CLINICAL STUDY PROTOCOL

Protocol Title:	**An International Multicenter Randomized Double-blind Adaptive Placebo-controlled Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 with Standard Therapy in Patients with Severe SARS-CoV-2 Virus Infection (COVID-19)**
Protocol ID:	CL04041078
Date of the Report:	April 26, 2020
Protocol amendment No:	2
Date of Protocol amendment issue:	April 26, 2020
Protocol version:	Version 3.0
Name and address of the clinical study Sponsor:	R-Pharm International LLC, Russia Legal address and physical location: 123154, Russian Federation, Moscow, 19 Berzarina str., bldg. 1, floor 1, office V, room 9 TIN 7734406215 Phone: +7 (495) 956-79-37
Full name, position of persons authorized on behalf of the Sponsor to sign the protocol and amendments to the protocol:	Mikhail Samsonov, MD PhD. Chief Medical Officer, R-Pharm JSC Address: Moscow, Leninsky 111 bldg.1 Phone: +74 959 567 937 Email: samsonov@rpharm.ru
Full name, position, address and telephone number of the medical experts appointed by the Sponsor for this study:	Boris Berezhanskiy, Senior Medical Advisor of Medical Affairs Group, R-Farm JSC Address: 119421 Moscow, 111 Leninsky Prospekt bldg. 1 Phone: +7 (968) 776-81-37 Email: berezhanskiy@rpharm.ru

CONFIDENTIALITY STATEMENT

The confidential information in this document is provided to you as an Investigator, member of the applicable Institutional Review Board/Independent Ethics Committee or Heath Authority Officer. The acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from R-Pharm International, unless it is necessary to obtain the consent of patients to participate in the study.

These requirements come into force upon signing this protocol.

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SIGNATURE PAGE 1 (PRINCIPAL INVESTIGATOR)

to version No. 3.0 of April 26, 2020 of the protocol "An International Multicenter Randomized Double-blind Adaptive Placebo-controlled Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 with Standard Therapy in Patients with Severe SARS-CoV-2 Virus Infection (COVID-19)" (protocol number: CL04041078)

I, the undersigned, agree to the following:

1. I have completely reviewed the provisions of this protocol, accept them and undertake to conduct the study in accordance with this protocol, as well as in accordance with the requirements of the ICH GCP, the Helsinki Declaration, and the requirements of the national regulatory authorities of the participating countries.
2. I will not depart from the protocol without the prior written permission of the Sponsor, approved by the regulatory authorities and local ethics committees/IRBs of the participating countries unless it is necessary to prevent any immediate harm to the subject of the study.
3. I work with a team of qualified personnel, have the necessary equipment and enough time to conduct a study in accordance with this protocol.
4. I will make all my efforts to ensure that all personnel involved in the study are adequately familiar with this protocol and correctly fulfill their responsibilities during the study.
5. I agree with the audit and inspection procedures in accordance with the rules set by the Sponsor and state regulatory authorities.
6. I understand that the text of this protocol, as well as all other materials and the study results are confidential and are the property of the Sponsor. I undertake not to disclose them to third parties, except as otherwise provided by applicable laws of the participating countries.
7. I agree to comply with all other requirements regarding the responsibilities of clinical Investigators, as well as all other important requirements of Good Clinical Practice.

Principal Investigator:

_____
Signature

_____
Full name

_____
Date

SIGNATURE PAGE 2 (SPONSOR)

to version No. 3.0 of April 26, 2020 of the protocol "An International Multicenter Randomized Double-blind Adaptive Placebo-controlled Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 with Standard Therapy in Patients with Severe SARS-CoV-2 Virus Infection (COVID-19)" (protocol number: CL04041078)

I, the undersigned, approve the study protocol and undertake to conduct the study in accordance with all protocol requirements.

I hereby confirm that the protocol has been developed in accordance with the following standards:

- Ethical principles defined in the Helsinki Declaration.
- The International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP; document E6), current edition.
- All the applicable laws and regulatory documents, including (but not limited to) laws on data confidentiality, laws on disclosure of clinical study data, etc.

Authorized Sponsor Representative:
(according to the Power of Attorney No. 25 dated May 14, 2018 issued by R-Pharm International LLC)

_____
Signature

Mikhail Samsonov, MD PhD

_____
Date

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ARDS	Acute respiratory distress syndrome
ARVI	Acute respiratory viral infection
AST	Aspartate aminotransferase
CI	Confidence interval
CoV	Coronavirus
COVID	Coronavirus disease
CPAP	Constant positive airway pressure
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
EAEU	Eurasian Economic Union
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ESR	Erythrocyte sedimentation rate
EU	European Union
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GIT	Gastrointestinal tract
HCG	Human chorionic gonadotropin
HR	Heart rate
IC	Informed consent
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IL	Interleukin
INN	International nonproprietary name
ITT	Intent-to-treat population
mITT	Modified ITT
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
LFT	Liver function tests
LHD	Last day of hospitalization
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MoH	Ministry of Health
MV	Mechanical ventilation
NEWS	National Early Warning Score
OKZ	Olokizumab
OR	Odds ratio
PCR	Polymerase chain reaction
PE	Primary endpoint
PEEP	Positive end expiratory pressure
PI	Principal Investigator

RF	Russian Federation
RNA	Ribonucleic acid
RR	Relative risk; respiratory rate
SAE	Serious adverse event
SARS	Serious acute respiratory syndrome
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumour necrosis factor
ULN	Upper limit of normal
USA	United States of America
WHO	World Health Organization

DOCUMENT HISTORY

Rationale for Version 1.1:

- clarification of inclusion criterion No. 4; addition of information about the procedure for conducting a council of physicians; addition of information on effective methods and terms of contraception for patients; the description of the procedures for individual visits has been adjusted in accordance with the visit schedule table; addition of information on the assessment of available safety data by an Independent data monitoring committee.

The remaining changes/corrections were made to ensure the consistency of the protocol text, technical errors were corrected.

Rationale for Version 2.0, with Amendment 1 incorporated:

- based on the recommendations of the Ministry of Health of the Russian Federation, Version 2.0 was withdrawn and is not used; only the changes specified in Version 3.0 should be considered.

Rationale for Version 3.0 with Amendment 2 incorporated (all changes from Version 1.1 are indicated):

- Section 2. Study rationale was adjusted and updated;
- the study flow chart (Figure 2), the table with the schedule of study visits and procedures (Table 2) and the table of the specifics of laboratory tests (Table 3) were adjusted;
- the duration of the screening period and the treatment period of the study was clarified, the term “calendar day” used in the study was defined;
- it was allowed for the screening period to take into account results of laboratory tests, anthropometric data, and the patient’s medical history obtained outside the protocol before the screening period; the laboratory tests (complete blood count and blood chemistry tests) should be performed no earlier than 48 hours before randomization;
- the procedures for Visit 15 were specified depending on ongoing hospitalization or discharge on the Visit 15 day;
- the procedures for the end-of- study visit on Day 29 were specified;
- the procedures for a withdrawal visit were described;
- the inclusion criteria were clarified: criteria No. 3 and No. 5 were combined and adjusted as options for confirming the diagnosis of COVID-19; non-inclusion criterion No. 7 was added regarding the administration of plasma from COVID-19 convalescent donors; non-inclusion criteria No. 1, No. 8, No. 9 and No. 12 were adjusted;
- inaccuracies in the introductory information on the study therapy were corrected;
- the maximum dose of OKZ used in previous studies was clarified (regarding overdose of the drug);
- sections regarding the labeling of the primary and secondary packages of the study drugs were added;
- information was added about the possibility of subcutaneous injections of the study drugs into additional areas of the patient’s body used for subcutaneous injection;

- it was clarified that concomitant standard therapy of COVID-19 adopted at the institution may include drugs other than those indicated in the list of drugs prohibited during the study; examples of INNs from classes of prohibited drugs were provided;
- the administration of plasma from COVID-19 convalescent donors was added to the list of drugs prohibited during the study;
- tocilizumab and sarilumab were excluded from the list of prohibited drugs; instructions were given on the possible use of tocilizumab or sarilumab in the absence of improvement in the patient's condition by Investigator's discretion within 24 hours after the administration of one of the study drugs;
- information on the procedure for assigning numbers to study centers and screening numbers for patients was updated;
- Section 8.2.2. Medical Consilium was adjusted;
- the information that should be obtained when collecting the history of allergies and information about bad habits, medical history, previous and concomitant diseases, as well as data on previous and concomitant therapy, was described in detail;
- clarification was added that the physical examination procedures are optional and depend on the specifics of the organization of work with patients with the new coronavirus infection (for example, personal protective equipment, patient's position in the ICU, etc.);
- the assessment of the results of PCR analysis and their recording were described in detail;
- the procedure for evaluating chest CT results was described in detail;
- a definition of “response to treatment” was given for this protocol;
- the procedure for evaluating and recording the clinical status of a patient in intensive care was clarified;
- the correct current version of the NEWS2 scale was added;
- the contact details of the medical expert appointed by the Sponsor for this study, as well as of the responsible project manager, were corrected;
- the list of countries expected to take part in the study was updated;
- the statistical section was updated; the calculated newly planned sample size was indicated (the expected number of patients randomized in the pilot phase of the study and in total), the analytical methods were described; the mITT analysis population was introduced; information about the planned early analysis of the pilot phase of the study was updated.

The remaining changes/corrections were made to ensure the consistency of the protocol text, and technical errors were corrected.

CONTACT INFORMATION

Study Sponsor: R-PHARM INTERNATIONAL LLC

The study is conducted by: R-Farm JSC, 119421, Russia, Moscow, Leninsky Prospekt 111/1; +7 (495) 956-79-37

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EMERGENCY COMMUNICATION CONTACT

For medical advice in an emergency, please, contact Boris Berezhanskiy, the on-duty expert on medical issues:

Emergency contact number
+7 (968) 776-81-37

When reporting serious adverse events, the procedures described in Section 10.4 SAE reporting should be followed. Investigators should inform the Sponsor about the development of serious adverse events within 24 hours of first becoming aware of the event. The completed SAE notification form should be sent to the following number/ email address:

Contact information for SAE reporting (24-hour)

Fax: +7 (495) 956-79-38

Safety@Rpharm.ru

Full name and positions of Investigators responsible for conducting the study with addresses and phone numbers of the clinical (study) sites

The list of study sites involved in this clinical study (name, address and telephone number of each study site) is presented in a separate List of Study Sites and Principal Investigators.

Names and addresses of clinical and other medical and/or technical services and/or organizations involved in the study

No.	Name of the institution	Study role:	Address of the institution	Phone, fax, email
1.	K-Research LLC	Applicable to the study in the Russian Federation: preparation of clinical study documents and biostatistics; clinical study monitoring	214019, Russia, Smolensk region, Smolensk, Marshal Konev passage, 29, building 43	Contact person: Julia Kramanovich, Phone: +7 (4812) 67-00-94; e-mail: julia.kramanovich @cromospharma.com
2.	Data Management 365 LLC	Applicable to the study in the Russian Federation: data management (access to the database, its configuration, adaptation, modification, validation, testing, maintenance; development of eCRF, randomization and drug management (IWRS)	197022, Russia, St. Petersburg, str. Vsevolod Vishnevsky, bldg. 12, letter A	Contact Person: Anna Polikarova Phone: +7 (812) 426-73-07 e-mail: anna.polikarova@datamanagement365.com

1. SYNOPSIS OF THE STUDY PROTOCOL CL04041078

Protocol ID:	CL04041078
Study title:	An International Multicenter Randomized Double-blind Adaptive Placebo-controlled Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 with Standard Therapy in Patients with Severe SARS-CoV-2 Virus Infection (COVID-19)
Clinical study phase:	II/III phase
Type of study:	interventional
Study Sponsor:	R-Pharm International LLC, Russia Legal address and actual address: 123154, Russian Federation, Moscow, 19 Berzarina str., bldg. 1, floor 1, office V, room 9 Phone: +7 (495) 956-79-37
Investigational drugs:	RPH-104, solution for subcutaneous injection, 40 mg/ml Olokizumab (OKZ), solution for subcutaneous injection, 160 mg/ml
Reference product:	Placebo
Study sites:	The study will be conducted in approximately 20 clinical sites of the Russian Federation. Study sites in the Republic of Belarus, Republic of Armenia, Georgia, Turkey, and EU countries are expected to open later. The list of study sites involved in this clinical study (name, address and telephone number of each study site) is presented in a separate List of Study Sites and Principal Investigators.
Study rationale	In December 2019, an outbreak of viral pneumonia of unknown etiology was detected by the public health authorities in Wuhan City, Hubei Province (China). Soon, coronavirus RNA was isolated from the cells of some patients. This newly discovered virus was named SARS-CoV-2, and the disease caused by this virus was named COVID-19. Severe COVID-19 may be complicated by the development of the life-threatening syndrome of a cytokine storm, with IL-1 and IL-6 playing a key role in the pathogenesis. There are currently no approved drugs for the treatment of COVID-19.
Study goal:	Evaluation of the efficacy and safety of RPH-104 (at a dose of 80 mg) or OKZ (at a dose of 64 mg) after a single administration compared with placebo in patients with severe SARS-CoV-2 virus infection (COVID-19)
Study objectives:	**Primary objective:** 1. To assess the efficacy of a single administration of RPH-104 (80 mg) or OKZ (64 mg) compared with placebo in patients with severe SARS-CoV-2 virus infection (COVID-19) on Day 15 of the study. **Secondary objectives:** 1. To evaluate the effect of a single administration of RPH-104 (80 mg) or OKZ (64 mg) compared with placebo on clinical status changes in patients with severe SARS-CoV-2 virus infection (COVID-19) during the study. 2. To compare mortality rates in the groups of single administration of RPH-104 (80 mg), OKZ (64 mg) or placebo in patients with severe SARS-CoV-2 virus infection (COVID-

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	19). 3. To compare the length of stay in the ICU, the duration of oxygen support and clinical parameters between the groups of single administration of RPH-104 (80 mg), OKZ (64 mg) or placebo in patients with severe SARS-CoV-2 virus infection (COVID -19) receiving the standard therapy. 4. To assess the safety of a single administration of RPH-104 (80 mg) or OKZ (64 mg) in patients with severe SARS-CoV-2 virus infection (COVID-19)
Study design:	This study is a multicenter randomized double-blind adaptive placebo-controlled clinical trial of phase II/III, evaluating the efficacy and safety of a single administration of RPH-104 80 mg or OKZ 64 mg compared with placebo (1: 1: 1) in patients with severe SARS-CoV-2 virus infection (COVID-19) receiving standard care. The study will consist of two phases: • the pilot phase: inclusion and randomization of the first 189 patients (63 patients in each group of OKZ, RPH-104, placebo), followed by an early analysis of efficacy and safety data, based on which the sample size will be finally defined; • the main phase is the further recruitment of patients and the conduct of all procedures prespecified in the protocol. After inclusion of a patient in the study (signing the Informed Consent Form or the decision of the Principal Investigator to enroll the patient following a recommendation of the medical consilium), the Investigator will assess the patient's condition to check whether the patient meets the eligibility criteria. Eligible patients will be randomized to one of three treatment groups for a single subcutaneous injection of RPH-104 80 mg or OKZ 64 mg or placebo. Next, a follow-up will be performed during the hospitalization period (Day 1 - Day 15 or the last day of hospitalization (LHD), whichever comes first). This is followed by a follow-up period from the LHD or Day 15 (whichever is earlier) until Day 29. Throughout the study, standard COVID-19 therapy accepted at the institution is allowed, except for drugs that are not allowed by this protocol throughout the study, as well as tocilizumab and sarilumab during the first 24 hours after administration of the study drugs. In the absence of improvement in the patient's condition, as judged by the Investigator, a single administration of tocilizumab or sarilumab is allowed 24 hours after the administration of one of the study drugs, in accordance with current recommendations. On Day 15, the primary endpoint of the study, response to treatment, is assessed. A response to treatment means an improvement in the clinical status of the patient by at least 1 point on the 6-point COVID-19 scale with no use of tocilizumab or sarilumab. The last study visit is the visit on Day 29. If the patient is discharged from the hospital before Day 15 or Day 29, the visit procedures will be performed via a telephone call.
Study schedule:	The study will include the following periods:

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	• **screening period** for no more than 48 hours before the sturt of the day of randomization (Day 1). During the screening period, an assessment is performed to determine whether the patient meets the eligibility criteria; • **treatment period** lasting from the end of screening (which is the start of Day 1) to 23:59 Day 1, including randomizing patients into treatment groups and then a single administration of the study drug; • **follow-up period** , lasting from 00:00 Day 2 - to 23:59 Day 29, including an assessment of the efficacy and safety after administration of a study drug.
The total duration of the study:	The total expected duration of the study for each patient will be not more than 31 days, including 48 hours of screening, 1 day of study drug administration and 28 days of observation.
Planned sample size:	Preliminary sample size: 372 randomized patients. The first phase of the study will include 189 patients (63 patients in each group of OKZ, RPH-104 or placebo). After analyzing the data of 189 patients, a decision will be made about the final sample size.
Population:	Male and female patients over the age of 18 years (inclusive) diagnosed with COVID-19 and hospitalized with a severe illness in the sites of the Russian Federation, Republic of Belarus, Republic of Armenia, Georgia, Turkey, and EU member states.
Inclusion criteria:	1. Male or female patient aged 18 years (inclusive) or older (at the beginning of the screening period). 2. The presence of a voluntarily signed and dated Patient Informed Consent Form for participation in this study, or a record of an Medical Consilium decision justifying patient's participation in case of patient is unable to state his/her will. 3. Having either of the following COVID-associated respiratory syndromes: • Pneumonia with oxygen saturation SpO2 ≤ 93% (on room air) or RR greater than 30/min; • ARDS (PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 315 if PaO2 is not available). 4. A diagnosis of COVID-19 based on: • Laboratory confirmed f SARS-CoV-2 infection as determined by PCR **OR** • Bilateral changes in the lungs characteristic of COVID-19 on chest CT.
Non-inclusion criteria	1. A history of hypersensitivity to the study drugs (RPH-104 and/or OKZ), and/or their components. 2. The presence of any of the following laboratory deviations: – absolute neutrophil count <0.5 x 10^9/l, – white blood cell count <2 x 10^9/l, – platelet count <50 x 10^9/l, – ALT and/or AST ≥ 3.0 x ULN.

