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OBSERVATIONAL STUDY PROTOCOL

N **COVID v1.0 final** dated March **30, 2020**

Open multi-centre observational study to evaluate efficacy and safety of adding Polyoxidonium lyophilizate to a complex therapy of hospitalized patients with COVID-19.

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GENERAL INFORMATION ABOUT THE OBSERVATIONAL STUDY. AUTHORIZED SIGNATURES

STUDY TITLE	Open multi-centre observational study to evaluate efficacy of adding Polyoxidonium lyophilizate to a complex therapy of hospitalized patients with COVID-19.
STUDY CODE	COVID
PROTOCOL	*N* COVID *version* v1.0 final *dated* March 30, 2020
INVESTIGATIONAL PRODUCT	Polyoxidonium
INTERNATIONAL NONPROPRIETARY NAME	azoximer bromide
DOSAGE FORM	lyophilizate
STUDY DESIGN	Open multi-centre observational
SPONSOR	NPO Petrovax Pharm LLC Sosnovaya ul. 1, s. Pokrov, Podolsk, Moscow Oblast, 142143 Russia. Tel.: +7 (495) 730-75-45
LIST OF HEALTHCARE INSTITUTIONS	A list of the centres participating in this observational study with the names, addresses, and principal investigators will be provided separately.
NAME AND POSITION OF THE PERSON AUTHORIZED BY THE SPONSOR TO SIGN THE PROTOCOL AND THE PROTOCOL AMENDMENTS	Dodonov N.S. Head of Medical Affairs March 30, 2020

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LIST OF ABBREVIATIONS

MedDRA	Medical Dictionary for Regulatory Activities
NEWS	National Early Warning Score
SOFA	Sepsis-Related Organ Failure Assessment
$T_{1/2}$	elimination half-life
T_{max}	Time to maximum concentration
AU	absolute units
BP	blood pressure
ALT	alanine transaminase
APC	antibody-producing cells
AST	aspartate transaminase
IB	Investigator's Brochure
IV	intravenous
IM	intramuscular
HIV	human immunodeficiency virus
WMA	World Medical Association
WHO	World Health Organization
PI	Principal Investigator
IHU	Instructions for human use of a drug product
IP, T	investigational product
CRF	Case Report Form
CRO	Contract Research Organization
CoV	coronavirus
CT	computer tomography
ENT	Ear-Nose-Throat
LEC	Local Ethics Committee
mg	milligram
MH RF	Ministry of Health of the Russian Federation
mL	millilitre
INN	international Non-proprietary Name
MMPMT	metachronous multiple primary malignant tumours
DSMB	Independent Data Monitoring Board
SPA	Scientific Production Association
IEC	Independent Ethics Committee

AE	adverse event
LLC	Limited Liability Company
ARVI	acute respiratory viral infection
ARI	acute respiratory infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
SW	Software
CP, R	comparator
PCR	polymerase chain reaction
BC	breast cancer
RNA	ribonucleic acid
RF	Russian Federation
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
ESR	erythrocyte sedimentation rate
PJSIC	Public Joint-Stock Insurance Company
AIDS	acquired immune deficiency syndrome
CRP	C-reactive protein
d	day
US	United States
SARS	Severe Acute Respiratory Syndrome
FZ	Russian abbreviation for “Federalniy Zakon” (Federal Law)
COX	cyclooxygenase
h	hour
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation

