD

14.2. APPENDIX 2 - INVESTIGATOR'S SIGNATURE PAGE

Investigator's Statement

I have read study protocol REP0321 *(Reparixin 1200 mg three times a day as add-on therapy to standard of care to limit disease progression in hospitalised adult patients with COVID-19* and other community-acquired pneumonia. *A multinational, multicentre, randomised, double-blinded, placebo-controlled, parallel-group phase III trial (REPAVID-22*) and agree to conduct the study as outlined in the protocol, and in accordance with the Declaration of Helsinki, ICH-GCP and any local regulations, being responsible for personally supervise the study conduct and ensure study staff complies with protocol requirement.

Principal Investigator: Name (block letters) PPD

Signature: PPD Dat PPD

14.3. APPENDIX 3 - PACKAGING AND LABELING DETAILS

A Patient Kit will be prepared for each patient [redacted]

Sample label content is summarized below and will be adjusted to meet local regulatory requirements.

NOTE:

Patient Kit No. XXYY [redacted]

Patient No. _____ [redacted]

Investigator: _____ [redacted]

The following represent a template of the minimal details to be presented in labels.

Content of the Label for each Patient Kit

STUDY REP0321 **Sponsor Dompé farmaceutici s.p.a.; Via Santa Lucia 6, Milan – Italy**
Telephone: [redacted]

INVESTIGATOR: _____

PATIENT KIT No. XXYY **PATIENT No. _____**

INVESTIGATIONAL PRODUCT: reparixin (600 mg) or placebo oral tablets

CONTAINS: [redacted]

coded BATCH No. coded EXPIRY DATE mm/yyyy **DO NOT STORE AT >30°C**
DO NOT FREEZE

DIRECTIONS: Dispense the Patient Kit, [redacted]

For any questions, please contact <to be identified in the final label>

For clinical trial use only. Caution: New Drug-Limited by Federal law to investigational use.*

***For US labels only**

Content of the Label [redacted]

STUDY REP0321 **Sponsor Dompé farmaceutici s.p.a.; Via San Martino 12, Milan – Italy**
INVESTIGATOR: _____

PATIENT KIT No. XXYY **PATIENT No.**

INVESTIGATIONAL PRODUCT: reparixin (600 mg) or placebo oral tablets

CONTAINS: [redacted]

coded BATCH No. coded EXPIRY DATE mm/yyyy **DO NOT STORE AT >30°C**
DO NOT FREEZE

DIRECTIONS: Take the drug three times a day, 2 tablets for each administration (2 tablets at a time about [redacted]).

For clinical trial use only.

Caution: New Drug-Limited by Federal law to investigational use*

***for US label only**

14.4. METHODOLOGICAL DETAILS

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

COVID-19 disease severity score will be evaluated according to the following scale[19]

NIAID-OS (National Institute of Allergy and Infectious Disease Ordinal Scale)	
SCORE	**Descriptor**
OS 1	Not hospitalized, no limitations on activities
OS 2	Not hospitalized, limitation on activities and/or requiring home O2
OS 3	Hospitalized, no supplemental O2 – no longer requires ongoing medical care
OS 4	Hospitalized, no supplemental O2 – requiring ongoing medical care
OS 5	Hospitalized, requiring supplemental O2
OS 6	Hospitalized, on non-invasive ventilation or high-flow oxygen devices
OS 7	Hospitalized, on invasive mechanical ventilation or ECMO
OS 8	Death

14.4.2. Calculation of eGFR

Renal function will be evaluated by estimated Glomerular Filtration Rate (eGFR), calculated using the Modification of Diet in Renal Disease study equation (MDRD) as per the following formula:

$$Estimated\_GFR = Creatinine\_assay * Serum\_creatinine^{-1.154} * Age^{-0.203} * Sex * Race$$

Levey AS et al. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000; 11: A0828

14.4.3. Handling of samples for assays

Local laboratories will be involved for the assay haematology/biochemistry (Safety Laboratory Tests) and inflammatory markers (LDH, CRP, ferritin, D-dimer, PCT and cytokines).

All steps will be tracked to ensure correct data reporting.

All samples submitted to these labs will be destroyed after the CSR has been issued or after the patient has withdrawn his/her consent.

14.4.4 National Early Warning Score (NEWS)

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

*The NEWS initiative flowed from the Royal College of Physicians' NEWSDIG, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation.

Royal College of Physicians NHS Training for Innovation

Royal College of Physicians. National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS. Report of a working party. London: RCP, 2012

14.4.5. Pneumonia Severity Index (PSI)

Patient Characteristics	Points
Demographics	
Age(years): Male: age	—
Female: age	—
Nursing home resident	+10
Co-morbidities	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Examination findings	
Altered mental status	+20
Respiratory rate ³30/minute	+20
Systolic blood pressure <90 mmHg	+20
Temperature <35°C or ³40°C	+15
Pulse ³125/minute	+10
Laboratory findings	
pH <7.35 (do ABG only if hypoxic or COPD)	+30
BUN >10.7 mmol/ L	+20
Sodium <130 mEq/L	+20
Glucose ³13.9 mmol/L	+10
Hematocrit <0.30	+10
PaO_2 <60mmHg or oxygen saturation <90%	+10
Pleural effusion	+30

14.4.6 SpO_2/FiO_2 - PaO_2/FiO_2, and SpO_2 - PaO_2 conversion tables

FiO_2	SpO_2	P/F
30%	80%	147
	85%	170
	90%	150
	95%	200
	96%	287
	97%	320
40%	80%	110
	85%	127
	90%	150
	95%	198
	96%	215
	97%	240

FiO_2	SpO_2	P/F
50%	80%	88
	85%	102
	90%	120
	96%	172
	97%	192
	98%	224
60%	80%	73
	90%	100
	96%	143
	97%	160
	98%	187
	99%	242

FiO_2	SpO_2	P/F
70%	85%	73
	90%	86
	96%	123
	97%	137
	98%	160
	99%	207
80%	85%	64
	90%	75
	95%	99
	97%	120
	98%	140
	99%	181

SpO2 (%)	PaO2 (mmHg)
80	44
82	46
84	49
86	52
88	55
90	60
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Adapted from Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol Respir Environ Exerc Physiol. 1979 Mar;46(3):599-602