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	3. Severe renal failure: creatinine clearance <30 ml/min. 4. Septic shock (vasopressors are required to maintain mean arterial pressure ≥65 mm Hg and lactate ≥ 2 mmol/L in the absence of hypovolemia). 5. The disease progresses to death over the next 24 hours, regardless of treatment, according to Investigator. 6. Perforation of the gastrointestinal tract, a history of diverticulitis 7. Administration of plasma from COVID-19 convalescent donors within 4 weeks before study enrollment and/or planned administration during the study. 8. Recent (less than 5 elimination half-lives) use of tocilizumab or sarilumab. 9. Recent (less than 5 elimination half-lives) or planned use during the study of: – biologics (except RPH-104 or OKZ) with immunosuppressive effect, including, but not limited to: IL-1 inhibitors (anakinra, rilonacept, canakinumab), IL-6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumor necrosis factor α (TNFα) inhibitors (infliximab, adalimumab, etanercept, etc.), anti-B-cell drugs, etc.; – other immunosuppressive drugs (with the exception of methotrexate in a dose of up to 25 mg/week), including, but not limited to: • high doses of glucocorticoids (equivalent to prednisolone > 1 mg/kg) orally or parenterally; • JAK kinase inhibitors; cyclophosphamide, etc. 10. Concurrent participation in another clinical trial. 11. Pregnancy, breastfeeding. 12. A history of active tuberculosis, or active tuberculosis suspected by the Investigator.
Concomitant therapy drugs:	Throughout the study, it is allowed to use standard COVID-19 therapy accepted at the institution, with the exception of drugs that are not allowed by this protocol throughout the study, as well as tocilizumab and sarilumab during the first 24 hours after administration of the study drugs. Tocilizumab or sarilumab at the doses recommended for the treatment of this disease may be added to concomitant therapy in the absence, in the Investigator's opinion, of improvement in the patient's condition within 24 hours after the administration of one of the study drugs.
Prohibited or not planned drugs:	The following medications are prohibited throughout the study: • immunosuppressive biologics (with the exception of RPH-104 or OKZ), including, but not limited to: IL-1 inhibitors (anakinra, rilonacept, canakinumab), IL-6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumor necrosis factor α

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	(TNFα) inhibitors (infliximab, adalimumab, etanercept, etc.), anti-B-cell drugs, etc.; • other immunosuppressors (with the exception of methotrexate in a dose of up to 25 mg/week), including, but not limited to: – high-dose glucocorticoids (> 1 mg / kg of prednisolone equivalent) orally or parenterally; – JAK inhibitors; cyclophosphamide and others; • administration of plasma from COVID-19 convalescent donors; • during the first 24 hours after the administration of the study drugs, the use of tocilizumab and sarilumab is prohibited.
Efficacy assessment	**Primary endpoint:** 1. Proportion of responders in each treatment group A responder is a patient who has not received tocilizumab or sarilumab and who has a clinical status improvement of ≥1 point on the 6-point COVID-19 scale (where 1 is the most favorable outcome and 6 is the most undesirable outcome) 15 days after the administration of the study drug. **Secondary Endpoints:** 1. Change over time in the clinical status of patients using a 6-point ordinal scale 2. The proportion of patients with an improvement in clinical status by 2 or more points on the 6-point ordinal scale during the study with no use of tocilizumab or sarilumab 3. The proportion of patients who received tocilizumab or sarilumab for COVID-19 during the follow-up period 4. Mortality during the follow-up period **Exploratory Endpoints:** 1. The proportion of patients with a score of ≤ 4 using the National Early Warning Score 2 (NEWS2) for 2 consecutive days; 2. The proportion of patients with a score of ≤ 2 using the National Early Warning Score 2 (NEWS2) for 2 consecutive days; 3. Time to reaching a NEWS2 score ≤ 4 for 2 consecutive days; 4. Time to reaching a NEWS2 score ≤ 2 for 2 consecutive days; 5. Change from baseline in the level of surrogate markers of the cytokine storm: leukocytes, lymphocytes, neutrophils, CRP, ferritin (if applicable), D-dimer (if applicable); 6. Mortality during an ICU stay, at study days 7, 15, 29; 7. Time to reaching SpO2≥94% without oxygen support, for 2 consecutive days; 8. Change from baseline in the oxygenation index of PaO2/FiO2 (if applicable) during hospitalization; 9. Duration of stay in ICU, in days; 10. Change from baseline in ARDS severity defined according to WHO criteria (if applicable);

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	11. Time to ARDS improvement according to the WHO criteria by one category compared to baseline (if applicable); 12. Duration of mechanical ventilation and/or ECMO (if applicable), in days; 13. Duration of oxygen support (if applicable), in days; 14. Time until resolution of fever, i. e. axillary body temperature <38 °C without the use of antipyretics for 2 consecutive days (if applicable); 15. Time to clinical status improvement by 1 point on the 6-point COVID-19 scale; 16. Time to clinical status improvement by 2 points on the 6-point COVID-19 scale; 17. The proportion of patients with a clinical status worsening by 1 point on the 6-point COVID-19 scale during the study (if applicable); 18. The proportion of patients with a clinical status worsening by 1 point on the 6-point COVID-19 scale during the study, excluding patients moving to category 6 (if applicable); 19. Time to a clinical status worsening by 1 point on the 6-point COVID-19 scale (if applicable).
Safety assessment:	**Endpoints for safety assessment:** 1. Incidence, severity, nature and outcomes of AEs (grades 4 and 5 according to CTCAE v.5.0) and SAEs during the study; 2. The proportion of patients with AEs (grades 4 and 5 according to CTCAE v.5.0) and SAEs; 3. Changes in physical examination findings, vital signs, and laboratory safety parameters during the study
Ethical and regulatory aspects:	The study will be conducted in full compliance with this protocol, the requirements of ICH GCP E6 R2, the principles of Good Clinical Practice of the EAEU, Russian National Standard P52379-2005 "Good Clinical Practice", Order 200н "On Approval of the Principles of Good Clinical Practice", ethical principles of the Helsinki Declaration, the latest revision, as well as current legislation and regulatory requirements of the participating countries
Statistical Methodology and Analysis Steps	**Justification of the planned sample size:** there are no reliable data on the course of COVID-19 disease and the distribution of hospitalized patients by the severity of the disease after receiving standard therapy and the study drugs. The study will include a pilot phase recruiting 63 patients in each treatment group. The final sample size will be determined based on analysis of the results of the pilot phase. If about 60% of patients enrolled in the study fall into category 4 on the clinical status scale ("Hospitalized, supplemental oxygen with independent breathing") and about 40% fall into category 5 ("Hospitalized, mechanical ventilation (invasive/non-invasive) or ECMO"), the estimated proportion of patients responding to treatment will be 40% in the placebo group and 60% in the active therapy groups. To demonstrate the superiority of any of the study drugs over placebo

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	with a statistical power of 80% and a general critical level of α = 2.5%, 372 patients will have to be randomized (taking into account 20% drop-out). **Efficacy analysis:** in this study, the proportion of patients responding to treatment in each of the therapy groups is the primary endpoint. A responder is a patient who has not received tocilizumab or sarilumab and who has a clinical status improvement of ≥1 point on the 6-point COVID-19 scale (where 1 is the most favorable outcome and 6 is the most undesirable outcome) 15 days after the administration of the study drug. To compare each of the active therapy groups with placebo relative risks [RR] with a bilateral 97.5% CI (the ratio of the probability of response in each of the active treatment groups to the probability of response in the placebo group) will be calculated by mathematical modeling methods. To test a superiority hypothesis for each of the active drugs compared with placebo, the null hypothesis RR ≤ 1 will be tested with a statistical power of 80% at a general critical level of α = 2.5% for each of the comparisons. **Safety analysis**: safety analysis will be performed by descriptive statistics methods in the safety population and the population of patients who received the study treatment and who did not receive tocilizumab or sarilumab; additionally, data from the subgroup of patients who received tocilizumab or sarilumab as part of standard therapy will be separately summarized and presented. The safety assessment will include the following parameters: • The frequency, severity, nature and outcome of AEs (grades 4 and 5 according to CTCAE v.5.0) and SAEs during the study; • The frequency of AEs and/or SAEs related to the study drugs in the treatment groups; • Key vital signs (blood pressure, pulse rate, respiratory rate, body temperature); • Results of laboratory and instrumental investigations; • Changes in physical examination findings, vital signs and laboratory safety indicators during the study.

2. STUDY RATIONALE

2.1. Overview of data on pathogenesis, epidemiology and current treatment options for the disease

At the end of 2019, an outbreak of a new coronavirus infection occurred in the People's Republic of China with an epicenter in Wuhan (Hubei Province), causing by pathogen provisionally named 2019-nCoV.

On February 11, 2020, the World Health Organization assigned the official name to the infection caused by the new coronavirus, COVID-19 ("Coronavirus disease 2019"). The International Committee on Taxonomy of Viruses on February 11, 2020 officially named the infectious agent as SARS-CoV-2.

Coronaviridae is a large family of RNA viruses that can infect humans and some animal species. In humans, coronaviruses can cause a range of diseases, from mild forms of acute respiratory infection to severe acute respiratory syndrome (SARS). Currently, it is known that four coronaviruses (HCoV-229E, -OC43, -NL63, and -HKU1) circulate in the population and occur year-round in the pattern of acute respiratory viral infections being the cause of mostly mild and moderate damage to the upper respiratory tract.

Until 2002, coronaviruses were considered as agents causing mild diseases of the upper respiratory tract (with extremely rare fatal outcomes). At the end of 2002, emerged the new coronavirus SARS-CoV being the causative agent of atypical pneumonia and SARS in humans. In total, over the period of the epidemic in 37 countries, more than 8,000 cases were recorded, of which 774 were fatal. Since 2004, no new cases of atypical pneumonia caused by SARS-CoV have been reported.

In 2012, the world faced the new MERS coronavirus (MERS-CoV), the causative agent of the Middle East respiratory syndrome. Since the emergence of the new virus strain until January 31, 2020, 2519 cases of coronavirus infection caused by the MERS-CoV virus were reported with 866 fatal cases. Currently, MERS-CoV continues to circulate and cause new cases of the disease.

The new SARS-CoV-2 coronavirus (name assigned by the International Committee on Taxonomy of Viruses on February 11, 2020) is a single-stranded RNA-containing virus that belongs to the Coronaviridae family, Beta-CoV B lineage. The virus is assigned to pathogenicity group II, like some other members of this family (SARS-CoV virus, MERS-CoV virus).

SARS-CoV-2 coronavirus is thought to be a recombinant virus containing sequences of bat coronavirus and a coronavirus of unknown origin. The genetic sequence of SARS-CoV-2 is similar to the sequence of SARS-CoV by at least 79%.

Initially, the virus was widely spread in the territory of the People's Republic of China (PRC), where confirmed cases of the disease were reported in all administrative entities. The largest number of cases was detected in the southeastern part of China with an epicenter in Hubei province (more than 80% of cases).

Imported cases of COVID-19 have been reported in more than 190 countries, some of them have been associated with trips to China, and since late February 2020, with trips to Italy, South Korea, and Iran. In many countries, cases were not associated with visiting China. Since March 11, 2020, WHO has announced the COVID-19 pandemic.

The initial source of infection has not been identified. The first cases of the disease could be associated with a visit to the seafood market in Wuhan (Hubei Province), where poultry, snakes, bats and other animals were sold.

Currently, the main source of infection is a sick person, including those in the incubation period of the disease.

The infection is transmitted through airborne droplets (with coughing, sneezing, talking), airborne dust and contact routes. Transmission factors are air, food and household items contaminated with SARS-CoV-2.

The emergence of COVID-19 posed challenges for healthcare professionals due to the need in rapid diagnosis and the provision of medical care to patients. Currently, information on the epidemiology, clinical features, prevention and treatment of this disease is limited. Immunity to the infections caused by other members of the coronavirus family is not persistent and re-infection is possible [1].

The most common symptoms of COVID-19 are fever (83-98%), cough (46-82%), myalgia and weakness (11-44%), shortness of breath (31%) [2, 3]. According to preliminary estimates, about 80% of patients with COVID-19 have mild or asymptomatic disease, 13.8% of cases are moderate and severe, and 6.1% of cases develop respiratory/multiple organ failure and septic shock. According to various estimates, mortality is up to 4%, which is less than mortality due to pneumonia (12-15%), but higher than mortality due to influenza (about 0.1-0.5%, depending on the strain). Acute respiratory distress syndrome (ARDS) is observed in 17-29% of cases in the Chinese cohort of patients [2], and kidney damage is reported in 2.5% [4]. The basis of ARDS pathogenesis is hyperactivation of innate immunity, while IL-1 levels correlate with lung damage [5].

High levels of cytokines and chemokines in the blood were observed in patients with COVID-19 infection: IL1-β, IL-1RA, etc. [6]. However, only elevated levels of IL-6 and the receptor for IL-2 were predictors of severe disease [7]. The risk of death increases in patients older than 60 years with comorbid diseases. In such patients, the acquired immune response can be weakened and more compensated by the innate immune response, which not only leads to the elimination of the virus, but also causes extensive tissue damage as the patient develops a cytokine storm that accompanies ARDS.

Currently a vaccine to prevent SARS-CoV-2 infection and the development of COVID-19, as well as approved drugs for the etiotropic treatment of Coronavirus infection are not available. As of today the treatment of coronavirus infection is based on symptomatic therapy and minimizing disease complications [1].

At the same time, mathematical epidemiological models predict a further spread of the disease and an increase in the number of cases. Thus, the development of new drugs for the treatment of coronavirus infection is currently an acute challenge health systems are facing worldwide.

Scientists around the world are making efforts to assess and study the new antiviral drugs for the treatment of COVID-19, as well as drugs for the treatment of the cytokine storm, a formidable complication of COVID-19 and the cause of a high mortality rate.

It is expected that the most effective drugs for the treatment of cytokine storms will be drugs from the group of IL-6 and IL-1 blockers. Many researchers consider the use of glucocorticoids to be dangerous because of the increased risk of infections and prothrombotic effects [8]. There is evidence of the successful use of IL-1 inhibitors in the treatment of patients with a cytokine storm during sepsis [9-11]. Tocilizumab has successfully passed clinical trials and was approved for the treatment of a cytokine storm during the CAR-T immunotherapy [12]. In an open-label, retrospective, non-comparative study, the efficacy of the IL-6 receptor blocker tocilizumab was demonstrated in 21 patients with severe COVID-19 [13]. A randomized controlled phase IV trial (ChiCTR2000029765) of tocilizumab was initiated in China (188 patients are expected to be enrolled by May 10, 2020). In addition, a double-blind, randomized, placebo-controlled phase II/III trial (NCT04315298) of sarilumab, another IL-6 receptor blocker (400 patients planned), was initiated in the United States. In addition, numerous studies have been initiated in China and Italy to assess the efficacy of IL-6 inhibitors in the treatment of patients with severe COVID-19 (NCT04315480, NCT04306705, NCT04310228, NCT04317092).

An open, non-comparative study conducted in February 2020 in China in patients with severe COVID-19 showed the efficacy of tocilizumab used together with the standard care. After the drug administration, a reduction of fever and a significant improvement in other symptoms were observed. The need for additional oxygen therapy decreased in 75% of patients (15 out of 20

patients), oxygen therapy was completely canceled in one patient due to a condition improvement. The relative number of lymphocytes that was increased in 85% of patients before treatment (mean 15.52 ± 8.89%) after the administration of tocilizumab returned to normal in 52.6% of patients. Positive changes were also observed in CT scans of the lungs. Initially elevated CRP decreased significantly in 84.2% of patients. At the same time there were no adverse events clearly associated with the drug. 90.5% of patients were discharged on average 13.5 days after the use of tocilizumab, the health status of the remaining patients also improved over time [13]. Considering that this study had an open label design without comparison groups, the results obtained require further evaluation and study.

2.2. Background information on the study therapy

Currently R-Pharm is developing two biological products: RPH-104 (a fusion protein that selectively binds IL-1β) and olokizumab (a humanized monoclonal antibody that binds IL-6). Both IL-1 and IL-6 are the key cytokines involved in the inflammation, and blocking effect of the biological agents is currently successfully used in the treatment of a wide range of auto-inflammatory diseases, rheumatoid arthritis, giant cell arteritis, cytokine storm, and etc. Both R-Pharm drugs are administered subcutaneously.

Detailed information on the physicochemical and pharmacological properties, as well as the results of preclinical and clinical studies of the formulations is contained in the current versions of the RPH-104 and OKZ Investigator Brochures.

2.2.1. RPH-104

The RPH-104 molecule is a fusion protein that selectively binds and inactivates IL-1β. 2 active parts of this molecule are responsible for the binding of RPH-104 to IL-1β: the extracellular part of the human type 1 IL-1 receptor and part of the human IL-1 receptor accessory protein (IL-1RAcP), which is the co-receptor of IL-1.

The RPH-104 has passed the full range of preclinical studies in vitro and in vivo and entered the clinical development phase. In vivo studies have shown good tolerability of the drug in animals.

The RPH-104 formulation has linear pharmacokinetics and a two-phase excretion profile in animals and humans, indicating the presence of a distribution phase and an excretion phase. Following subcutaneous administration in preclinical animal studies, the bioavailability of the drug was 52-85%.

In 2018, the first clinical study RPH104FIH01 was completed to evaluate the tolerability, safety, pharmacokinetics, pharmacodynamics and immunogenicity of RPH-104 in healthy male and female volunteers in Turkey.

During the use of RPH-104 in healthy volunteers, there were no reported cases of serious adverse events (SAE), as well as adverse events (AE) that led to the withdrawal from the study. Only 70 AEs were reported during the entire period of the study. All reported AEs in all dose groups were mild and resolved completely without sequelae. Thus, a study in healthy male and female volunteers demonstrated the safety and good tolerability of single subcutaneous injection of RPH-104 at doses from 4 mg to 160 mg [14].

To date, RPH-104 is undergoing clinical trials phase II/III in patients with gout (CL04018054) and idiopathic recurrent pericarditis (CL04018068) in the Russian Federation, the study of RPH-104 in Schnitzler syndrome was approved in the USA (CL04018066) and the study in colchicine-resistant Mediterranean fever was approved in the Russian Federation and Armenia (CL04018065; C04018071). The decision of the Ministry of Health of the Russian Federation on a clinical study of RPH-104 in patients with acute myocardial infarction with ST-segment elevation (CL04018075) is expected.

2.2.2. Olokizumab

Olokizumab is a humanized ([CDR]-grafted variable region) immunoglobulin G4/kappa isotype monoclonal antibody (mAB), developed as an IL-6 antagonist with expected activity in a broad spectrum of autoimmune/inflammatory processes.

The inhibition of IL-6 signaling was shown in nonclinical studies to have no life-threatening effects both in animal models and in formal toxicology studies [15].

OKZ has successfully passed phase IIa and IIb clinical studies, which included a total of 380 patients with rheumatoid arthritis, The results of these studies were published in two articles [16, 17]. The Phase III research program in patients with rheumatoid arthritis includes 2443 patients and comprises the following international projects: CREDO 1 (CL04041022) (successfully completed: a total of 428 patients with RA were included, of which 381 in the Russian Federation, the efficacy and safety of OKZ 64 mg every 2 or 4 weeks were demonstrated), the results of which were presented in 2019 at ACR and published [20], CREDO 2 (CL04041023) and CREDO 3 (CL04041025), the results of which will become available in May-June 2020, as well as the open-label study CREDO 4 (CL04041024) including patients who have completed the first three studies.

In phase I and II studies, the pharmacokinetic bioavailability of subcutaneous olokizumab was 63% [15].

Currently available results of the clinical development program suggest that olokizumab is effective in improving symptoms of rheumatoid arthritis patients and is well tolerated. The safety profile of olokizumab is consistent with known effects of IL-6 blockers.

2.3. Summary of known and potential risks and benefits for clinical trial subjects (risk/benefit ratio)

2.3.1. Benefit evaluation

The benefit that patients can obtain from participating in the study is the chance to receive therapy, which may potentially help to improve the symptoms of the disease and the respiratory function as well as reduce the need for oxygen therapy in patients with severe COVID-19 caused by new SARS-CoV-2 virus, under the lack of an approved therapy. A significant decrease in mortality and reduced duration of stay in the ICU is expected in patients receiving OKZ and RPH-104. Moreover, a shorter period when intensive therapy is required will help reduce the burden on ICUs in epidemic settings.

These expectations are based on the pathogenetic mechanisms of ARDS and cytokine storm and the mechanisms of action of OKZ and RPH-104, as well an on preliminary results on the efficacy of IL-6 inhibitors in COVID-19 patients. Considering the IL-1-mediated mechanism of IL-6 inhibition, which was also demonstrated in nonclinical studies of RPH-104, and the data on the successful use of a product from the same class in patients with sepsis and cytokine storm, the use of both RPH-104 and OKZ is justified.

2.3.2. Risk evaluation

The risks for patients, associated with their participation in this study, include the risks associated directly with the use of the study drug, the risks associated with treatment inefficacy in the subjects randomized to the placebo group, the risks related to study procedures, as well as the risks determined by the experimental nature of the study.

Since both RPH-104 and OKZ are protein preparations, anaphylactic and anaphylactoid reactions may occur with their use. These reactions can manifest as acute infusion reactions, allergic reactions or delayed-type hypersensitivity reactions. To minimize this risk, the study drugs

will be administered only at medical facilities and only if medications and equipment necessary for the treatment of anaphylactic or anaphylactoid reactions are available.