1. SYNOPSIS

JUSTIFICATION	In December 2019, the Wuhan Municipal Health Committee identified an outbreak of pneumonia cases of unknown cause. Shortly, coronavirus RNA was identified in the patient biomaterials. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. According to WHO, currently there are no approved therapeutic agents with proven efficacy against SARS-CoV-2. Multiple findings of Chinese studies show that the coronavirus disease is associated with significant disorders of the immune system: changes in cytokine production (increased level of IL-6) and decreased level of CD4+ and CD8+ lymphocytes, phenotypic changes in myeloid lineage. These data indicate the need to search not only for aetiotropic drugs, but also for drugs that can restore the immune response which is necessary both in fight against the infection and in the subsequent recovery period. Polyoxidonium® has been used to treat infectious diseases of various origin for more than 20 years. The drug is indicated for treatment of viral infections as a part of complex therapy, and the mechanism of action affects the immune system. Polyoxidonium® increases resistance of the human body to local and general viral infections. It restores immunity in patients with secondary immunodeficiencies caused by various infections and injuries. Polyoxidonium® is characterized by the ability to activate factors of the early defence against infection. The use of Polyoxidonium® in immunocompromised patients with infectious diseases has been extensively studied in Russia. Polyoxidonium® is a very promising molecule against SARS-CoV-2 that has been confirmed to cause serious disease in immunocompromised patients. According to available data, two-thirds of patients with coronavirus have lymphopenia and most of those who died from the virus had concomitant diseases or were over 50 years old. Therefore, treatments that enhance immune functions might reduce the mortality and the disease severity as well. Polyoxidonium® in combination with antibiotics shortened the duration of symptoms greatly compared to monotherapy with antibiotics in HIV-infected patients with pneumonia. The CD4 count also increased in patients who were treated with Polyoxidonium®. This effect was confirmed in two-year-old patients with pneumonia. Polyoxidonium® reduced the duration of episodes of infectious diseases and prolonged remission in patients with primary immunodeficiencies. Administration of Polyoxidonium® to patients with acute pancreatitis led to a 2-fold decrease in mortality. Administration of Polyoxidonium® to cancer patients receiving chemotherapy led to a significant increase in the number of CD4 and CD8 cells in blood in the clinical trials. The safety of Polyoxidonium® has been proven in more than 20 clinical studies both in Russia and in other countries, including Slovakia. Polyoxidonium® can be used to increase efficacy of the immune response in patients with SARS-CoV-2, based on its effects on the number of lymphocytes and on the duration of pneumonia in immunocompromised patients. Thus, immune stimulating therapy with Polyoxidonium is expected to reduce mortality and disease severity in patients with COVID-19.
PROTOCOL TITLE	Open multi-centre study to evaluate efficacy of adding Polyoxidonium® lyophilizate to a complex therapy of hospitalized patients with COVID-19.
STUDY PERIOD	2020
STUDY AIM	To evaluate safety and efficacy of Polyoxidonium® (azoximer bromide) as an

	addition to complex treatment of hospitalized patients with COVID-19.
KEY OUTCOMES	**EFFICACY OUTCOMES**
SAFEY AND EFFICACY	**PRIMARY EFFICACY ENDPOINT** *Subject clinical status using the WHO 7-point ordinal scale* on day 15 as compared to baseline. 1. Not hospitalized, no limitations on activities. 2. Not hospitalized, limitation on activities. 3. Hospitalized, not requiring supplemental oxygen. 4. Hospitalized, requiring supplemental oxygen. 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices. 6. Hospitalized, on invasive mechanical ventilation or ECMO 7. Death. **SECONDARY EFFICACY ENDPOINTS** Clinical severity assessed on scales 1. *Subject clinical status using the WHO 7-point ordinal scale:* o Time to improvement of each parameter of the primary scale from admission. o Subject clinical status at days 3, 5, 8, 11, and 29. o Average change in the clinical status at days 3, 5, 8, 11, 15, and 29 as compared to baseline. 2. *The NEWS Score (National Early Warning Score) describes the vital signs (pulse rate, breathing rate, temperature, blood pressure etc.) and its deviation from the reference ranges):* is evaluated daily and on day 15. o The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. o Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS. *3. Oxygenation, including mechanical ventilation:* o Change (day by day) in the need for oxygenation in the first 28 days (up to day 29). *4. Hospitalization* o Duration of hospitalization (days). *5. Mortality (date, cause)* o 28-day mortality. *6. SOFA scale (evaluation of organ failure associated with sepsis):* is evaluated daily and on day 15. o Change from baseline to days 3, 5, 8, 11, 15, and 29 in SOFA. **SAFETY OUTCOMES** o Cumulative incidence of serious adverse events/reactions (SAEs, SARs). o Cumulative incidence of adverse events/reactions (AEs, ARs). o Permanent or temporary discontinuation of infusions/injections (by any cause). o Clinically significant changes in the levels of leukocytes, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, CRP, and other parameters.
STUDY DESIGN	Open multi-centre observational study of efficacy and safety of a medicinal