Risks associated with RPH-104

Based on data on the safety of drugs with a similar mechanism of action (canakinumab, rilonacept, anakinra), other risks of administering the study drug to study participants are associated primarily with AEs typical for drugs with a similar mechanism of action, i.e. interleukin-1 blockers [14].

These include an increased probability of infectious diseases, neutropenia, and thrombocytopenia.

During a phase I study of RPH-104 in healthy volunteers, 70 AEs were reported. All AEs reported in all dose groups were mild and completely resolved.

Table 1 shows a summary of AEs observed in healthy volunteers by administered dose. It should be noted that only 2 patients received placebo in each dose group.

No serious adverse events (SAEs) were reported in this study.

Table 1. Overview of adverse event profile: Number of patients with adverse events (study RPH104FIH01/CL04018045)

	Dose Group 1 (4 mg) (N = 7)	**Dose Group 2 (20 mg) (N = 7)**	**Dose Group 3 (40 mg) (N = 7)**	**Dose Group 4 (80 mg) (N = 7)**	**Dose Group 5 (160 mg) (N = 7)**
Subjects with any AEs (n)	6 (85.7%)	5 (71.4%)	6 (85.7%)	6 (85.7%)	6 (85.7%)
Receiving RPH104	5 (71.4%)	3 (42.9%)	4 (57.1%)	5 (71.4%)	5 (71.4%)
Receiving placebo	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)	1 (14.3%)
Subjects with any SAEs (n)	0	0	0	0	0
Subjects with any AEs leading to death (n)	0	0	0	0	0
Subjects with any AEs leading to permanent treatment discontinuation (n)	0	0	0	0	0

AE = adverse event; SAE = serious adverse event; N = number of subjects receiving treatment in each group; n = number of subjects with at least one AE in each category.

The most common adverse events in all dose groups were nervous system disorders (52% in the RPH-104 group vs. 40% in the placebo group), gastrointestinal disorders (32% in the RPH-104 group vs. 40% in the placebo group), and infections and infestations (24% in the RPH-104 group vs. 30% in the placebo group).

In the 4 mg and 20 mg dose groups, 3 out of 5 subjects (60%) receiving RPH-104 in each group experienced gastrointestinal disorders. In the 20 mg dose group, nervous system disorders were reported with a similar frequency (60%). In the 40 mg dose group, the most commonly reported AEs were from the system organ class (SOC) Infections and Infestations (40%). AEs related to Nervous system were reported in all 5 subjects (100%) receiving RPH-104 80 mg, and in 3 subjects (60%) receiving RPH-104 160 mg.

The data on SAEs and other RPH-104 safety profiles registered in ongoing clinical studies is presented in the current version of the Investigator's Brochure.

Risks associated with olokizumab

Based on the currently available data on the safety of 24-week OKZ therapy in patients with rheumatoid arthritis who failed methotrexate treatment, obtained from a well-designed placebo-controlled, pivotal phase III study, the following AEs are expected:

- Liver function test abnormalities (preferred terms according to Medical Dictionary for Regulatory Activities [MedDRA] included ALT increased, AST increased and abnormal LFTs);
- Elevated total cholesterol, LDL cholesterol and triglyceride levels (MedDRA preferred terms cholesterol increased, blood triglycerides increased and hypertriglyceridemia);
- Decreased leukocyte and neutrophil count (MedDRA preferred terms included neutropenia, neutrophil count decreased, leukopenia and leukocyte count decreased);
- Increased rate of infections: in the phase III pivotal study, no increase in the rate of infections was reported for olokizumab versus placebo, both in patients receiving the cumulative dose of 64 mg/4 weeks and in those receiving 128 mg/4 weeks. The percent of patients with at least one AE attributed to the SOC Infection and infestations was 14.1%, 15.4%, and 16.2% for olokizumab 64 mg/4 weeks, olokizumab 128 mg/4 weeks and placebo, respectively. However, a higher number of serious infections were reported in patients receiving olokizumab at the cumulative dose of 128 mg/4 weeks compared to placebo.

In addition, following side effects beingcharacteristic to other IL-6 inhibitors are considered expected AEs for olokizumab as well:

Gastrointestinal disorders: diverticular perforation.

Injection site reactions: injection site erythema, injection site hematoma, injection site pruritus.

Other important potential risks identified for other IL-6 inhibitors and observed in nonclinical studies include:

Immune system disorders: anaphylactic reaction, hypersensitivity, hypersensitivity to administered product.

Skin and subcutaneous tissue disorders: pruritus, rash, dermatitis, ecchymosis, pruritic rash, sweat discoloration.

Developmental disorders: reproductive toxicity was demonstrated in nonclinical studies. IL-6 presumably plays an important role in cervical dilation and, possibly, in the placental expulsion. Thus, olokizumab therapy can impair labor and delivery.

Drug-drug interactions: olokizumab was reported to reverse the inhibitory effects of IL-6 on CYP1A1/2, 2B6, 2C9, 3A4/5, 2C19, and NTCP activity in *in vitro* studies on cryopreserved human hepatocytes. For other inhibitors of IL-6 signaling pathway, this effect was observed *in vivo* at 1 week after a single administration of the drug. Consequently, the potential need for dose adjustments of drugs metabolized by these CYP isotypes after the administration of olokizumab should be taken in consideration.

Risks associated with placebo

Since this clinical trial is placebo-controlled, there is also a risk of treatment failure in patients randomized to the placebo group. Nevertheless, regardless of the therapy group assigned at randomization, patients will receive standard therapy for the treatment of COVID-19 accepted at the institution, which will help reduce this risk. In addition, in the absence of improvement in the patient's condition 24 hours after the administration of one of the study drugs, the protocol allows a single administration of tocilizumab or sarilumab recommended for the treatment of this disease in order to minimize risks.

Risks associated with diagnostic study procedures

The risks associated with diagnostic study procedures do not exceed the risks that normally occur in routine medical practice.

Other risks to which subjects may be exposed in association with their participation in this clinical study are determined by **the experimental nature of the study,** since its exact outcomes are not known: the efficacy of the study drug may be insufficient.

2.3.3. Conclusions

Since there is limited data on potential adverse reactions to RPH-104 and OKZ in humans, safety and tolerability of the drugs will be closely monitored. All adverse events reported in patients will be recorded and appropriate medical care will be promptly given within this clinical study. The Investigator must be vigilant towards any changes in clinical and laboratory data raising concerns regarding patient safety. The Investigator must be prepared to implement all necessary measures to resolve such events.

The protocol provides for additional safety precautions at the enrollment stage precluding the enrollment of subjects in whom the use of the study drug may be associated with additional health risks.

If the patient is unable to provide informed consent and sign the Informed Consent Form, e.g., in case of patients in severe condition or unconscious patients, in the absence of his/her legal representative, he/she may be enrolled in the study based on the decision of a council of physicians; in these cases, it is mandatory to obtain the patient's informed consent as soon as it becomes possible.

To reduce the risk of adverse reactions, the protocol provides for regular safety monitoring of the patients, including periodic assessment of the general condition, vital signs, laboratory parameters, as well as adverse events monitoring.

The study also provides for an Independent Data Monitoring Committee (IDMC), that will review the available efficacy and safety data, and based on this review the Sponsor will receive recommendations on further conduct of the study.

Thus, it may be concluded that the risks associated with potential adverse reactions are generally known and characterized. At the same time, the benefit that the patients may obtain in this study is quite high: improved symptoms, improved respiratory function and reduced need for oxygen therapy, as well as a shorter length of stay in the ICU and reduced mortality.

Consequently, the overall risk-benefit ratio for RPH-104 and OKZ in patients appears to be favorable.

2.4. Rationale for study design

A randomized, double-blind, adaptive, placebo-controlled design was chosen for this clinical study.

Randomized controlled double-blind studies are currently the gold standard design for clinical trials.

In this study, the randomized blinded administration of therapy will allow to obtain placebo-controlled data on the efficacy and safety of the study drugs, while excluding the potential for subjective assessments.

The adaptive design implies an early data analysis by the Independent Data Monitoring Committee (IDMC) after the first 189 patients has been randomized and evaluated on Day 15 or complete participation in the study, whichever comes first. Based on the analysis of the efficacy and safety data obtained from these subjects, the final sample size will be determined (which will

help to avoid the inclusion of an excessive number of patients that may be exposed to the risk associated with their participation in the study).

Thus, the adaptive design of this study involves the inclusion of a small number of patients in the pilot phase for an early risk assessment and preliminary assessment of the course of the disease. This approach is widely used in the treatment of patients with serious illnesses, including ARDS [19].

The use of standardized methods and timeframes for data collection in the study will allow a detailed evaluation of the specific characteristics and consequences of the disease in the adult population hospitalized for severe COVID-19.

In addition, retrospective data of patients with severe COVID-19 who did not receive subcutaneous OKZ and RPH-104 may be used in comparative analysis in the future.

2.5. Justification for the route of administration, dose, dosage regimen, and treatment course

RPH-104 will be administered once at a dose of 80 mg (2 mL) by subcutaneous injection.

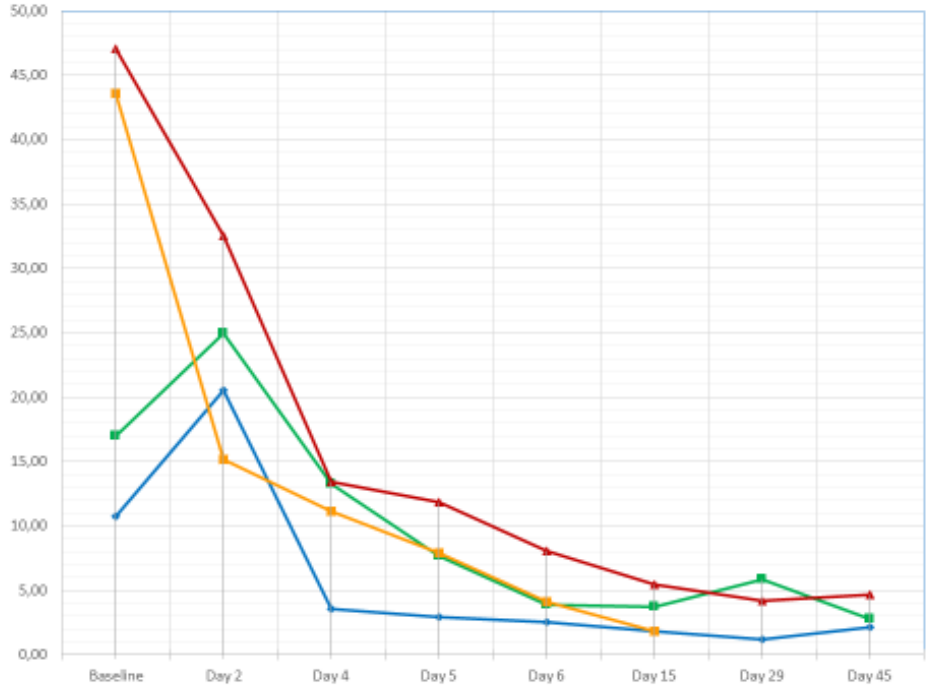
OKZ will be administered once at a dose of 64 mg (0.4 mL) by subcutaneous injection.

The selected route of administration (subcutaneous) is standard for drugs of this class.

Data on RPH-104 use in healthy subjects suggests a good tolerability of a single administration of the drug in doses ranging from 4 to 160 mg, inclusive. Single doses of 4 mg, 20 mg, 40 mg, 80 mg and 160 mg were selected for phase II studies. A single dose of RPH-104 80 mg will be administered in this study.

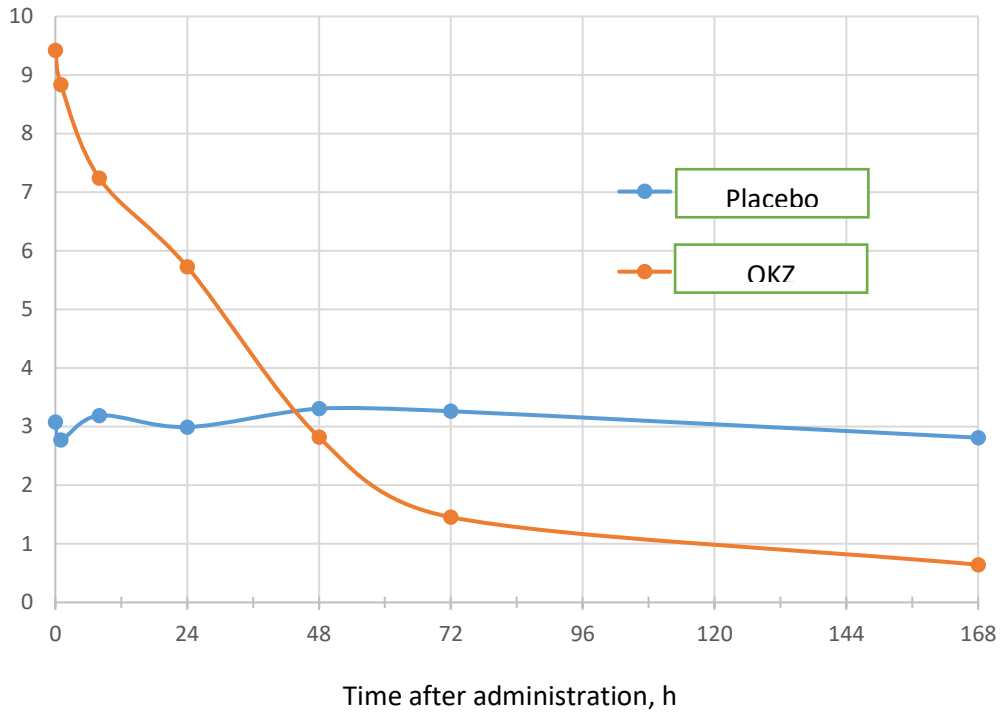
CRP is one of the most well-established inflammation markers. This marker is also elevated in COVID-19 patients with ARDS and cytokine storm [20]. Preliminary results of an open-label phase IIa study in patients with gout show a clear trend of CRP reduction in the RPH-104 80 mg and 160 mg groups (Figure 1) compared with RPH-104 20 mg and 40 mg groups. Data is presented as mean reduction in CRP (mg/L). In patients with acute gouty arthritis receiving the drug at doses of 20 mg and 40 mg, an increase in CRP is observed at 24 hours after the administration with a subsequent reduction in CRP, whereas in patients receiving 80 mg and 160 mg, a reduction in CRP is observed as early as 24 hours after the injection. Thus, using a dose of 80 mg is justified for this study.

Figure 1. Reduction in CRP levels after a SC injection of **RPH-104**: **20 mg (blue line), 40 (green line), 80 mg (red line), 160 mg (yellow line)**



Dose levels for phase III studies of OKZ (64 mg subcutaneously every 2 weeks or 64 mg subcutaneously every 4 weeks) were chosen based on primary efficacy endpoint data obtained in individual phase II studies, and the results of an additional dose-dependency analysis conducted using a pooled database of these studies. The same dose will be administered once in this study. A phase II study in patients with rheumatoid arthritis showed that a single dose of OKZ 1 mg/kg s.c., approximately the dosage to be used in this study, caused a rapid decrease in CRP compared to placebo as soon as within the first 24 hours (Figure 2).

Figure 2. CRP reduction after a subcutaneous injection of OKZ 1 mg/kg (blue line) and placebo (orange line)



2.6. Justification for placebo use

As shown above, the placebo-controlled design is the "gold standard" for randomized clinical studies. All subjects of this study, including those in the placebo group, will receive standard therapy for COVID-19 as per routine practice of participating facility.

The inclusion of the standard therapy + placebo group in this study is necessary due to the following considerations:

1. The absence of a well-studies reference drug for the treatment of cytokine storm in patients with severe coronavirus infection.
2. Rapid changes in the standard therapy for COVID-19 as new data becoming available. The latest standards of care as they are updated are planned to be used in this study to avoid the exposure of patients to an additional risk and ensure most favorable treatment outcomes. Therefore, it will not be possible to interpret the efficacy and safety data for the study drugs without comparing them with placebo.
3. The need for a reliable assessment of the risk/benefit ratio of immunosuppressive drugs in patients with viral infection. The main risks associated with the use of IL-6 antagonists are the increased rate of serious infections, neutropenia, leukopenia, increased level of liver enzymes, GI perforation and hypersensitivity reactions. The main risks associated with the use of IL-1 antagonists are the increased rate of serious infections, neutropenia and hypersensitivity reactions. Such an assessment requires to exclude as much as possible potential bias, which cannot be attained using a non-comparative design.
4. Low reliability of non-comparative data. For example, the combination drug lopinavir/ritonavir, which was included in the standard therapy based on promising observation data on its off-label use, was shown in a randomized controlled study

to be ineffective in reducing the duration of COVID-19, in lowering the rate of deaths and in improving disease outcomes compared with supportive therapy [21].

5. High variability of clinical parameters and disease outcome statistics. Demographic characteristics of patients, rate of complications, and mortality values may vary dramatically in different countries [22]. This excludes the use of designs based on historical control data.

2.7. Rationale for the choice of study population

Patients with COVID-19 caused by the SARS-CoV-2 virus discovered for the first time in December 2019 are planned to be included in this study. No etiotropic or pathogenesis-based therapy is currently approved for this disease with a mortality rate of 3.4% in the general population and up to 14.8% in elderly patients (older than 80 years). In March 2020, the WHO declared a global pandemic, and 2,171,031 cases of the disease and 146,201 deaths had already been reported worldwide by April 17 [23]. In view of the above, COVID-19 patients were selected to participate in this study.

The rationale for including in the study patients with severe disease and ARDS is, firstly, the high mortality in this population, and secondly, the potential benefit of drugs from the same group as the study therapy (IL-6 and IL-1 blockers) in such patients being suggested by preliminary data. At the base of the ARDS pathogenesis and multiple organ failure in COVID-19 patients lies the cytokine storm, i.e. an uncontrolled hyperactivation of innate immunity in response to viral infection [9, 24, 25]. High levels of IL-6 cytokine were observed as predictors of severe and critical course of COVID-19 [8, 24, 25]. There is evidence of successful use of IL-1 and IL-6 inhibitors in the treatment of patients with cytokine storm during sepsis [9-11]. Tocilizumab has successfully passed clinical trials and was approved for the treatment of cytokine storm associated with CAR-T immunotherapy [12]. The results of a recent Chinese study which included COVID-19 patients with severe or critical disease demonstrated the clinical efficacy of a single administration of tocilizumab [13]. COVID-19 is a life-threatening disease which leads to death in a significant number of cases, especially in elderly patients with such comorbidities as hypertension, COPD, malignancies and diabetes mellitus. No medicinal products were shown to be effective in the treatment of this disease.

2.8. Clinical study compliance with standard regulatory requirements

The study will be conducted in full compliance with this protocol, as well as the following regulatory requirements:

- ICH GCP E6 (R2) (2016);
- ethical principles set out in the latest revision of the Declaration of Helsinki (2013),
- Principles of Good Clinical Practice of the Eurasian Economic Union, approved by Decision No. 79 of the Council of the Eurasian Economic Commission “On approval of the Principles of Good Clinical Practice of the Eurasian Economic Union”, dated November 03, 2016;
- Current legislation and regulatory requirements; Current legislation and regulatory requirements of the member-states.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study goal

- To evaluate the efficacy and safety of a single administration of RPH-104 (80 mg) or OKZ (64 mg) compared with placebo in patients with severe SARS-CoV-2 virus infection (COVID-19).

3.2. Study objectives and their corresponding endpoints

OBJECTIVES	ENDPOINTS [assessment timeframes]
Primary objective	**Primary endpoint**
1. To assess the efficacy of a single administration of RPH-104 (80 mg) or OKZ (64 mg) compared with placebo in patients with severe SARS-CoV-2 virus infection (COVID-19) on Day 15 of the study.	1. Proportion of responders in each treatment group. A responder is a patient who has not received tocilizumab or sarilumab and who has a clinical status improvement of ≥1 point on the 6-point COVID-19 scale (where 1 is the most favorable outcome and 6 is the most undesirable outcome) 15 days after the administration of the study drug [Day 15]: 1). Not hospitalized; no activity limitations; 2). Not hospitalized; limited activity; 3). Hospitalized, not requiring supplemental oxygen; 4). Hospitalized, supplemental oxygen with independent breathing; 5). Hospitalized; mechanical ventilation (invasive/non-invasive) or ECMO; 6). Death.
Secondary objectives	**Secondary endpoints**
1. To evaluate the effect of a single administration of RPH-104 (80 mg) or OKZ (64 mg) compared with placebo on clinical status changes in patients with severe SARS-CoV-2 virus infection (COVID-19) during the study .	1. Change over time in the clinical status of patients on a 6-point ordinal scale [Day 2 – Day 15, Day 29]; 2. The proportion of patients with an improvement in clinical status by 2 or more points on the 6-point ordinal scale during the study with no use of tocilizumab or sarilumab [from Day 2 to Day 15, Day 29]; 3. The proportion of patients who received tocilizumab or sarilumab for COVID-19 during the follow-up period [from Day 2 to Day 29];
2. To compare mortality rates in the groups of single administration of RPH-104 (80 mg), OKZ (64 mg) or	4. Mortality during the follow-up period [Day 1 – Day 29].

placebo in patients with severe SARS-CoV-2 virus infection (COVID-19).	
Secondary objectives	**Exploratory endpoints**
3. To compare the length of stay in the ICU, the duration of oxygen support and clinical parameters between the groups of single administration of RPH-104 (80 mg), OKZ (64 mg) or placebo in patients with severe SARS-CoV-2 virus infection (COVID-19) receiving the standard therapy.	1. The proportion of patients with National Early Warning Score 2 (NEWS2) ≤ 4 for 2 consecutive days [Day 3 – Day 15]; 2. The proportion of patients with a score of ≤ 2 using the National Early Warning Score 2 (NEWS2) for 2 consecutive days [Day 3 – Day 15]; 3. Time to reaching a NEWS2 score ≤ 4 for 2 consecutive days [Day 1 – Day 15]; 4. Time to reaching a NEWS2 score ≤ 2 for 2 consecutive days [Day 1 – Day 15]; 5. Change from baseline in the level of surrogate markers of the cytokine storm: leukocytes, lymphocytes, neutrophils, CRP, ferritin (if applicable), D-dimer (if applicable) [Day 2, Day 3, Day 5, Day 7, Day 15]; 6. Mortality during an ICU stay, at study days 7, 15, 29 [Day 7, Day 15, Day 29]; 7. Time to reaching SpO2≥94% without oxygen support, for 2 consecutive days [Day 2 – Day 15]; 8. Change from baseline in the oxygenation index of PaO2/FiO2 (if applicable) during hospitalization [Day 2 – Day 15]; 9. Duration of stay in ICU, in days [Day 2 – Day 15]; 10. Change from baseline in ARDS severity defined according to WHO criteria (if applicable) [Day 1 – Day 15]; 11. Time to ARDS improvement according to the WHO criteria by one category compared to baseline (if applicable) [Day 1 – Day 15]; 12. Duration of mechanical ventilation and/or ECMO (if applicable), in days [Day 2 – Day 15]; 13. Duration of oxygen support (if applicable), in days [Day 1 – Day 15]; 14. Time until resolution of fever, i. e. axillary body temperature <38 °C without the use of antipyretics for 2

	consecutive days (if applicable) [Day 1 – Day 15]; 15. Time to clinical status improvement by 1 point on the 6-point COVID-19 scale [Day 1 – Day 29]; 16. Time to clinical status improvement by 2 points on the 6-point COVID-19 scale [Day 1 – Day 29]; 17. The proportion of patients with a clinical status worsening by 1 point on the 6-point COVID-19 scale during the study (if applicable) [Day 2 – Day 15, Day 29]; 18. The proportion of patients with a clinical status worsening by 1 point on the 6-point COVID-19 scale during the study, excluding patients moving to category 6 (if applicable) [Day 2 – Day 15, Day 29]; 19. Time to a clinical status worsening by 1 point on the 6-point COVID-19 scale (if applicable) [Day 2 – Day 15, Day 29].
Secondary objectives	**Safety endpoints**
4. To assess the safety of a single administration of RPH-104 (80 mg) or OKZ (64 mg) in patients with severe SARS-CoV-2 virus infection (COVID-19)	1. Incidence, severity, nature and outcomes of AEs (grades 4 and 5 according to CTCAE v.5.0) and SAEs during the study; 2. The proportion of patients with AEs (grades 4 and 5 according to CTCAE v.5.0) and SAEs; 3. Changes in physical examination findings, vital signs, and laboratory safety parameters during the study.

LHD = last day of hospitalization

4. STUDY DESIGN

4.1. Description of the study design

This study is a multicenter randomized double-blind adaptive placebo-controlled phase II/III clinical trial to evaluate the efficacy and safety of a single administration of RPH-104 80 mg or OKZ 64 mg compared with placebo in hospitalized patients with a confirmed diagnosis of COVID-19 in severe condition.

The study will consist of two phases:

- pilot phase: inclusion and randomization of the first 189 patients (63 patients in each group of OKZ, RPH-104, placebo), followed by an early analysis of efficacy and safety data, based on which the sample size will be finally defined;
- pivotal phase: subsequent subject enrollment and the conduct of all procedures specified in the protocol.

The preliminary sample size is 372 randomized patients hospitalized with severe or critical COVID-19. The final sample size will be determined by the results of the pilot phase of the study. A patient is considered enrolled in the study after signing the Informed Consent Form or by decision of a medical consilium (see Section 8.2. Description of individual study procedures).

For each patient, the study will consist of 3 periods with a total duration of up to 31 days:

- screening period for up to 48 hours before the start of the day of randomization (Day 1). During the screening period, subject eligibility is assessed;
- treatment period lasting from the end of screening (which is the start of Day 1) to 23:59 of Day 1, including randomization of patients into the treatment groups, followed by a single administration of the study drug;
- follow-up period, lasting from 00:00 on Day 2 to 23:59 on Day 29, which includes the assessment of the efficacy and safety after the administration of one of the study drugs.

After enrollment into the study (signing of the Informed Consent Form or, if the patient is unable to express his/her will, a documented decision of a medical consilium on the need to include the patient in this clinical study), subjects will be screened for compliance with eligibility criteria. Eligible patients will be randomized 1:1:1 to one of three treatment groups to receive a single subcutaneous injection: RPH-104 80 mg or OKZ 64 mg or placebo. Regardless of the treatment group to which a patient is randomized, they will receive standard COVID-19 therapy accepted at the institution, with the exception of the drugs specified in section 6.5.2 Prohibited concomitant therapies, as well as tocilizumab and sarilumab during the first 24 hours after the administration of the study drugs. In the absence of improvement in the patient's condition, by Investigator's discretion, within 24 hours after the administration of one of the study drugs, a single administration of tocilizumab or sarilumab is allowed, in accordance with current recommendations. Evaluations of efficacy and safety, including laboratory and instrumental investigations, will be performed in study subjects on a daily basis during the hospitalization period until Day 15 or the LHD (whichever comes first). Blood samples for complete blood count, blood chemistry tests, determination of the cytokine storm markers, as well as urine samples will be taken on Days 1, 3, 5, 7, and 15 of the study. Additionally, blood samples for the cytokine storm markers will be taken on Day 2 of the study, as well as before the administration of tocilizumab or sarilumab (if applicable). On Day 15, the primary endpoint of the study, response to treatment, will be assessed. A response to treatment is an improvement in the clinical status of the patient by at least 1 point on the 6-point COVID-19 scale with no use of tocilizumab or sarilumab. The last study visit is on Day 29. If a patient is discharged earlier than Day 15 and/or Day 29 of the study, the clinical status, concomitant therapy, and AE assessments on this/these day(s) will be evaluated via a telephone call. The adaptive design of this study entails the inclusion of a small number of patient in the pilot phase to ensure an early assessment of the risk and a preliminary assessment of the course of the disease. This approach is used in the treatment of patients with severe disease, including ARDS [19].

The inclusion of the standard therapy + placebo group in this study is necessary due to the following:

1. The absence of a well-studied reference drug for the treatment of cytokine storm in patients with severe coronavirus infection.
2. Rapid changes in the standard therapy for COVID-19 as new data becomes available. The latest standards of care as they are updated are planned to be used in this study to avoid the exposure of patients to an additional risk and ensure most favorable treatment outcomes. Therefore, it will not be possible to interpret the efficacy and safety data for the study drugs without comparing them with placebo.
3. The need for a reliable assessment of the risk/benefit ratio of immunosuppressive drugs in patients with viral infection. The main risks associated with the use of IL-

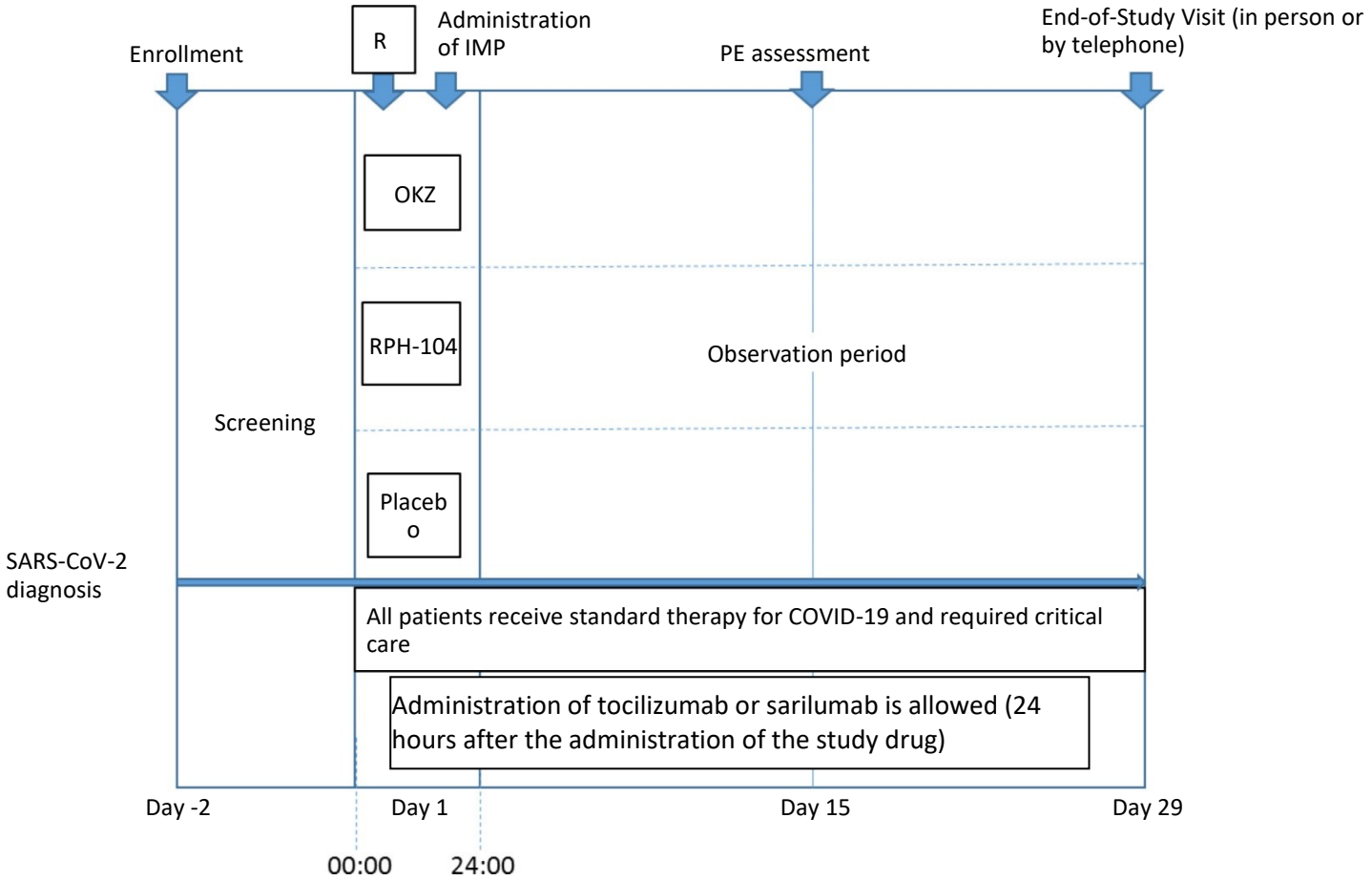
6 antagonists are the increased rate of serious infections, neutropenia, leukopenia, increased level of liver enzymes, GI perforation and hypersensitivity reactions. The main risks associated with the use of IL-1 antagonists are the increased rate of serious infections, neutropenia and hypersensitivity reactions. Such an assessment requires to exclude as much as possible potential bias drugs, which cannot be attained using a non-comparative design.

4. Low reliability of non-comparative data. For example, the combination drug lopinavir/ritonavir, which was included in the standard therapy based on promising observation data on its off-label use, was shown in a randomized controlled study to be ineffective in reducing the duration of COVID-19, in lowering the rate of deaths and in improving disease outcomes compared with supportive therapy [21].
5. High variability of clinical parameters and disease outcome statistics. Demographic characteristics of patients, rate of complications, and mortality values may vary dramatically in different countries [22]. This excludes the use of designs based on historical control data.

4.2. Study flow chart

The study flow chart is shown in Figure 3.

Figure 3. Study flow chart



PE = primary endpoint; OKZ = olokizumab; IMP = investigational medicinal product; R = randomization;
Day = calendar days from 00:00 to 23:29 beginning from Day 2.

5. STUDY POPULATION

The preliminary sample size is 372 randomized male and female patients aged 18 years (inclusive) or older, admitted to healthcare institutions with COVID-19 in severe or critical condition; of them, 189 patients will be included in the pilot phase of the study. The final sample size will be determined by the results of the pilot phase of the study..

5.1. Inclusion criteria

Patients meeting all of the criteria below may be included in the study:

1. Male or female patients aged 18 years (inclusive) or older (at the beginning of the screening period).
2. Voluntarily signed and dated Patient Informed Consent Form for participation in this study, or record of a Medical Consilium decision justifying patient's participation in case of patient is unable to express his or her will.
3. Having either of the following COVID-associated respiratory syndromes::
   - Pneumonia with oxygen saturation SpO2 ≤93% (on room air) or RR greater than 30 breaths/min;
   - ARDS (PaO2/FiO2 ≤300 mmHg or SpO2/FiO2 ≤315 if PaO2 is not available).
4. A diagnosis of COVID-19 based on:
   - Laboratory confirmed SARS-CoV-2 infection as determined by PCR
     OR
   - Bilateral changes in the lungs characteristic of COVID-19 on chest CT

5.2. Non-inclusion criteria

To be eligible for the study, patients must not meet any of the following criteria:

1. A history of hypersensitivity to the study drugs (RPH-104 and/or OKZ), and/or its components.
2. Any of the following laboratory abnormalities:
   - absolute neutrophil count <0.5 x 10^9/L,
   - white blood cell count <2 x 10^9/L,
   - platelet count <50 x 10^9/L,
   - ALT and/or AST ≥3.0 x ULN.
3. Severe renal failure: creatinine clearance <30 mL/min.
4. Septic shock (vasopressors are required to maintain mean blood pressure ≥65 mmHg and lactate ≥2 mmol/L in the absence of hypovolemia).
5. Disease progression to death within the next 24 hours, regardless of therapy, in the physician's opinion.
6. History of gastrointestinal perforation or diverticulitis.
7. Administration of plasma from COVID-19 convalescent donors within 4 weeks before study enrollment and/or planned administration during the study.
8. Recent (less than 5 elimination half-lives) use of tocilizumab or sarilumab.
9. Recent (less than 5 elimination half-lives) or planned use during the study of:
   - biologics (except RPH-104 or OKZ) with immunosuppressive effect, including, but not limited to: IL-1 inhibitors (anakinra, rilonacept, canakinumab), IL-6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumor necrosis factor α (TNFα) inhibitors (infliximab, adalimumab, etanercept, etc.), anti-B-cell drugs, etc.;
   - other immunosuppressive drugs (except methotrexate at doses of up to 25 mg/week), including but not limited to:

- high doses of glucocorticoids (equivalent to prednisolone >1 mg/kg) orally or parenterally;
- JAK kinase inhibitors; cyclophosphamide, etc.

10. Concurrent participation in another clinical trial.
11. Pregnancy, breastfeeding.
12. A history of active tuberculosis, or active tuberculosis suspected by the Investigator.

5.3. Restrictions for patients during the study

The Investigator will explain to the patient that during his/her participation in the study, certain restrictions must be followed:

- **treatment regimen:** during hospitalization, patients should comply with applicable study center policies and follow Investigator's instructions; after discharge, subjects should also follow all the Investigator's recommendations regarding treatment and lifestyle and contact the Investigator on Day 15 and/or Day 29 of the study (whichever is applicable);
- **contraception:** female subjects should use effective contraception methods from the time of inclusion in the study to 3 months after the administration of the study drugs. Male subjects must inform their female partners of the need for effective contraception methods and use them from the time of the inclusion of the male subject in the study to 3 months after he receives the study drugs. These methods include:
  - Sterilization: surgical bilateral oophorectomy (with or without hysterectomy), or tubal ligation at least 6 weeks before the beginning of the study. In case of oophorectomy alone, the woman's reproductive status should be confirmed by a subsequent assessment of hormone levels.
  - Male partner sterilization (with appropriate documentation of the absence of sperm in the ejaculate after vasectomy) at least 6 months before the start of the study. In this case, the vasectomized male must be the sole partner of the female subject.
  - A combination of any two (i.e., a+b or a+c or b+c) of the methods below:
    a) Oral, injectable, or implantable hormonal contraceptive drugs. If an oral contraceptive drug is used, it must not be changed for at least 3 months prior to study therapy.
    b) Intrauterine device or intrauterine system.
    c) Barrier contraception methods: condom or occlusive cap (diaphragm or cervical cap/vault cap) with spermicidal foam/gel/film/cream/vaginal suppository.

These restrictions are also detailed in the Patient Information Leaflet with the Informed Consent Form.

5.4. Exclusion criteria (early study termination)

Subject will be completely withdrawn from all assessments in the following cases:

- The subject chooses to withdraw from the study, i.e. withdraws informed consent.
- The subject is lost to follow-up.
- Death of the subject.

The study is terminated early by the decision of the Investigator, Sponsor, or at the request of the regulatory authorities of the country where the study is conducted, ethics committees or other authorities (see Section 14. STUDY STOPPING RULES).

The subjects may decide to withdraw from the study at any time without giving a reason. However, the Investigator should make a reasonable effort to find out the reasons for the subject's withdrawal.

Subjects lost to follow-up should be indicated accordingly in the eCRF. If a subject is lost to follow-up, the Investigator should appropriately attempt to contact him/her and record in the primary documents the steps taken in this respect, for example, the dates of telephone calls, registered letters, etc.

The Investigator should inform the Sponsor about early patient withdrawal **within 24 hours**, specifying the reasons for withdrawal.

In case of early discontinuation of a patient from the study, the Study Completion Form in eCRF should be filled out.

If a patient discontinues the study and withdraws his/her consent to the disclosure of future information, any further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use the data obtained prior to withdrawal of consent.

If a subject decides to withdraw from the study or does not complete the study for any reason, his/her individual screening number should not be reused.

Patients who are prematurely discontinued from the study for any reason should not be replaced.

6. STUDY THERAPY

Detailed information on the labeling, receipt, storage, accountability, preparation, dispensation, administration to the patients, and disposal of study drugs is provided in the Pharmacy Manual.