	product. The clinical efficacy will be assessed by changes in the patient's clinical status, duration of hospitalization, oxygenation/mechanical ventilation. The clinical examination will include clinical, laboratory, and instrumental investigations according to the current guidelines on treatment of COVID-19 in the Russian Federation.
POPULATION	Hospitalized patients of 18 years and older with confirmed COVID-19.
SAMPLE SIZE	At least 50 patients
TREATMENT ALLOCATION	All study subjects will receive treatment with Polyoxidonium, lyophilizate, 12 mg, in addition to the standard treatment
DIAGNOSIS	Verified COVID-19
ENROLLMENT CRITERIA	**INCLUSION CRITERIA** 1. The patient is taking or have been prescribed Polyoxidonium® in accordance with the approved labelling in combination with COVID-19 therapy recommended by the Ministry of Health of the Russian Federation. 2. Verified diagnosis: COVID-19 . 3. Severity of the disease at hospitalization: – severe disease: requiring mechanical ventilation or oxygen, a SpO_2 ≤ 94% on room air or tachypnoea (respiratory rate ≥ 24 breaths/min) – mild-moderate disease: SpO_2 ≥ 94% and respiratory rate ≤ 24 breaths/min without supplemental oxygen. 4. Patients who signed the informed consent. 5. Understands and agrees to comply with planned study procedures. 6. Age ≥18 years old at the enrolment. 7. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen prior to enrolment. **EXCLUSION CRITERIA** 1. Pregnancy and lactation. 2. Pathological conditions that make participation in the study impossible for the patient (as judged by the investigator). 3. Participation in any other clinical study during this study, including participation in a clinical study within 30 days before the informed consent. 4. Increased sensitivity to any component of the investigational product. 5. Acute or chronic renal failure. **WITHDRAWAL CRITERIA** 1. The investigator decided that withdrawal from the study is in the patient's interests. 2. Withdrawal of the informed consent (the patient does not want to continue participation in the study). 3. Serious deviation from the study protocol. 4. Idiosyncrasy to the investigational products that developed during the treatment period. 5. AE/SAE that requires an examination and/or treatment that would affect the study procedures significantly. 6. Patient non-compliance. 7. The patient was enrolled by mistake. 8. The patient receives/needs an additional treatment that could affects result of the study or the patient safety. 9. Other conditions or events that require patient withdrawal, as judged by the study doctor.
INVESTIGATIONA	**INVESTIGATIONAL PRODUCT**

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PRODUCT, DOSAGE, TREATMENT REGIMEN	Polyoxidonium® (azoximer bromide), lyophilizate for solution for injections and topical application. **DOSAGE** 12 mg intravenously (IV) once daily for the first 3 days, then 12 mg every other day intramuscularly (IM). The total treatment course is 10 intravenous / intramuscular injections. **TREATMENT REGIMEN** *Intravenous administration, 12 mg* **[days 1, 2, 3]** For intravenous drip injection: Dissolve Polyoxidonium® (6 mg of the active substance) in 2 mL of sterile 0.9% sodium chloride solution. Leave the dissolved product for 2–3 minutes to swell, then mix by swirling. Prepare 2 vials containing 6 mg each, as described above. Transfer the prepared 12 mg dose (two vials) into a 200–400 mL bottle/bag with 0.9% sodium chloride solution. Administer the solutions with the flow rate of 540 mL/h (180 drops/min). Do not keep the prepared solution for parenteral administration. Do not dissolve the drug in protein-containing infusion solutions for intravenous drop infusion. *Intramuscular administration, 12 mg* **[days 5, 7, 9, 11, 13, 15, 17]** For intramuscular injection: Dissolve Polyoxidonium® (6 mg of the active substance) in 2 mL of sterile 0.9% sodium chloride solution in the original bag. Leave the dissolved product for 2–3 minutes to swell, then mix by swirling. Prepare 2 vials containing 6 mg each, as described above. Draw the prepared 12 mg dose (two vials, 4 mL in total) into a 5 mL syringe and inject it intramuscularly. Do not keep the prepared solution for parenteral administration.
TREATMENT DURATION	17 days
FOLLOW-UP PERIOD	29 days
STUDY PROCEDURES	**INSTUMENTAL INVESTIGATIONS** (See Table 1.) The investigations are performed according to current guidelines of the Ministry of Health of the Russian Federation. **LABORATORY DIAGNOSTICS** (See notes to Table 1.) The investigations are performed according to current guidelines of the Ministry of Health of the Russian Federation in the study centre. The following biological materials will be analysed in this study: nasal, nasopharynx and/or oropharynx swabs, bronchial washings obtained by fibrobronchoscopy (bronchoalveolar lavage), endotracheal, tracheal, and nasopharyngeal aspirate, sputum, biopsy or autopsy lung specimens, whole blood, serum, urine. The main biomaterials for the laboratory investigations are nasopharyngeal and/or oropharyngeal smears and blood.
STATISTICAL CONSIDERATIONS	*Analysis of the primary endpoint* The primary efficacy outcome for the first part of the study is: Clinical status of