6.1. Doses and dosing schedules of the study drugs

In this study, patients will receive a single injection of one of the study drugs below, according to the treatment group to which they are randomized:

- OKZ 64 mg, one injection 0.4 mL, OR
- RPH-104 80 mg, one injection 2 mL, OR
- Placebo, one injection of a corresponding volume of 2 mL.

No dose adjustments are planned in this study.

6.2. Preparation of the study drugs for administration and the administration procedures

An independent pharmacist or a designee who is unblinded to the treatment assignements will prepare OKZ, RPH-104 or placebo in 2 mL syringes for subcutaneous injections. To maintain the blinded design of the study, the syringes for subcutaneous injections will be blinded prior to the administration of the drug as specified in the Pharmacy Manual so that all three products being identical in appearance. Appropriate measures should be taken at the study site to prepare the syringes for subcutaneous injections so that the specified time of stability of the prepared product is not exceeded. The study drug solution may remain in the syringe for up to 4 hours prior to use. The syringes prepared for subcutaneous injection should be warmed to room temperature for at least 30 minutes prior to administration to the patient.

The study drugs should be prepared in a secure place, not accessible to the blinded members of the study team (including the blinded study stuff from the Sponsor).

The unblinded qualified personnel of the study will administer single subcutaneous injections (0.4 mL olokizumab or 2 mL RPH-104 or 2 mL placebo) to each subject.

The date, time, and place of subcutaneous injection should be documented and entered into the eCRF. The Investigator should also document in the eCRF if the full dose of the drug was administered.

The blinded study drug (OKZ or RPH-104) will be injected subcutaneously, preferably in one of the abdominal areas shown on Figure 4. Alternatively, if the indicated areas are inaccessible, another area acceptable for subcutaneous injection may be used: the outer surface of the shoulder, the front surface of the thigh. If subcutaneous injection in these areas is technically impossible due to the patient's body position, a subcutaneous injection may be performed in another area with a sufficiently developed subcutaneous fat layer.

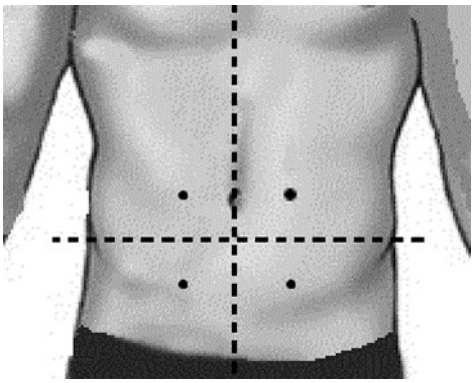


Figure 4. The abdominal areas where the study drugs may be injected.

6.3. Overdose

6.3.1. Olokizumab overdose

No cases of OKZ overdose have been reported yet from clinical experience. The maximum dose administered in the phase I studies was 3 mg/kg for a single subcutaneous administration and 10 mg/kg for a single intravenous administration. In this group, the rate of AEs was not different from other dose groups and no SAEs were reported (see Section 2.2.2. Olokizumab (OKZ)).

The antidote to OKZ is not known. Overdose signs and symptoms should be treated in accordance with the local standards of care.

6.3.2. RPH-104 overdose

No cases of RPH-104 overdose were reported. The maximum amount of the drug that can be safely administered has not been determined. In a phase I study, the maximum single dose was 160 mg. This dose was safe and well tolerated (see Section 2.2.1. RPH-104).

The antidote to RPH-104 is not known. In case of an overdose, symptomatic therapy is recommended.

6.4. Treatment compliance

The assigned dose, regimen, and method of administration should not be changed. The date and time of administration of all doses of the drug and any deviation from the specified treatment regimen should be documented in the relevant eCRF section.

An unblinded monitor who is aware of the therapy receiving by individual patients will review the pharmacy records at each clinic, including the dispensing log, where the pharmacist or a designated person should record all the study drugs dispensed to patients. This monitor shall compare the dispensing records with the vials labeled with individual subject IDs and the visit schedule to confirm that the patients have received the appropriate treatment and dose and have followed the treatment schedule. The site personnel will be informed of the identified errors to

prevent such errors in the future. The study stuff knowing about the treatment administered to individual patients will receive the unblinded information, b, whereas the other study stuff will receive blinded data.. The monitor's report will include detailed information on any missed doses, dose errors, treatment errors, or scheduling errors and relevant explanations. All the supplies and pharmacy documents should be made available to the monitor for review throughout the study.

The study sites will not be required to keep used syringes. Any patient with deviations from the treatment regimen should be immediately reported to the Sponsor or its representative to decide on subsequent actions.

6.5. Concomitant therapies

6.5.1. Allowed concomitant therapies

The administration of standard COVID-19 therapy approved at the healthcare institution is allowed during the study, with the exception of drugs specified in section 6.5.2 Prohibited concomitant therapies, throughout the study, as well as tocilizumab and sarilumab during the first 24 hours after the administration of the study drugs.

Patients should inform the study site personnel about any new drugs they use after they start receiving the study therapy. All drugs (except the study drugs) and significant non-drug therapies used during the study should be recorded in the eCRF section "Concomitant therapy" (including medicinal products, herbal/natural products, etc.) or "Concomitant procedures" (including MV, blood transfusions, etc.).

If a concomitant disease is not a criterion for excluding the patient from the study, it should be treated according to the accepted standard of care under this protocol. In this case, concomitant therapy drugs should not be included in the list of those prohibited by the protocol.

Tocilizumab and sarilumab

If, in the opinion of the Investigator, there is no improvement in the patient's condition 24 hours after the administration of one of the study drugs, tocilizumab or sarilumab at the doses recommended for the treatment of this disease may be added to concomitant therapy. The administration of tocilizumab or sarilumab before this time is impractical in view of the pharmacokinetic/pharmacodynamic properties of the study drugs. The Sponsor will not provide the study centers with tocilizumab and sarilumab for use as standard therapy for the disease investigated in the study.

Allowed concomitant therapies requiring special precautions and/or any actions

Both OKZ (directly) and RPH-104 (by inhibiting IL-1) are expected to reduce IL-6-mediated inhibition of CYP or transmembrane transporters, as CYP1A1/2, 2B6, 2C9, 3A4/5 and 2C19, as well as of the sodium/taurocholate co-transporting polypeptide (NTCP). A reduced inhibition of CYP or transporters may lead to reduced levels of the drugs metabolized via these enzymes. This decrease in drug levels may be clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is adjusted individually (for example, warfarin). In patients receiving these types of drugs, therapeutic monitoring by the attending physician is recommended (without entering additional information into the eCRF).

6.5.2. Prohibited concomitant therapies

The following medications are prohibited during the study:

- Immunosuppressive biologics (with the exception of RPH-104 or OKZ), including, but not limited to: IL-1 inhibitors (anakinra, rilonacept, canakinumab), IL-6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumor necrosis

factor α (TNFα) inhibitors (infliximab, adalimumab, etanercept, etc.), anti-B-cell drugs, etc.;

- other immunosuppressants (with the exception of methotrexate in a dose of up to 25 mg/week), including, but not limited to:
  - high doses of glucocorticoids (equivalent to prednisolone >1 mg/kg) orally or parenterally;
  - JAK kinase inhibitors;
  - cyclophosphamide etc.;
- administration of plasma from COVID-19 convalescent donors;
- during the first 24 hours after the administration of the study drugs, the use of tocilizumab and sarilumab is prohibited.

6.6. Dosage form, packaging and labeling of the study drugs

6.6.1. Olokizumab

Trade name: Not assigned.
Product Internal Code: CDP6038, L04041.
International non-proprietary name: Olokizumab.
Pharmaceutical form: Solution for subcutaneous injection.
Strength: 160 mg/mL.
Composition:

Component	Content per 1 mL	Relative content
Active substance		
Olokizumab	160.000 mg	-
Excipients		
Sodium chloride	3.51 mg	60 mM
Polysorbate 80	0.3 mg	0.03%
L-Histidine hydrochloride	6.29 mg	30 mM
Sorbitol	36.434 mg	200 mM
Water for injection	QS to 1.0 mL	-

QS = quantity sufficient

Storage and shipping conditions: Store and ship at +2 to +8°C.
Primary and secondary packaging:
Primary packaging: 2 mL type I clear glass vial with a target volume of 0.4 mL. The vials are sealed with a chlorobutyl rubber stopper and an aluminium and polypropylene crimp.
Secondary packaging: 1 vial is packed in a labeled carton.

6.6.2. RPH-104

Trade name: Not assigned.
Product Internal Code: RPH-104, L04018
International nonproprietary name: Not assigned.
Pharmaceutical form: Solution for subcutaneous injection.
Strength: 40 mg/mL.
Composition:

Component	Content per 1 mL	Relative content
Active substance		
RPH-104	40 (± 4) mg	-

Excipients		
Sucrose	60 mg	6%
Polyethylene glycol (PEG) 3350	30 mg	3%
Sodium chloride	2.92 mg	50 mM
L-Histidine	3.1 mg	20 mM

Storage and shipping conditions: Store and ship at +2 to +8°C.
Primary and secondary packaging:
Primary packaging: 4 mL transparent glass vial sealed with a rubber stopper with an aluminum crimp and covered with a red cap. 1 vial contains 2 mL of 40 mg/mL drug product solution.
Secondary packaging: 1 vial is packed in a labeled carton.

6.6.3. Placebo

Trade name: Not applicable.
International nonproprietary name: Not applicable.
Pharmaceutical form: Solution for subcutaneous injection.
Composition:

Component	Content per 1 mL	Relative content
Sodium chloride	9 mg	0.9%
Water for injection	To 1 mL	99.1%

Storage and shipping conditions: Store and ship below +25°C.
Primary and secondary packaging: According to the commercial packaging.

6.6.4. Labeling

According to the regulatory requirements of the member states, the following information will be presented on the primary and secondary packaging of the study drugs:

- name and dosage of the corresponding study drug,
- Sponsor's company name, address and contact information (secondary packaging only),
- name of the study drug manufacturer, address and contact information (secondary packaging only),
- batch number,
- release date,
- expiration date,
- method of administration,
- dosage form,
- storage conditions,
- individual primary package number,
- protocol number,
- warning statements.

The primary and secondary packaging of the study drugs will additionally be labeled with: “For clinical studies only.”

The primary and secondary packaging will also have space for information to be entered by the designated unblinded member of the study team:

- number of the study site, full name of the Principal Investigator,
- visit date,
- patient ID.

6.7. Handling of study drugs

The Investigator is responsible for the appropriate administration, accountability and storage of the study drugs at the study site. The study drugs may be stored only at the official study site involved in this study. The access to the study drugs shall be restricted to authorized study site employees only. The Investigator should ensure drug storage under secure conditions that prevent loss, theft and deviations from the environmental conditions (temperature) specified in the Pharmacy Manual and indicated the Investigator's Brochure for the respective drug (RPH-104 or OKZ), and also proper maintaining of records of study product receipt, accountability, storage, and dispensation of study drugs. At the study site, OKZ and RPH-104 must be stored in the refrigerator at +2 to +8°C; placebo must be stored below +25°C. The Investigator must keep a storage temperature log for the study drugs.

The study drugs should always be prepared and administered to the patients at the study site, by a designated unblinded member of the study team (see Section 6.2. Preparation of the study drugs for administration and the administration procedures).

7. SUBJECTIVITY MINIMIZATION/EXCLUSION MEASURES

7.1. Patient disposition by study site

Enrollment at the study sites will be competitive. Recruitment will be terminated after the inclusion of the number of patients determined by the analysis of the pilot phase of the study. The preliminary plan is to include 372 patients.

7.2. Assignment of screening numbers

Assignment of screening numbers will be carried out in accordance with internal instructions of the Sponsor.

Each study center will be assigned a three-digit identification number starting with "101", with the last two digits indicating the center's number in the MoH permit. If a clinical center under a single Principal Investigator has more than one actual study address, each actual address of such a clinical center will be assigned a three-digit number, for example, "101", "201", "301", etc. (the number of each of the actual addresses of the clinical center will be encoded by the first digit of the three-digit number, and the last two digits will indicate the number of the clinical center in the MoH permit common to all actual addresses) for correct display in the IWRS system.After a patient has signed the Informed Consent Form or is included in the study based on a Medical Consilium decision, the patient is assigned an individual eight-digit screening number recorded in the source documentation, where 78 at the beginning is the last two digits of the clinical study protocol number, the next three digits are the center number, starting with 101, and the last three digits represent the patient's number in the center, starting with 001; thus, the full individual screening number will be shown, for example, as 78101001. During randomization, the patient retains this individual eight-digit number.

The Investigator must maintain a separate log containing information about patients' screening numbers, which must be stored in compliance with the rules applicable to confidential documents.

If a patient completes the study prematurely (is withdrawn from the study for any reason), their screening number will not be reused.

7.3. Randomization

If the Investigator decides that a patient is eligible for the study after performing all screening procedures, the patient is randomized. Randomization is necessary to minimize subjectivity in the allocation of patients to treatment groups. Randomization is carried out in accordance with internal instructions of the Sponsor.

Randomization of patients in this study will be centralized and performed using the Interactive Web Response System (IWRS). Patients will be randomized into 3 groups in a ratio of 1:1:1.

Before the study, each Investigator will be trained to use the system and receive unique access codes and IWRS Manual.

A confirmation of randomization will be available for print. A notification of randomization will be sent by e-mail to the addresses of the authorized members of the project team.

The number of the drug assigned at the randomization must be registered in the source documentation and in the patient's eCRF.

The randomization codes are also kept by the Sponsor in strict confidence.

7.4. Blinding

This study is designed as a double-blind trial, which means that neither the Investigator nor other members of the study site team nor Sponsor representatives nor the patient will be aware of which drug is being used (as well as which group the patient was allocated to).

Since the study drugs differ in appearance, they will be prepared and administered by an openly acting, designated member of the study team who is not involved in the management of patients and the study assessments and who has no access to the patient’s medical records.

All drugs to be administered will be drawn into identical 2 mL syringes.

Preparation and administration of drugs for a patient should be carried out separately from other study participants so that it is impossible to see the differences between OKZ, RPH-104, and placebo. Additional conditions will be in place during the administration of the test drug to limit visibility to the patient (see section 6.2. Preparation of the study drugs for administration and the administration procedures).

Monitoring procedures for the study drugs will be carried out by an unblinded clinical research associate.

Unblinding will only be possible in the event of a safety emergency. Unblinding of the treatment group is performed by IWRS at the request of the Investigator. The Investigator sends a request to IWRS stating the reasons for unblinding, after which, with the permission of the Sponsor, receives the treatment group information (in the system).

Unblinding will also be done for the final analysis.

7.5. Compliance with study therapy

The administration of the study drugs will be carried out only by qualified members of the study team. The date, time, and place of drug administration will be recorded in the patient's eCRF.

8. STUDY PROCEDURES

The visit schedule with all study procedures are presented in Table 2.

A deviation is allowed only for Day 29 (± 1 day).

The day of randomization (Visit 1, Day 1) continues from the end of screening until 23:59 of the same calendar day; the drug administration should be performed on Day 1 after

randomization of the patient. Starting from Day 2, the study days are the calendar days from 00:00 to 23:59.

Table 2. Schedule of study visits and procedures.

Procedures	**Schedule****																	**Unscheduled visit (safety)**
Visit number	**screening**	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15*****	**EoS**	During the study
Study day	-48 h to Day 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[9]	29[9]	
Obtaining IC/ Enrollment based on a medical consilium recommendation	+																	
Preparation of the Patient's Card and insurance policy	+																	
Demographics	+[1]																	
Allergy history, bad habits	+[1]																	
History of the present illness	+[1]																	
Information about previous and concomitant diseases	+[1]																	
Evaluation of the results of SARS-CoV-2 PCR analysis	+[1]																	
Assessment of chest CT findings	+[1]																	
Prior therapy review	+[1]																	
Anthropometry [2]	+[1]																	
Vital signs [3]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Physical examination	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Hematology [4]	+[1]	+	+	+		+		+								+		+
Blood chemistry panel [5]	+[1]	+		+		+		+								+		+
CRP [12]	+	+	+	+		+		+								+		+
Ferritin [12] (if applicable)	+	+	+	+		+		+								+		+
D-dimer (if applicable) [12]	+	+	+	+		+		+								+		+
Urinalysis [6]		+		+		+		+								+		+
Pregnancy test (urine) [7]	+																	
Evaluation of the inclusion/non-inclusion criteria		+																
Randomization		+																
Blinded administration of OKZ/RPH-104/placebo		+																
Assessment of the clinical status using a 6-point ordinal scale		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+[9]	+[9]	
NEWS2 score		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
SpO_2 assessment	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
PaO_2/FiO_2 assessment (if applicable)	+[10]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		

Procedures	Schedule**																	Unscheduled visit (safety)
Visit number	**screening**	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15***	**EoS**	During the study
Study day	-48 h to Day 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[9]	29[9]	
ECG		+						+								+		+
Concomitant medication review	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+[9]	+[9]	+
AE/SAE recording	+[8]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+[9]	+[9]	+
Collection of retrospective data [11]																	+	

Notes: LDH – last day of hospitalization; EoS – end-of-study visit. Day 1, Visit 1, (randomization day) continues from the end of screening until 23:59 of the same calendar day. Starting from Day 2 of the study Study Day corresponds to calendar day defined as a continuous period from 00:00 to 23:59.
* If the screening procedures period coincides with the calendar day of Visit 1, laboratory tests and other duplicate procedures are not performed on Day 1; the data obtained at the screening visit and entered into the eCRF screening record are also transferred to the eCRF Day 1 record.
** For the efficacy and safety follow-up period: daily during the hospitalization until Visit 15 (Day 15) inclusive or the last day of hospitalization (LHD), whichever comes first.
*** Visit 15 procedures can be carried out on any other LDH day (before discharge of the patient); no procedures or evaluations are carried out from the LHD to Day 29 except those specified in Footnote 9.

1. Results of SARS-CoV-2 PCR tests, chest CT, laboratory tests, anthropometric data, and the patient's medical history data obtained outside the Protocol may be taken into account. Laboratory tests (complete blood count, blood chemistry tests) should be performed within 48 hours prior to randomization.
2. Includes height and weight measurements, BMI. Body weight and height are measured once at the screening. If the anthropometric parameters cannot be evaluated during the screening period, it is allowed to use the data closest to the screening period or to make a measurement during the hospitalization, where applicable. BMI is calculated in the eCRF automatically.
3. Measurements include: blood pressure, pulse rate, respiratory rate, body temperature.
4. The analysis includes: hemoglobin, red blood cells, platelets, white blood cells, neutrophils, lymphocytes, basophils, monocytes, eosinophils (% and absolute values), ESR.
5. The analysis includes: total protein, albumin, glucose, total bilirubin, indirect bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, GGT, LDH, creatinine, sodium, potassium, calcium, chlorides, blood urea nitrogen.
6. The analysis includes: color, clarity, specific gravity, pH, glucose, protein, bilirubin, ketones, nitrites, white blood cells and red blood cells, sediment microscopy.
7. The urine pregnancy test is performed using test strips in all female participants of the study.
8. Only SAEs are registered.
9. If a patient is discharged before the specified study day, the indicated procedures are carried out by telephone; retrospective data are also collected (if applicable); no other procedures are conducted.
10. If the PaO2 cannot be determined, the SpO2/FiO2 is determined.
11. The following should be included: the date of the last day of hospitalization, the date of switching from MV, the end date of oxygen therapy, the date of transfer from the ICU, the results of the PCR tests (primary and confirmatory).
12. Performed in accordance with the schedule of procedures, as well as before the administration of tocilizumab or sarilumab (if applicable).

8.1. Procedures of individual visits

Prior to the start of any study procedures, including other screening procedures, the Investigator provides the patient with all the necessary information about the study and the conditions for participation, as well as sufficient time to decide whether to participate in the clinical study or refuse to participate (see section 8.2.1. Obtaining written informed consent for participation in the clinical study). The patient is guaranteed that he/she will be provided with qualified medical care both in the course of the study and after the study and that the data related to the patient, which is obtained during the study, will be kept confidential. After receiving all the necessary information and making a decision on participation, the patient should personally sign and date the Informed Consent Form for participation in the clinical study in 2 hard copies. One hard copy of the Informed Consent Form is given to the patient. Together with the Informed Consent Form, the patient is given a life and health insurance policy for a patient participating in a clinical study of a medicinal product and a Patient's Card.

If the patient's condition is severe, when neither the patient personally nor their legal representative are able to read and sign the Patient Information Sheet and the Informed Consent Form, the patient may be enrolled in the study by the Principal Investigator's decision based on a Medical Consilium's recommendation (see section 8.2.2. Medical Consilium).

The moment when the patient signs the Informed Consent Form or the PI's decision to include the patient based on a Medical Consilium's recommendation on the advisability of the patient's participation in this study is taken, is considered the time of enrollment of the patient in the study and the start of the screening period.

8.1.1. Screening period

The screening period involves a complex of patient examinations aimed to assess the patient's compliance with all the inclusion/non-inclusion criteria (see sections 5.1. Inclusion criteria and 5.2. Non-inclusion criteria) for participation in the study.

The maximum duration of the screening period is 48 hours, before the start of the day of randomization (Day 1).

If lab test results for a patient do not meet the inclusion/non-inclusion criteria, the patient may be retested during the screening, after receiving the original test results.

If lab test results for a patient do not meet the inclusion/non-inclusion criteria on the basis of laboratory tests during the entire screening period, the patient may be rescreened after obtaining a confirmation from the medical monitor of the study.

Results of SARS-CoV-2 PCR tests, chest CT, laboratory tests, anthropometric data, and the patient's medical history data obtained outside the Protocol, prior to the start of the screening period, may be accepted. Laboratory tests (complete blood count, blood chemistry tests) should be performed within 48 hours prior to randomization.

If the anthropometric parameters cannot be evaluated during the screening period, it is allowed to use the data closest to the screening period or to evaluate them later during the hospitalization, when this becomes possible. If there is no body weight data available at the time of screening, creatinine clearance values are calculated using any other applicable formula that does not include body weight, rather than the Cockcroft-Gault formula.

The screening period includes the following procedures:

- Obtaining IC / PI's decision to include the patient based on a Medical Consilium's recommendation
- Preparation of the Patient's Card and insurance policy
- Collection of demographic data
- Allergy history, bad habits
- History of the present illness

- Information about previous and concomitant diseases
- Evaluation of the results of SARS-CoV-2 PCR analysis
- Assessment of chest CT findings
- Prior and concomitant therapy review
- Anthropometry
- Vital signs
- Physical examination
- Hematology
- Blood chemistry panel
- CRP
- Ferritin (if applicable)
- D-dimer (if applicable)
- Pregnancy test (hCG urine test using a test strip); if the test is positive, the patient is withdrawn from the study
- SpO_2 assessment
- PaO_2/FiO_2 assessment (if applicable); if the PaO2 cannot be determined, determine the SpO2/FiO2;
- Serious adverse event recording.

Patients with a confirmed diagnosis of COVID-19 who meet the inclusion/non-inclusion criteria based on the screening results may be transferred to the treatment period.

8.1.2. Treatment period

Visit 1 (Day 1, from the end of screening to 23:59 of Day 1):

Patients transferred to the treatment period undergo the randomization procedure after completing all other Visit 1 procedures. The patient receives an injection of the study drug on this day. All subsequent events are timed from Day 1. The study drugs are administered no later than 23:59 of Day 1.

If the screening procedures period coincides with the calendar day of Visit 1, laboratory tests and other duplicate procedures are not performed on Day 1; the data obtained at the screening visit and entered into the eCRF screening record are also transferred to the eCRF Day 1 record

The visit procedures are listed below:

- Vital signs
- Physical examination
- Blood sampling for:
  - Complete blood count;
  - Blood chemistry tests;
  - CRP determination;
  - Ferritin determination (if applicable);
  - D-dimer determination (if applicable);
- Urine sampling for urinalysis;
- ECG
- Clinical status assessment using a 6-point ordinal scale
- SpO_2 assessment
- PaO_2/FiO_2 assessment (if applicable)
- NEWS2 score
- Concomitant medication review
- Study eligibility check

- Randomization
- Blinded administration of OKZ/RPH-104/placebo
- Recording of AEs/SAEs (after drug administration).

Patients are transferred to the follow-up period after the study drug injection and other procedures of this visit. All procedures of this visit, except for the recording of AEs/SAEs, are performed before the administration of the study drug.

8.1.3. Follow-up period

During the follow-up period (from 00:00 on Day 2 to 23:59 on Day 29), the efficacy and safety assessments are performed daily during the hospitalization until Visit 15 (Day 15) inclusive or the last day of hospitalization (LHD), whichever comes first. If the patient is discharged earlier than Day 15, no procedures are performed between the LHD and Day 15. If a scheduled session before Day 15 coincides with the LHD, the LHD procedures are performed. Further, the efficacy and safety assessments are performed on Day 15 and Day 29. If the patient continues to be hospitalized until Day 29, no scheduled procedures are carried out between Day 15 and Day 29.

The following procedures are performed at **Visits 2 (Day 2) through 14 (Day 14) or the LHD** (whichever comes first):

- Vital signs
- Physical examination
- SpO_2 assessment
- PaO_2/FiO_2 assessment (if applicable)
- Clinical status assessment using a 6-point ordinal scale
- NEWS2 score
- Concomitant medication review
- AE/SAE recording.

The following procedures are performed only at **Visit 2 (Day 2), Visit 3 (Day 3), Visit 5 (Day 5), Visit 7 (Day 7), and the LHD Visit**:

- Blood sampling for:
  - Complete blood count;
  - Blood chemistry tests (except Visit 2);
  - CRP determination;
  - Ferritin determination (if applicable);
  - D-dimer determination (if applicable);
- Urine sampling for urinalysis (except Visit 2).

Additional procedure for **Visit 7 (Day 7)** and **the LHD Visit**:

- ECG.

If the patient is discharged earlier than Day 14, no procedures are performed from the LDH to Day 15.

Visit 15 (Day 15):

If the patient is discharged earlier than **Day 15,** the following procedures are performed via telephone contact (if applicable):

- Assessment of the clinical status using a 6-point ordinal scale;

- Concomitant medication review;
- AE/SAE recording.

If the patient could not be contacted via telephone in person, the Investigator should make reasonable efforts to find out the necessary information (by interviewing relatives, studying available medical documents or officially published data).

If the hospitalization is ongoing at **Day 15** or the LHD coincides with Day 15, these procedures are performed during face-to-face contact with the patient. In addition, the following procedures are carried out:

- Assessment of vital signs;
- Physical examination;
- SpO2 assessment;
- PaO2/FiO2 assessment (if applicable);
- NEWS2 score;
- Blood sampling for:
  - Complete blood count;
  - Blood chemistry tests;
  - CRP determination;
  - D-dimer determination (if applicable);
  - Ferritin determination (if applicable);
- Urine sampling for urinalysis;
- ECG.

Afterwards, from Day 15 to Day 29 of the study, no procedures are carried out regardless of whether the patient is still hospitalized or has been discharged.

8.1.4. End-of-study visit

The end-of study visit (EoS) will be performed on **Day 29** as telephone contact with the patient and/or retrospective analysis of the patient's medical records (if the patient is discharged before Day 29).

The following information should be collected during the telephone contact (if applicable):

- Clinical status assessment using a 6-point ordinal scale
- Concomitant medication review
- AE/SAE recording.

If personal telephone contact with the patient cannot be established, the Investigator should make reasonable efforts to collect the necessary information (by interviewing relatives, studying available medical records or officially published data).

Based on the patient's medical records, the following information is retrospectively obtained and recorded (if applicable):

- The date of the last day of hospitalization
- The date of switching from mechanical ventilation
- The end date of oxygen therapy
- The date of transfer from the ICU
- The results of the PCR tests (primary and confirmatory).

If the hospitalization is ongoing at **Day 29**, these procedures are performed during contact in person.

A patient is considered having completed the study per protocol after finishing all the procedures scheduled for Day 29.

After finishing all the procedures scheduled for this visit, a Study Completion Form in the eCRF is filled out.

8.1.5. Study withdrawal visit

A patient is considered withdrawn from the study if they meet the criteria specified in Section 5.4. Exclusion criteria (early study termination).

If a patient is withdrawn from the study, the Study Completion Form in the eCRF is filled out, where the following information must be recorded, depending on what is applicable at the time of completion of the patient's participation:

- Assessment of the clinical status using a 6-point ordinal scale
- Concomitant medication review
- AE/SAE recording
- The date of the last day of hospitalization
- Results of physical examination findings, laboratory tests and other investigations applicable to the study and available at the time of the patient’s withdrawal from the study
- The date of switching from mechanical ventilation
- The end date of oxygen therapy
- The date of transfer from the ICU
- The date of and reason for the administration of tocilizumab or sarilumab, if tocilizumab or sarilumab was administered
- The results of the PCR tests (primary and confirmatory).

If a patient is withdrawn from the study and withdraws their consent to data disclosure in the future, it is prohibited to conduct any additional assessments or collect any additional data. The Sponsor may retain and continue to use the data received prior to revocation of consent.

8.1.6. Additional unscheduled visits

At the discretion of the Investigator, an unscheduled visit may be arranged to perform additional safety assessments (repeated laboratory tests, evaluation of AEs) or for other additional assessments during the study.

At an unscheduled visit due to an AE, at least the following assessments may be performed at the discretion of the Investigator:

- Body weight measurement
- Physical examination
- Vital signs
- Hematology
- Blood chemistry panel
- CRP determination
- Ferritin determination (if applicable)
- D-dimer determination (if applicable)
- Urinalysis
- ECG
- Concomitant medication review
- AE/SAE recording.

8.2. Description of individual study procedures

8.2.1. Obtaining written informed consent for participation in the clinical study

Prior to the start of any procedure scheduled for the screening, the Investigator should provide the patient or his/her legal representative with comprehensive information about the study and the conditions for participation, including the following information:

- that the clinical study is experimental in nature, participation of the patient in the clinical study is voluntary, and he/she may refuse to participate in the clinical study at any time;
- the objective of the clinical study, its duration, and the approximate number of participants;
- the treatment options available within the clinical study and the likelihood of random allocation to the treatment groups;
- about the clinical study procedures, including all invasive procedures;
- about the responsibilities of a participant (patient) of the clinical study;
- about the expected risks and/or benefits for a participant of the clinical study, as well as the risks of pregnancy in a female participant during the study;
- about the procedures or treatment options (other than those stipulated by the protocol) that may be available to a participant of the clinical study, as well as their potential benefits and risks;
- about the compensation and/or treatment available to a participant of the clinical study in case of harm to his/her health as a result of participation in the clinical study;
- about the planned expenses for a participant of the clinical study, if any, expected to be associated with his/her participation in the clinical study;
- that the clinical study participant, by signing the Patient Information Sheet with the Informed Consent Form, gives permission to access to his/her medical records: to the person designated for monitoring; auditors, members of independent ethical committees, employees of authorized bodies;
- that the records identifying the participant of the clinical study will be kept confidential and that their disclosure is permitted only in accordance with the legislation of the participating countries; that the data of the clinical study participant will be kept confidential if results of the clinical study are published;
- that the clinical study participant will be immediately notified of any new information that could affect his/her willingness to continue to participate in the clinical study;
- about the persons who can be contacted for more information about the clinical study, and the rights of participants of the clinical study;
- about the possible circumstances of and/or reasons for withdrawal of a participant from the clinical study.

Before obtaining voluntary informed consent, the Investigator must give the patient sufficient time necessary for making a decision whether to participate in the clinical study or not. The patient has the right to receive comprehensive and reliable answers to all questions about the clinical study.

After receiving all the necessary information, the patient should sign and date two copies of the Patient Information Sheet and the Informed Consent Form for participation in the study. The Investigator should also sign and date the Patient Information Sheet with the Informed Consent Form, thereby confirming that the Investigator has discussed them with the patient, the patient has had the possibility to ask questions and received comprehensive answers, and the patient's consent has been obtained.

The patient will receive one copy of the Patient Information Sheet with the Informed Consent Form, and the second copy will be kept by the Investigator at the study site along with other study documents.

After signing the Informed Consent Form, Investigator should also give the patient a copy of the insurance policy and the Patient's Card.

8.2.2. Medical Consilium

The Medical Consilium is a meeting of several doctors of one or several specialties to establish patient's health status, diagnosis, determine the prognosis and management, the advisability of referring a patient to specialized departments of the health care organization or other health care organizations, and to resolve other issues in cases stipulated by the legislation of participating countries. The Medical Consilium is conducted in accordance with the applicable regulatory requirements of the participating countries.

The Principal Investigator must notify the Head of ICU of the study start and the patient inclusion/non-inclusion criteria. In view of the specificity and mode of operation of these units, notification (informing) may take any form: an oral conversation over the telephone, providing an electronic or printed version of the Protocol synopsis. The main task of the notification is to inform the Head of the ICU about the conduct of this clinical study at the health center and the possibility of patients' participation in it. Documentation of the notification process is regulated by local regulations of the health center.

When a patient is admitted at the intensive care unit, before he/she is included in the study, he/she receives standard COVID-19 therapy as per routine practice of participating facility. If the Head of ICU establishes at daily rounds that the patient has no improvement or his/her condition worsens while on standard therapy, while neither the patient personally nor his legal representative have an opportunity to read and sign the Patient Information Leaflet and the Informed Consent Form, the Head of ICU shall make a decision to call a Medical Consilium to recommend including the patient in the clinical study.

The Medical Consilium includes (but is not limited to) the attending critical care physician, the Head of ICU and the supervising Deputy Chief Physician. If any of these persons participates in the clinical study, independent physicians must be invited to the consilium, and at least one of the consilium participants must be an anesthesiologist-resuscitator. The Principal Investigator is invited to the council, he/she does not make decisions, but advises on questions related to the study, if the members of the Consilium have any. The Medical Consilium is aimed at establishing the patient's health status, diagnosis, and prognosis, working out a plan of medical examination and treatment, identifying any need to change therapy, including evaluation of the benefit-risk ratio (expediency) of the patient's participation in the clinical study in each case where obtaining the informed consent of the patient or their legal representative is impossible. Based on the Consilium decision, the attending critical care physician prints minutes indicating the names of the doctors involved in the Consilium, information about the reasons for the Consilium, the course of the patient's disease, the patient's condition at the time of the council, including interpretation of clinical data, laboratory, instrumental and other investigations and the decision of the Medical Consilium. If there is a dissenting opinion of the member of Consilium, an appropriate entry is made in the minutes; the minutes should also indicate the date and time; the minutes are signed by all members of the Medical Consilium (attending physician, Head of ICU, Deputy Head Physician, etc., if applicable). The decision of the Medical Consilium does not imply inclusion (randomization) of the patient in the study, but gives the Principal Investigator a recommendation and a right (but not an obligation) to start the screening procedures according to the Protocol. The selection of patients who have medical indications for participation in a clinical study of a medicinal product for human use is a function of the Investigator.

If the decision of the Medical Consilium is positive, the Investigator can include the patient in the study and start performing the screening procedures.

At the earliest opportunity, the patient or his/her legal representative should be informed as soon as possible about the study, and they should be asked for consent to continue participation in the study in accordance with section 8.2.1. Obtaining written informed consent for participation in the clinical study.

8.2.3. Collection of demographic data, life history, medical history, and prior therapy

Based on the patient's medical records and the results of questioning the patient, the following parameters will be recorded (if applicable):

Demographics:
- date of birth (age);
- sex;
- race and ethnicity;
- assessment of childbearing potential (use of contraception, presence of menopause, its duration, sterilization data)

Bad habits:
- information about bad habits (smoking and drinking).

History of allergies:
- information about any allergic reactions in the patient.

History of the present illness:
- medical history of the primary disease.

Previous and concomitant diseases:
- medical history of past/concurrent diseases (past oncological and infectious diseases, chronic infectious and inflammatory diseases, concomitant somatic diseases) with an indication of the known onset/end date.

Prior and concomitant therapies:
- collection of data on previous and concomitant therapy that the patient has received earlier and is receiving at the time of screening for the treatment of the primary disease, including the names of the drugs, doses, regimens;
- collection of data on medicines that the patient received within 1 month (for drugs listed in the non-inclusion criteria: within 5 half-lives of the drug or 1 month, whichever is longer) prior to screening or is receiving at the time of screening for the treatment of concomitant diseases, indicating the doses, frequency of administration and duration of use.

8.2.4. Evaluation of the results of SARS-CoV-2 PCR analysis

Results of laboratory tests for 2019-nCoV RNA by polymerase chain reaction (PCR) obtained earlier during the patient's examination may be used to assess the compliance of the patient with the inclusion/non-inclusion criteria of the study if applicable. If no PCR results are available at the time of screening, the results of the primary and confirmatory tests (in accordance with the diagnostic standards for the disease) should be recorded in the patient's eCRF retrospectively, after they become available. The test results, together with the reports of the relevant specialists, are stored as source documentation.

8.2.5. Anthropometric parameters

Anthropometric parameters include the following:

- body weight (kg) – measured once at a screening visit;
- height (cm) – measured once at a screening visit;
- body mass index (BMI) – the calculation is made in the eCRF automatically using the following formula:

$$BMI = \text{body weight (kg)}/(\text{height (m)}^2)$$

If it is not possible to evaluate anthropometric data during the screening period, it is allowed to use the data closest to the screening period or to make measurements later during the hospitalization, when this becomes possible.

8.2.6. Physical examination

A physical examination will include examinations of the following systems:

- skin, visible mucous membranes, hair, nails (examination),
- lymph nodes (examination, palpation),
- ENT organs, respiratory system (examination, auscultation of the lungs),
- cardiovascular system (auscultation of the heart, examination of the area of large vessels),
- gastrointestinal tract (examination, palpation of the abdomen),
- assessment of the liver size (palpation, percussion).

The sequence of assessments during the visit is not strictly defined.

In view of the specific arrangements of work with patients with the new coronavirus infection, the mandatory use of personal protective equipment and the need to have the patient in the prone position may preclude a full physical examination. Therefore, physical examination procedures are optional, if applicable.

8.2.7. Vital signs

Assessment of vital signs includes the following:

- body temperature (in Celsius degrees),
- blood pressure (BP) (on one arm, in mmHg),
- pulse (per minute),
- respiratory rate (RR) (resp. per min.), except for mechanically ventilated patients.

Blood pressure (systolic and diastolic blood pressure) will be determined using blood pressure cuff on the same arm. Body temperature is measured in the same way throughout the study.

When a patient is in ICU, the pulse is measured using a cardiac monitor. After transferring patients to the specialized department, the pulse is measured by a health care professional. Pulse rate and RR measurements are performed for 1 minute.

When the patient is outside the ICU, vital signs are measured after a 5-minute rest in a sitting position (if applicable).

The sequence of assessments during the visit is not strictly defined.

8.2.8. Laboratory tests

During the study, blood and urine samples will be taken from each patient for laboratory tests, efficacy and safety assessments. Laboratory tests include an assessment of the main parameters of hematology, blood chemistry, and urinalysis. The levels of cytokine storm markers: CRP, ferritin (if applicable) and D-dimer (if applicable) will also be determined. If necessary, additional laboratory tests may be carried out to assess changes in the analyzed parameters over time.

To exclude pregnancy, all women participating in the screening study will have urine hCG levels measured.

All analyses are performed at the local laboratory of the study site.

If the screening procedures period coincides with the calendar day of Visit 1, then laboratory tests on Day 1 are not performed again; the data obtained at the screening visit and entered into the eCRF record for screening are also transferred to the eCRF record for Day 1.

Laboratory test results obtained outside the Protocol, prior to the start of the screening period may be taken into account. In any case, a complete blood count and blood chemistry tests should be performed no earlier than 48 hours before randomization.