	the patient (according to 7-point ordinal scale) on day 15 as compared to baseline. *Analysis of the secondary endpoints* The interval (quantitative) data will be described with arithmetic mean, standard deviation, median, lower quartile (25%) and higher quartile (75%), minimum, maximum, coefficient of variation, and 95% confidence interval for the mean. The categorical (qualitative) data will be described with incidences, percentage, or proportions, and 95% confidence interval for percentage or proportions. The time to event data will be processed via survival analysis with the use of Kaplan-Meier curves and 95% confidence intervals. The following standard parametric tests are planned for comparison of quantitative data with normal distribution: Student t-test, analysis of variance (ANOVA) for repeated measurements. The following standard non-parametric tests are planned for comparison of quantitative data with distribution other than normal: Mann-Whitney U-test, Wilcoxon T-test, Friedman test. Shapiro-Wilk test will be used to test normality of the distribution. The incidences will be compared with Pearson's $\chi 2$-test or Fischer's exact test.
CONCOMITANT AND PROHIBITED TREATMENT	All study subjects will receive pharmacological treatment according to the current clinical guidelines on COVID-19 management of the Ministry of Health of the Russian Federation.

2. STUDY RATIONALE

2.1. Importance of the study

The emergence of the disease caused by the new coronavirus (2019-nCoV) in December 2019 posed difficult challenges for healthcare professionals and doctors related to the rapid diagnosis and clinical management of patients with this infection. Currently, information on the epidemiology, clinical features, prevention, and treatment of this disease is limited. It is known that the most common clinical manifestation of the new variant of coronavirus infection is pneumonia, and a significant number of patients have developed the acute respiratory distress syndrome [Temporary guidelines, 2020].

Coronaviruses (CoV) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild disorders. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS- CoV) [MASTER PROTOCOL].

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS-COV-2. It has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV [Chan JF et al., 2020]. Most of the infections outside China have been travel-associated cases in people who had recently visited Wuhan City and are thought to have acquired the virus through contact with infected animals or contact with infected people.

This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19 [MASTER PROTOCOL].

The pathogenesis of the novel coronavirus infection is not well understood. Data on the duration and intensity of immunity to SARS-CoV-2 are currently not available. Immunity to the infections caused by other coronaviruses is not persistent and the re-infection is possible [Temporary guidelines, 2020].

Outbreak forecasting and mathematical modelling suggest that these numbers will continue to rise [Wu JT, Leung K, Leung GM, 2020].

Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified. There is an urgent public health need for rapid development of novel therapeutic agents [MASTER PROTOCOL].

Polyoxidonium® (azoximer bromide) is a high molecular analytically pure synthetic immunomodulator. The active substance is produced by target-oriented chemical synthesis. Chemical structure of Polyoxidonium® is close to that of natural substances. Polyoxidonium contains N-oxide groups that are widely spread in human body, because nitrogen compounds are metabolised via N-oxidation [Luss L.V., Martynov-Radushinskiy A.A., 2013; Luss L.V. 2015].