The list of parameters determined by individual laboratory tests, their specifics and the frequency are presented in Table 3.

Table 3. The list of parameters determined by individual laboratory tests, their specifics and frequency

Procedure	Parameters	Specifics	Dosing frequency
Hematology	• Hemoglobin (g/L) • Red blood cells (x10^{12}/L) • Platelets (x10^{9}/L) • White blood cells (x10^{9}/L) • WBC differential: – Neutrophils (% and x10^{9}/L) – Lymphocytes (% and x10^{9}/L) – Basophils (% and x10^{9}/L) – Monocytes (% and x10^{9}/L) – Eosinophils (% and x10^{9}/L) • ESR (mm/h)	Whole blood is sampled using standard methods.	x 7: screening Visit, Visits 1, 2, 3, 5, 7, 15/LHD.
Blood chemistry	• Total protein (g/L) • Albumin (g/L) • Glucose (mmol/L) • Total bilirubin (μmol/L) • Indirect bilirubin (μmol/L) • Direct bilirubin (μmol/L) • ALT (U/L) • AST (U/L) • ALP (U/L) • GGT (U/L) • LDH (U/L)	Whole blood is sampled using standard methods.	x6: screening Visit, Visits 1, 3, 5, 7, 15/LHD.

Procedure	Parameters	Specifics	Dosing frequency
	• Creatinine (μmol/L) • Sodium (mmol/L) • Potassium (mmol/L) • Total calcium (mmol/L) • Chloride (mmol/L) • Blood urea nitrogen (μmol/L)		
Determination of CRP levels	• C-reactive protein (mg/L), the reference range is established by the local laboratory	Whole blood is sampled using standard methods.	x7: screening Visit, Visits 1, 2, 3, 5, 7, 15/HD.
Determination of D-dimer level (if applicable)	• D-dimer (ng/mL), the reference range is established by the local laboratory	Whole blood is sampled using standard methods.	x7: screening Visit, Visits 1, 2, 3, 5, 7, 15/LHD.
Determination of ferritin level (if applicable)	• Ferritin (μg/L), the reference range is established by the local laboratory	Whole blood is sampled using standard methods.	x7: screening Visit, Visits 1, 2, 3, 5, 7, 15/LHD.
Urinalysis	• Color • Clarity • Specific gravity • pH • Glucose • Protein • Bilirubin • Ketone bodies • Nitrites • White blood cells • Red blood cells •	Carried out according to the standard method	x5: Visits 1, 3, 5, 7, 15/LHD.
Pregnancy test	• Urine hCG	Test dip-sticks are used Tests are performed for all women participating in the study. The test drugs may be used only if the test result is negative An indecisive test result is regarded as positive. If the test result is positive or erroneous, the test drugs are not used, the patient is excluded	x1: Screening Visit

Procedure	Parameters	Specifics	Dosing frequency
		from the study and followed-up in accordance with generally accepted standards of care	

8.2.9. Electrocardiography

An electrocardiogram (ECG) will be recorded after the patient rested lying down for at least 10 minutes (if applicable).
ECG data will be entered into the patients' eCRFs. The heart rate will be measured and a conclusion will be made on normal results or presence of clinically significant or clinically insignificant ECG abnormalities. Original electrocardiograms with expert opinions will be stored as source documentation.

8.2.10. Assessment of chest CT findings

Chest CT results obtained earlier during the patient's examination may be used to assess whether the patient meets the inclusion/non-inclusion criteria of the study. The results of investigations, together with the conclusions of the relevant specialists, are stored as source documentation.

8.2.11. Determination of oxygenation parameters

SpO_2 is determined using a pulse oximeter.

PaO_2/FiO_2 is a parameter used in anesthesiology, critical and intensive care to evaluate the oxygen exchange function in the lungs. The oxygenation index is calculated using the formula, such as the PaO_2/FiO_2 ratio (the ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen). It is determined in patients in ICU, including mechanically ventilated patients. If the PaO2 cannot be determined at the screening visit, the SpO2/FiO2 should be determined.

9. EFFICACY ASSESSMENT

According to efficacy endpoints, the following should be evaluated at study visits from Day 1 to Day 15:

1. Clinical status of the patient;
2. The fact of administration of tocilizumab or sarilumab (not earlier than 24 hours after the administration of the study drugs);
3. Changes in oxygenation parameters over time;
4. The need for non-invasive ventilation;
5. The need for invasive mechanical ventilation (IMV) and/or ECMO;
6. Changes in cytokine storm biomarkers: blood sampling is performed on Days 1, 2, 3, 5, 7 and Day 15.

9.1. Assessment of treatment response

A treatment response is an improvement of 1 point or more on the 6-point scale (section 9.2 Assessment of the clinical status of the patient) after the administration of the study drugs, provided that tocilizumab or sarilumab was not administered to the patient before the assessment.

9.2. Assessment of the clinical status of the patient

The clinical status of the patient is evaluated on a 6-point ordinal scale daily during hospitalization (Day 1 to Day 15). If the patient is discharged before Day 15 or Day 29, the clinical status on these days is assessed by contacting the patient on the telephone.

The 6-point ordinal scale includes the following categories:

1. Not hospitalized; no activity limitations;
2. Not hospitalized; limited activity;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, supplemental oxygen; with independent breathing;
5. Hospitalized, mechanical ventilation (invasive/non-invasive) or ECMO;
6. Death.

Activity limitations are defined as absent if the patient, at the time of assessment, is able to perform all the daily physical activity that he/she could perform before the disease. The clinical status is evaluated daily.

The clinical status of patients in the intensive care unit is assessed at each visit for the day preceding the day of the visit (i.e., the status of Day 2 is recorded on Day 3 and is indicated as “status on Day 2”). The worst value of the estimated parameter obtained within 24 hours is recorded in the eCRF.

The clinical status of patients undergoing treatment in specialized departments and those followed-up outpatiently is recorded at the day of assessment in accordance with the schedule of visits (Table 2).

9.3. NEWS2 score

The National Early Warning Score 2 (NEWS2) scale allows identifying patients with an increased risk of adverse outcome based on 7 clinical parameters: respiratory rate (RR), blood oxygen saturation (SpO_2), use of oxygen therapy or room air breathing, body temperature, systolic blood pressure (SBP), pulse, level of consciousness. The scale has a special section (SpO2 2) for use in patients with hypercapnic respiratory failure.

Physiological parameter	3	2	1	0	1	2	3
respiration rate (per minute)	≤ 8		9-11	12-20		21-24	≥ 25
SpO_2 Scale 1 (%)	≤ 91	92-93	94-95	≥ 96			
SpO2 Scale 2 (%)	≤ 83	84-85	86-87	88–92 ≥93 (air)	93–94 (oxygen)	95-96 (oxygen)	≥97 (oxygen)
Air or oxygen?		Oxygen		Air			
Body temperature, °C	≤ 35.0		35,1-36,0	36,1-38,0	38,1-39,0	≥ 39.1	
SBP, mm Hg	≤ 90	91-100	101-110	111-219			≥ 220
Pulse, per minute	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Consciousness				A			C, V, P or U

Levels of consciousness: A - alert, V (voice) - responds to voice, P (pain) - responds to pain, C - confusion, U (unresponsive) - unconscious, does not respond.

The scores for each physiological parameter are summarized, the final score can be range from 0 to 20. A higher score means a more severe condition of the patient.

The NEWS2 scale score is recorded directly on the day of assessment (i.e., Day 3 score is recorded on Day 3) from Day 1 to Day 15 (LHD) inclusive. The score is estimated as the sum of all the scale parameters. During the stay in the ICU, the maximum and minimum scale scores are recorded; when the patient is outside the ICU during hospitalization, the scale is evaluated once a day at the same time with an acceptable time window of ± 2 hours.

9.4. Assessment of surrogate cytokine storm markers

During the study, on Days 1, 2, 3, 5, 7, and Day 15 (LHD), blood samples will be collected to evaluate surrogate cytokine storm markers (blood CRP, ferritin (if applicable), D-dimer (if applicable), neutrophil count, white blood cell count, lymphocyte count) (see Tables 2, 3). Additionally, blood samples to determine cytokine storm markers will be collected before the administration of tocilizumab or sarilumab (if applicable).

9.5. Determination of oxygenation parameters

During the patient's stay in the ICU, the following oxygenation parameters will be determined: SpO2, PaO2/FiO2.

During the stay in the ICU, the maximum and minimum scale scores are recorded; when the patient is outside the ICU during hospitalization the scale is evaluated once a day at the same time with an acceptable time window of ± 2 hours. For a description of the procedure, see section 8.2.11. Determination of oxygenation parameters.

9.6. Assessment of ARDS severity

ARDS severity is assessed (when applicable) based on PaO2/FiO2a and corresponds to the following categories:

- Mild ARDS: 200 mm Hg <PaO2/FiO2a ≤ 300 mm Hg (with PEEP or CPAP ≥ 5 cm H2O or without ventilation)
- Moderate ARDS: 100 mm Hg <PaO2/FiO2 ≤ 200 mm Hg (with PEEP ≥ 5 cm H2O or without ventilation)

- Severe ARDS: PaO2/FiO2 ≤ 100 mm Hg (with PEEP ≥ 5 cm H2O or without ventilation)
- If it is not possible to evaluate PaO2, ARDS is assumed in SpO2/FiO2 ≤ 315 (including in non-ventilated patients).

10. SAFETY ASSESSMENT

10.1. Adverse events

In this study, an adverse event (AE) means any untoward medical event in a patient receiving the study drugs that does not necessarily have a causal relationship with the study drug. Thus, an adverse event can be any unintended and adverse symptom (for example, a laboratory abnormality), a symptom or a disease with temporal relationship with the use of the drug, regardless of whether they are considered to be related to the drug.

All AEs should be followed-up until resolution or stabilization (as assessed by the Investigator).

10.2. Serious adverse events (SAEs)

A serious adverse event (SAE) is any adverse event that meets one or more of the criteria listed below:

- Resulted in the patient's death;
- Is life-threatening;
- Requires hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability or incapacity, or
- Is a congenital anomaly or developmental defect occurring in children born to patients treated with the study drug.

In addition, serious adverse events may include other important medical manifestations if the physician-Investigator believes, on the basis of his/her medical experience, that this manifestation may result in one of the outcomes described above if no medical intervention is undertaken.

An adverse event is considered to be “life-threatening” if the patient was at an immediate risk of death at the time of the event. This category does not include adverse events, which hypothetically might have caused the patient's death if they were more severe.

10.3. AE recording

Adverse events are registered either on the basis of complaints spontaneously reported by the patient or by the Investigator interviewing the patient or using physical examination findings and results of laboratory and instrumental investigations. The Investigator should formulate his / her questions to the patient so that they do not prompt the patient to report unreliable information.

Adverse events had to be registered in the respective sections of the eCRF, as well as in the patient's source medical documents.

All adverse events, except serious ones, are recorded from the moment of the use of the investigational drugs. Adverse events recorded prior to the start of the study therapy, but after the patient is included in the study, are recorded in the eCRF as “Concomitant diseases”. Adverse events will be registered until the end of the follow-up period.

The following information should be reported for registered AEs:

- The patient's identification number;

- The diagnosis made in connection with the adverse event (making a diagnosis should be preferred to listing symptoms);
- The start and resolution dates for the adverse event (and the times if applicable);
- AE severity;
- The relationship with the use of the investigational medicinal product;
- The measures that have been taken due to the adverse manifestation;
- Whether the adverse event fulfils the serious adverse event criteria;
- The outcome of the adverse event.

Assessment of the cause-and-effect relationship between the adverse event and the use of the investigational medicinal product

The Investigator is responsible for the assessment of the relationship between the investigational drug and AE. The Investigator should use his/her knowledge about the patient, the circumstances of the event, and assessed any potential alternative causes to determine whether or not the AE is related to the study drug. The relationship between the AE and the study drug should be characterized as either "related" or "unrelated". The following recommendations should be considered:

- Temporal relationship between the onset of the adverse event and the beginning of the study drug use.
- Evolution of the adverse event over time, discontinuation of the study drug.
- Known association of the adverse event with the study drug or a similar ttreatment.
- Risk factors in patients increasing the likelihood of an adverse event.
- Factors not related to treatment, associated with the event frequency.

The Investigator should report the relationship of each event to the study drug based on the most probable causality; the study staff is responsible for obtaining any missing information.

If the assessed relationship changes over time as a result of new or changing information, it may be revised.

Adverse event severity grade

AE severity is graded according to the CTCAE classification V5.0.

If certain adverse events were not listed in the CTCAE, the physician-Investigator will classify them according to the following grades and definitions:

Grade 0:	No AE (or within normal limits)
Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate; non-significant, local or noninvasive intervention indicated (e.g. wrapping, application of cauterants); limiting age-appropriate instrumental activities of daily living
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
Grade 4:	Life-threatening complications; urgent intervention is indicated
Grade 5:	Death related to AE

Severe AE may be not serious and, conversely, a serious AE is not necessarily severe.

Given the nature of the disease under study, it is expected that patients will develop frequent laboratory and vital sign abnormalities. During the study, all AEs will be recorded, only grade 4 and 5 AEs according to CTCAE v.5.0 will be included in the analysis.

Specific requirements for registration of AEs:

- Increasing severity of symptoms of the underlying disease (COVID-19) in this study will not be considered an AE.
- In patients with clinical and laboratory abnormalities or those with any other pathology at the time of screening, a change in the severity or other clinically significant deterioration should be recorded as AE, at the discretion of the Investigator.
- If hospitalization or its prolongation is a criterion for AE severity, the following hospitalizations are not considered as SAEs:
    - carrying out the procedures specified in the protocol, or administration of the study therapy; for example, hospitalization or prolongation of hospitalization are part of the routine practice at this study site;
    - treatment or examination due to a preexisting condition unrelated to the study therapy (administration of the study therapy) for the underlying disease, which did not worsen;
    - scheduled or unscheduled examination, rehabilitation for social reasons or surgical intervention not aimed at treatment of SAE;
    - social reasons, for example, additional supervision by a doctor or hospitalization in order to provide additional comfort in the winter season when there are multiple visits according to the Protocol, etc.

10.4. SAE reporting

SAEs are recorded after inclusion of the patient in the study (signing the Informed Consent Form or enrollment following the Principal Investigator's decision based on a Medical Consilium's recommendation). To ensure safety for study subjects in case of any SAE developing during the study, regardless of the suspected causes of the SAE or the relationship with the use of the investigational drug, the SAE should be reported to the study Sponsor within 24 hours after the Investigator becomes aware of the SAE.

If a patient develop a serious adverse event assessed by the Investigator as related to the use of the investigational drug, it should be reported even if the study has already been completed.

Filling out the serious adverse event reporting form.

SAEs should be reported by sending a scanned copy of the filled serious adverse event reporting form in paper format by e-mail to:

Safety@Rpharm.ru.

or by fax to:

+7 (495) 956-79-38

The principal person to contact on any issues related to the safety of the study drugs is Sergey, MD PhD., Head of Drug Safety and Pharmacovigilance, R-Pharm JSC.

Phone:+7 495 956-79-37, ext. 1506

fax: +7 (495) 956-79-38.

email: Safety@rpharm.ru

The Investigator should notify LEC of SAEs in accordance with LEC's standard operating procedures.

Reporting suspected unexpected serious adverse reactions (SUSAR).

The Study Sponsor should notify the regulatory authorities of all suspected unexpected serious adverse reactions within the time frame specified by the law. In the context of notifying regulatory authorities and Investigators, suspected unexpected serious adverse reactions will be

deemed to be unexpected serious adverse events assessed by the Investigator and/or Sponsor to be related to the study drug.

The sponsor will inform Investigators of all suspected unexpected serious adverse reactions recorded during the study. It is the Investigator's responsibility to submit appropriate reports to the Local Ethics Committees of healthcare institution.

Submission of other safety reports.

The Investigators will report to the Local Ethics Committees of the healthcare institutions on other treatment safety-related aspects subject to expedited reporting if they affect the benefit-risk ratio for the study therapy or can necessitate significant modification of the study therapy or study methods.

In addition to submitting expedited reports, the Sponsor will annually prepare safety update reports for OKZ and RPH-104, containing all new relevant safety information received during the reporting period. These reports will be forwarded to the Investigator for submission to the Local Ethics Committees of healthcare institutions once a year.

10.5. Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) will periodically review the available safety data on the investigational drugs from the study and provide the Sponsor with recommendations for further study based on these reviews. The frequency and procedure for conducting safety assessments of drugs will be determined in the IDMC procedures.

In addition, the IDMC will conduct an early analysis of the data obtained in the pilot phase of the study and provide recommendations to the Sponsor on changing the endpoint and the final sample size.

10.6. Pregnancies

Pregnancy is not an adverse event as such, except where there is reason to believe that the use of the investigational drug resulted in decreased effectiveness of the contraceptives used.

If there is a positive pregnancy test before the first use of the drug, the patient is excluded from the study before randomization.

Information concerning pregnancies in female patients or partners of male patients participating in the study should be recorded from the first dose of the study drug.

Male patients will receive instructions in the Patient Information Leaflet and Informed Consent Form to immediately inform the Investigator if the patient's partner becomes pregnant during the study.

If a female patient or a female partner of a male patient participating in the study becomes pregnant, the study Sponsor should be notified by filling out the "Pregnancy reporting". A pregnancy report should be filled out by an authorized employee of the study site within 24 hours after the pregnancy information is received. Pregnancy cases should be reported by sending a scanned copy of the filled pregnancy reporting form in paper format by e-mail to: Safety@Rpharm.ru.

Collection of pregnancy-related information should continue until the end of the pregnancy. After the end of the pregnancy, the study Sponsor should be informed about the outcome of the pregnancy (miscarriage, elective abortion, delivery of a healthy infant or infant with congenital anomalies or developmental defects). If possible, the newborn infant's health should be monitored until 6 weeks, 6 months, and 12 months of age.

Any complications of pregnancy should be recorded as adverse events or serious adverse events depending on the seriousness criteria. Congenital anomalies and developmental defects in subjects' children are serious adverse events. Miscarriages should be recorded as serious adverse

events. Elective abortions carried out at the woman's discretion, without medical indications for abortion and not associated with complications, are not adverse events.

10.7. Actions in emergency situations

The study site should have appropriate equipment and medications necessary for emergency care. Their use should be recorded in the e-CRF;

11. STATISTICAL ANALYSIS

11.1. Justification of the planned sample size

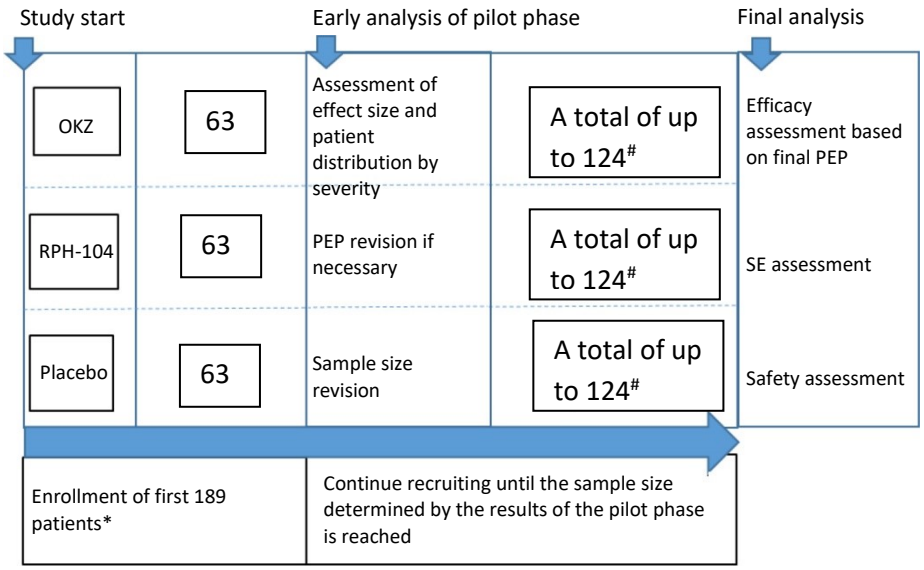
Since there is no reliable data on the course of COVID-19 and the distribution of hospitalized patients by disease severity after the use of standard therapy and the study drugs, the study will include a pilot phase during which it is expected to enroll 63 patients in each treatment group. The final sample size will be determined based on the results of the pilot phase data analysis.

Based on the literature data available as of April 15, 2020 [21, 27-29] and provided that approximately 60% of the patients enrolled in the study fall into category 4 on the clinical status scale ("Hospitalized, supplemental oxygen with independent breathing") and approximately 40% fall into category 5 ("Hospitalized, mechanical ventilation (invasive/non-invasive) or ECMO"), the estimated proportion of treatment responders will be 40% in the placebo group and 60% in the active therapy groups. Table 4 shows the calculation of the total number of patients who should be included in the early and final analysis in order to demonstrate the superiority of any of the study drugs over placebo with a statistical power of 80% and an overall critical level of $\alpha = 2.5\%$ [30]. The calculation was performed using the SAS procedure for planning sequential adaptive designs. Figure 5 shows the study enrollment scheme.

Table 4. Planned sample size for final analysis

Stage of analysis	Randomization	Overall α level	Power	Number of patients in the group	Total number of patients	Randomized patients (20% dropout)
Pilot	1:1:1	0.025	80%	50	150	189
Final	1:1:1	0.025	80%	99	297	372

Figure 5. Study enrollment scheme



OKZ = olokizumab; PE = primary endpoint; SE = secondary endpoints

* 63 patients will be randomized to each group and have the evaluation on Day 15 or complete the study, whichever comes first.

Preliminary number of patients to be randomized. It can be revised based on the results of the pilot phase of the study.

11.2. Analytical methods

Statistical analysis will be performed using specialized software, which will be selected at the stage of preparing the statistical analysis plan.

Continuous (quantitative) data to be presented include the number of observations, the arithmetic mean with standard deviation, the minimum and maximum. Presented qualitative data (ordinal, nominal) will include absolute frequencies (number of observations), relative frequencies (percentages) and 95% CIs.

Medical history, concomitant diseases and adverse events will be encoded using the MedDRA terminology (the Russian version corresponding to the current Medical Dictionary of Regulatory Activities terminology). Concomitant and prior therapy will be encoded using the ATX classifier.

This section briefly describes the planned analysis. The full analysis will be described in the statistical analysis plan.

11.3. Analysis sets

The intent-to-treat (ITT) population will include all randomized patients. Patients will be analyzed in accordance with the treatment group to which they are randomized. The ITT population will be the primary analysis population.

Modified intent-to-treat (mITT) population: the mITT population will include all randomized patients who received the study drug and did not require tocilizumab or sarilumab as part of standard therapy.

Safety population: The safety population will include all patients who have received at least one dose of the study drug. Patients will be analyzed based on the actually received treatment.

11.4. Demographic and other baseline characteristics

Demographic and other baseline characteristics will be presented using descriptive statistics tools by therapy group, as well as separately by therapy group for patients who received at least one dose of tocilizumab or sarilumab and for patients not receiving tocilizumab or sarilumab during the study.

11.5. Efficacy analysis

Analysis of the primary endpoint

In this study, the primary endpoint is the proportion of responders in each treatment group. A responder is a patient who has not received tocilizumab or sarilumab as part of standard therapy and who has a clinical status improvement of ≥1 point on the 6-point COVID-19 scale (where 1 is the most favorable outcome and 6 is the most undesirable outcome) 15 days after the administration of the study drug.

To compare each of the two active therapy groups with placebo, mathematical modeling of the response to treatment will be performed depending on prognostic factors (age and severity of the condition, gender, clinical center, and other significant factors). Relative risk [RR] with a two-way 97.5% CI (the ratio of the probability of response in each of the active treatment groups to the probability of response in the placebo group) will be calculated from the logistic model. To test the hypothesis of superiority of each of the active drugs over placebo, the null hypothesis RR ≤ 1 will be tested with a statistical power of 80% at an overall critical level $\alpha = 2.5\%$ for each of the comparisons. The overall alpha level for the early analysis will be controlled using the alpha spending function.

Analysis of the secondary endpoints

The distribution of patient outcomes on the 6-point ordinal COVID-19 clinical status scale will be presented using the absolute values (the number of patients in each category) and as a percentage for each assessment day, for each of the treatment groups. A detailed description of changes over time in the clinical status of patients using a 6-point ordinal scale will be presented in the statistical analysis plan.

The percentage of patients with a clinical status improvement of 2 or more points on a 6-point ordinal scale occurring during the study with no use of tocilizumab and sarilumab will be presented using the absolute values (number of patients) and as a percentage for each assessment day, for each of the treatment groups. The comparative analysis of the groups will be performed in the same way as the primary endpoint analysis.

The percentage of patients who received tocilizumab or sarilumab during the assessment period and the mortality rate during the follow-up period will be presented using the absolute values (number of patients) and as a percentage for each assessment day, for each treatment group. The comparison of the groups will be performed using a regression logistic model, taking into account the prognostic factors (age and severity of the condition, gender, clinical center, and other significant factors).

Handling missing values and subjects dropping out from the study

Every effort will be made to reduce the proportion of missing data, however, it is expected that a certain amount of data will be missing due to patient drop out of the study. Patients who do not have PE data will be excluded from the primary efficacy analysis.

A sensitivity analysis will be performed using data from the last available patient's observation.

11.6. Safety analysis

The safety analysis will be performed using descriptive statistics in the safety population and the mITT population, and data from the subgroup of patients who received tocilizumab or sarilumab will be separately summarized and presented.

The safety assessment will include the following parameters:

- Frequency, severity, nature and outcomes of AEs (grades 4 and 5 according to CTCAE v.5.0) and SAEs during the study;
- Frequencies of AEs and/or SAEs related to the study drugs observed in the treatment groups;
- Vital signs (BP, pulse rate, RR, body temperature);
- Results of laboratory and other investigations;
- Changes in physical examination findings, vital signs, and laboratory safety parameters during the study.

;

11.7. Early analysis of the pilot phase

The early analysis will be performed after the procedures of Visit 15 (Day 15) or completion of the study, whichever comes first, for the first 63 patients in each of the randomization groups (a total of 189 patients). Descriptive statistics will be used to evaluate the distribution of patients on a 6-point ordinal scale on Day 15 after randomization, the proportion of patients responding to treatment, and the proportion of patients requiring tocilizumab or sarilumab 24 hours after the administration of the study drugs. Mathematical modeling of the response to treatment will be carried out based on the prognostic factors (age, severity of the condition, clinical center, gender, and other significant factors).

All applicable secondary and exploratory endpoints, as well as applicable safety endpoints, will be evaluated as well.

Based on the results of the pilot phase, the final sample size will be calculated for the main phase of the study using the actual disease outcome data.

11.8. Interim analysis

There is no interim analysis in this study.

12. DATA MANAGEMENT AND RECORD KEEPING

12.1. Study site documentation

As defined by ICH GCP E6 (R2), the primary study documents include: signed Protocol and all Amendments, signed Informed Consent Forms for all patients, Investigator's Brochure, medical records and other source documents, approvals issued by the ethics committees and regulatory authorities, study drug accountability records, study-related correspondence, and a list of patient last names and addresses. These documents should be kept by Investigator.

12.2. Source documents

Source documents include the original documents that are relevant to the examination, treatment, medical history and description of the patient's condition. For example, these documents include original medical records and discharge summaries with the laboratory test results.

The responsibility to document the course of the study correctly and accurately lies with the InvestigatorInvestigator. Source documentation is kept according to regulatory requirements.

Records are introduced into the patient's source documents during each examination. The required data are transferred to eCRFs within the period specified in the SOPs of the CRO/Sponsor/Study Site or in other documents.

When there was a need to make corrections in the source documents, the corrector shall cross out the incorrect entry with a single horizontal line, enter the correct information, date of the correction and his/her initials. Do not use any means deleting the previous record or making it illegible.

12.3. Data collection

Electronic CRFs (eCRFs) will be used for this study. The Principal Investigator is responsible for the completeness and accuracy of all data introduced to the eCRF as well as for the proper timing of data entry and update.

The Monitor is responsible for verification of eCRFs for completeness and accuracy of records, instructions for the study site personnel regarding the required corrections or updates

To work in the eCRF system, the Principal Investigator and members of his/her team will receive logins and access passwords.

The eCRF should be completed within a period not exceeding 5 working days from the date of the visit. Screening data should be entered into eIRCs simultaneously, upon completion of screening.

If the screening procedures period coincides with the calendar day of Visit 1, laboratory tests and other duplicate procedures are not performed on Day 1, the data obtained at the screening visit and entered into the eCRF screening record are also transferred to the eCRF Day 1 record.

All data that should be present in the eCRF have to be present in the site source documents.

eCRFs used in this study does not envisage entry of any data that are not recorded in the source documents.

12.4. Data confidentiality

Information about the study subjects will be kept confidential. It will be processed in accordance with applicable laws and regulations.

In order to prevent unauthorized access to confidential information about the study subjects, security elements have been built into the data collection system for this study to encrypt all data when it is transmitted in both directions. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords that will be provided only to authorized employees.

12.5. Document archiving

By signing this Protocol, the Investigator agrees to comply with the rules for storage and archiving of the study documents. Source documents and the study site file including the Patient Information Leaflet as well as study-related correspondence should be retained. Study subject documents shall be archived according to the regulations adopted at the study site.

The Investigator shall inform the Sponsor about the place of storage of essential documents and contact the Sponsor to obtain his approval before destroying any of them. The Investigator shall take measures to prevent accidental or premature destruction of these documents.

The Sponsor is responsible for archiving the Master File of the Clinical Study.

If the Sponsor stops the clinical development of the study drug, the Investigator and regulatory authorities shall be informed of it.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Overall quality assurance information

The Sponsor should ensure an appropriate quality assurance and quality control system for this clinical study in accordance with the study protocol, Good Clinical Practice, and applicable regulatory requirements.

The study procedures specified in the protocol should be strictly followed by the Investigator and members of the study team.

13.2. Quality guarantees

In accordance with the ICH GCP E6 (R2) and regulatory requirements, the Sponsor, a third party on its behalf, regulatory authorities or Ethics Committees may conduct audits (inspections) to guarantee quality assurance at any time during the study or after completion of the study. The Investigator should provide the auditors with direct access to all study-related documentation, including source documents, and to ensure that he/she and his/her staff members dedicate time to discuss with the auditors the results of audits and inspections, as well as other issues.

13.3. Investigator's adherence to the protocol

Prior to the beginning of the study, the Investigator should fully review the provisions of this protocol, accept them, and conduct the study in accordance with this protocol, ICH GCP E6 (R2),, and other applicable regulatory requirements of the participating countries.

During the study, deviations from the protocol requirements are not allowed, unless they are necessary to prevent any immediate danger to the patient.

The Investigator should have sufficient time to conduct the study correctly and complete the study within the period approved by the Sponsor, as well as have a sufficient number of qualified staff members and adequate equipment to conduct the study according to this protocol.

Each co-Investigator involved in the study should be aware of the protocol requirements and his/her obligations within the study. The Principal Investigator shall document delegation of any of his/her functions in this study to co-Investigators in writing in the appropriate section of the Investigator's File.

In case of repeated deviations from the protocol, temporary suspension or permanent termination of the study at this study site will be considered.

13.4. Protocol deviations

A protocol deviation is any change in, non-compliance with, or deviation from the study design or procedures described in the study protocol, as well as the guidelines and instructions provided for in the study.

Any protocol deviation occurring during the course of the clinical study should be registered and recorded in the study documentation.

13.5. Liability for non-compliance with the study requirements

Failure to comply with the protocol, SOPs and/or applicable regulatory requirements by the Investigator / study site, CRO, or the Sponsor’s staff should prompt urgent actions by the Sponsor to ensure compliance.

If monitoring or auditing identifies serious and/or recurring cases of non-compliance with applicable requirements by the Investigator / study site or CRO, the Sponsor should terminate the participation of the violating party in the study and notify regulatory authorities as appropriate.

13.6. Study monitoring

Monitoring of the clinical study should be conducted by the Sponsor or the CRO authorized by the Sponsor for the following purposes:

- assurance of protection of the rights and wellbeing of study subjects;
- verification of the accuracy, completeness and reliability of the data recorded in the data collection system, and their compliance with the data of the source documentation;
- verification of the adherence of the Investigator and members of the study team to the procedures of the approved study protocol, amendments to the protocol in the current version (if applicable), the rules of Good Clinical Practice, and current regulatory requirements.

The clinical study is monitored according to the approved Monitoring plan described in a separate document. The clinical study monitor should ensure that the study is properly conducted and documented. The responsibilities of the clinical study monitor include the following functions:

- checking that the Investigator has the necessary qualifications and sufficient resources, including laboratories, equipment, and personnel, throughout the study;
- control of the use of the study drug (storage conditions and shelf life, availability of a sufficient amount of the drug in the study site, correctness of the administration of the study drug, drug accounting);
- checking that the Investigator adheres to the approved plan and all approved protocol amendments (if applicable);
- control of the timely (i.e., before the beginning of the patient's participation in the study) signing of the Patient Information Leaflet and Informed Consent Form or provision of an appropriately documented decision of the Principal Investigator based on a Medical Consilium’s recommendation to include the patient in the study;
- ensuring that the Investigator holds the current versions of the documents related to the conduct of the clinical study (protocol, amendments to the protocol (if applicable), Investigator's Brochure, Patient Information Leaflet and Informed Consent Form);
- ensuring that sufficient information about the study has been provided to the Investigator and members of the study team;
- monitoring the fulfillment by the Investigator and members of the study team of the responsibilities related to the study in accordance with the protocol and other applicable agreements/contracts between the Sponsor and the Investigator / health care institution, as well as the independence of the fulfillment of their responsibilities (identifying any delegation of the Investigator’s functions to unauthorized persons);
- control of the Investigator’s adherence to the eligibility criteria;
- notifying the Sponsor about the subject recruitment rate;
- control of the correctness and completeness of the data in the eCRFs, source documentation, and other study-related records by comparing them;
- notifying the Investigator about any errors, omissions, and illegible records made in the eCRFs;
- verification of the adherence to the adverse event reporting time frames laid down in this protocol;
- control of the maintenance of the essential documents by the Investigator;
- notifying the Investigator about any deviations from the protocol, SOPs, regulatory requirements; taking necessary actions to prevent the recurrence of such deviations.

The Investigator should provide the Monitor with direct access to all source documents of the patient.

Monitoring procedures related to the preparation, administration and recording of the drug in accordance with patient randomization groups are carried out by an unblinded monitor. A blinded monitor shall not have access to this data.

13.7. Sponsor's audit

Sponsor's audit is conducted separately and independently of routine clinical study monitoring and quality control functions. The objective of this audit is to evaluate the compliance of the conducted study with the protocol, SOPs, and applicable regulatory requirements.

For this audit, the Sponsor appoints persons independent of the conduct of this clinical study.

The Sponsor should make sure that the auditors have sufficient qualifications to conduct the audit properly. The auditor' qualifications should be documented.

The Sponsor or authorized organization develops an audit plan and audit procedures for this study, which should be followed during the audits.

13.8. Database management and quality control

In studies using eCRFs, the Sponsor's (or assigned CRO's) employees will analyze the data introduced by the study site personnel for accuracy and completeness. If inconsistencies or missing data are detected, data queries will be submitted to the study site specifying the nature of the problem and the required details. These queries will be sent to the study site. Designated study staff members shall promptly answer the queries and modify the data accordingly.

At the end of the study, protocol deviations will be identified. After these activities are completed and database accuracy and completeness are confirmed, it will be locked and prepared for data analysis.

After the database lock, the Investigator shall receive a CD-based or a hardcopy containing the patients' data for archiving at the study site.

14. STUDY STOPPING RULES

The study may be terminated for the following reasons:

1. By the decision of local Ethics Committees or regulatory authorities;
2. By decision of the Investigator / study site (in a specific study site).
3. By the decision of the Study Sponsor for the reasons related to safety, ethical principles, compliance with the Protocol or other reasons.

The Sponsor has the right to suspend the study at any time for the reasons related (but not limited to) to safety, ethical aspects or administrative issues. The sponsor has the right to terminate the study at any time if the goals and objectives of the study are not met. In this case, the Sponsor shall inform the Investigator or the management of the study site of suspension or termination of the study in writing.

If the Investigator / management of the study site prematurely terminates the study at a specific study site without the prior consent of the Sponsor, he/she should inform the management of the study site (if applicable) and inform the Sponsor and the local ethics committee (LEC), as well as provide the Sponsor and LEC with a detailed explanation of the reason for the suspension or termination of the study in writing.

If the study is suspended or terminated for safety reasons, the Sponsor shall immediately inform the Investigator as well as the regulatory authorities or ethics committees.

If, for any reason, the study is prematurely terminated or suspended, the Investigator (medical institution) shall immediately inform the patients, provide them with appropriate treatment and supervision and, if required by applicable requirements, inform the regulatory authorities.

15. ETHICAL ASPECTS

This study will be conducted in accordance with ethical concepts stated in the World Medical Association's Declaration of Helsinki and ICH GCP regulations.

The final Protocol version (including the Patient Information Leaflet and Informed Consent Form) shall be submitted for approval to the regulatory authorities of the member states, as well as to the local ethics committees of the study sites prior to the study beginning

All subsequent amendments to the Protocol, including purely administrative, will be approved in accordance with the procedure established in the respective country participating in the study. The procedure of obtaining the Informed Consent Form will be conducted prior to the beginning of any study procedures. The Patient Information Leaflet will contain all information about this clinical study that is needed to make a sensible and voluntary decision. If the patient's condition does not allow to express his/her will, the patient can be included in the study by decision of the Principal Investigator based on a Medical Consilium's recommendation in accordance with the applicable regulations of the country in which the study is conducted. The decision of the Medical Consilium is drawn up in minutes, signed by the participants of the Medical Consilium and entered into the patient's medical records. In this case, the procedure for obtaining informed consent from the patient shall be carried out as soon as the patient's condition permits. If the patient decides not to continue to participate in this clinical trial, he/she will be excluded from the study due to withdrawal of informed consent.

In the course of the study, all SAEs will be reported to the Sponsor (that may make a decision to suspend the study based on the analysis of submitted data) within 24 hours. Ethics Committee also shall be informed of SAEs, including unexpected and related, as believed by the Investigators to the study drug administration.

Information identifying the patients is confidential and may be disclosed only in cases provided for by law and upon decisions of the judicial bodies.

All study subjects will be insured as required by local regulatory requirements.

16. CONFIDENTIALITY

The Investigator undertakes to maintain confidentiality regarding the identity of patients, the text of this Protocol, as well as all other materials and study results.

The Investigator should ensure the anonymity of the volunteers. Electronic Case Report Forms and other documents submitted to the Sponsor shall not contain volunteers' names or last names and should use only assigned identification numbers and/or initials.

The Investigator should keep a special log to register identification numbers, last names, addresses, phone numbers and medical record numbers (if any). The Investigator shall keep the data intended for the Sponsor strictly confidential.

Any study materials that belong to the Sponsor should not be handed over to any third parties except as required by the applicable laws.

17. FUNDING AND INSURANCE

The patients will not receive any payment for participation in this study.

During the study, the patients will be insured as study subjects according to the legislation of the member state.

If the patient's health is damaged due to the use of the study drugs or medical procedures specified in the Study Protocol, he/she will be provided with free qualified medical care to the extent necessary, paid for by the Insurance company.

18. PUBLICATIONS

After the completion of the study and statistical data analysis, it data will be published. The Investigator should not publish the results of this study (including those obtained at the study site) without the Sponsor's consent. The results obtained in a specific study site should not be published prior to publication of general study results.

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