The main pharmacological effects of the drug Polyoxidonium® include: immunomodulating, antioxidant, antitoxic, membrane-protective, and chelating action. The drug increases production of immunoglobulins, stimulates phagocytes, increases inherent resistance of the human body to bacterial and viral infections, increases production of antibodies to various antigens (T-dependent and T-independent) of both animal and microbial origin. Polyoxidonium® also increases cytotoxic activity of NK cells (especially is their basic levels are low), activates resident macrophages of reticular endothelial system, thereby accelerating elimination of foreign particles [Luss L.V., Martynov-Radushinskiy A.A., 2013; Luss L.V. 2015].

Polyoxidonium® is one of the effective immunomodulating agents that are used to treat and prevent acute respiratory viral infections (ARVI). Polyoxidonium® (azoximer bromide) is a polymer immunotropic therapeutic agent that is produced by target-oriented chemical

synthesis. Polyoxidonium® was approved in Russia in 1996. It is a high molecular chemically pure immunomodulator with a complex pharmacological effect [Yu.A. Gornostaeva, 2010].

Polyoxidonium® has an immune modulating effect and thereby increases resistance to local and generalized infections. Polyoxidonium® effectively influences different components of the immune system and activates the 3 most important phagocyte sub-populations: mobile tissue macrophages, circulating blood phagocytes, and resident phagocytes of reticular endothelial tissue. Polyoxidonium® in the range of effective immunostimulant doses increases efficacy of cooperation between T-cells and B-cells in antibody response to foreign antigens. The drug product does not affect inherent mechanisms that inhibit immune response and does not deplete the haematopoietic system. Polyoxidonium® has an immune modulating effect and thereby increases resistance to local and generalized infections. The principal mechanism of action of Polyoxidonium is the direct effect on the phagocytic cells and natural killers together with antibody production stimulation. Polyoxidonium® recovers the immunity in different secondary deficiencies caused by bacterial, viral, and fungal infections, ageing, postoperative complications, traumas, burns, administration of cytostatic agents and steroid hormones [V.A. Dyakonova et. al 2004; G.I Klebanov et. al 2005; T.I. Grishina et al, 2008; S.M. Kharit, A.N. Galustyan 2017].

Polyoxidonium® also has significant detoxicating and antioxidant properties. It decreases cytotoxicity of chemical substances, medicinal products, and infective agents. These additional properties ensure a more pronounced clinical effect of the drug product. Administration of Polyoxidonium as a part of complex therapy can increase the treatment efficacy, decrease significantly the dose of antibacterial and antiviral agents, and reduce the duration of treatment [Yu.A. Gornostaeva 2010; M.V. Skachkov 2008; R.M. Khaitov, B.V. Pinegin 2003].

Polyoxidonium® is compatible with almost any course of treatment and has few contraindications. The drug product is tolerated well, does not have mitogenic, polyclonal activity, antigenic or allergenic properties [Yu.A. Gornostaeva 2010; V.N. Mineev 2006].

Thus, the efficacy of Polyoxidonium® in upper respiratory tract infections in various patient populations, beneficial safety profile, and characteristics of COVID-19 infection altogether justify the clinical study to evaluate efficacy of Polyoxidonium® in the novel coronavirus disease.

2.2. Study Product Name and Description

Investigational product: Polyoxidonium®, lyophilizate for solution for injections and topical application

TRADE NAME	Polyoxidonium®
INTERNATIONAL NONPROPRIETARY NAME	azoximer bromide
MANUFACTURER / MARKETING AUTHORIZATION HOLDER	**NPO Petrovax Pharm LLC** Legal address/manufacture address/Address for reclamations: Sosnovaya ul. 1, s. Pokrov, Podolsk, Moscow Oblast, 142143 Russia Tel/fax: +7 (495) 926-21-07, e-mail: info@petrovax.ru
DOSAGE FORM	lyophilizate for solution for injections and topical application
DOSAGE	6 mg
COMPOSITION	**Composition per vial** *Active substance:* Azoximer bromide - 6 mg *Excipients:* mannitol - 1.8 mg, povidone K17 - 1.2 mg.
APPEARANCE	White or yellowish-white porous mass.
STORAGE TERMS	Store at 2°C to 8°C. Keep away from children.
PACKAGE AND	9 mg of medicinal product are packaged into hydrolytic class 1

LABELLING	amber glass vial, air-tightly sealed with rubber stoppers, and crimped with aluminium caps. 5 filled vials are put in a polyvinyl chloride film blister. One blister together with the leaflet or 5 vials together with the leaflet are put in a cardboard pack with a cardboard insert element. For hospital use, 50 vials of the medicinal product together with 50 leaflets are packed in a box with carton inserts.

Pharmacotherapeutic group: immune modulator.

ATC Code: [L03].

Pharmacological properties

Pharmacodynamic properties

Azoximer bromide has a complex effect: immune modulating, detoxicating, antioxidant, and moderate anti-inflammatory effects.

Main mechanism of action of Polyoxidonium is the direct effect on the phagocytic cells and natural killers together with stimulation of antibody production, synthesis of interferon alpha and interferon gamma. Detoxicating and antioxidant properties of azoximer bromide are mainly explained by structure and high molecular nature of this therapeutic agent. Azoximer bromide increases resistance of the human body to local and general infections of bacterial, fungal, and viral nature. Polyoxidonium® recovers the immunity in patients with different secondary deficiencies caused by various infections, traumas, burns, autoimmune disorders, malignant neoplasms, postoperative complications, administration of chemotherapy, cytostatic agents, and steroid hormones.

Azoximer bromide is characterized by the ability to activate early defence factors during topical application (intranasal and sublingual): it stimulates bactericidal effects of neutrophils, macrophages, increases phagocytosis, bactericidal effects of saliva, and secretion of the upper respiratory tract mucosa.

Azoximer bromide inhibits soluble toxic substances and microparticles, eliminates toxins, salts of heavy metals, inhibits lipid peroxidation both by capturing free radicals and by elimination of catalytic Fe^{2+} ions.

Azoximer bromide suppresses inflammatory reactions as it normalizes synthesis of pro- and anti-inflammatory cytokines.

Azoximer bromide is tolerated well, does not have mitogenic, polyclonal effects, antigenic properties, does not have allergenic, mutagenic, embryotoxic, teratogenic, and cancerogenic effects. Azoximer bromide does not have any specific taste and odour and does not irritate mucous when applied topically.

Pharmacokinetic properties

Azoximer bromide is rapidly absorbed into the bloodstream and distributed in the body. The maximal blood level is reached in 40 minutes after intramuscular injection. The elimination half-life depends on the patient's age and equals 36 to 65 hours. The bioavailability is high and exceeds 90% after parenteral administration.

Azoximer bromide is rapidly distributed among all organs and tissues, crosses blood-brain and blood-ocular barriers. The effects are not cumulative. Azoximer bromide is metabolised to low molecular oligomers and is excreted primarily by kidney. Up to 3% of the dose is excreted with faeces.

Therapeutic indications

The drug product is used in adults and children of 6 months and older for treatment and prevention of infection and inflammatory diseases (of viral, bacterial, and fungal nature) in the acute phase and during remission.

In adults in complex therapy of:

- chronic recurrent infective and inflammatory diseases of various location and of bacterial, viral, and fungal nature during recurrence and remission,
- acute viral and bacterial infections of ENT organs and upper respiratory tract, gynaecological and urological diseases,
- acute and chronic allergic disturbances (including pollinosis, bronchial asthma, atopic dermatitis) complicated with chronic recurrent bacterial, viral, or fungal infection,
- in oncology: during and after chemo- and radio- therapy to alleviate immunosuppressive, nephro- and hepatotoxic action of other therapeutic agents,
- generalized surgical infections; activation of regeneration processes (in patients with fractures, burns, trophic ulcers),
- rheumatoid arthritis that is complicated with bacterial, viral, or fungal infection, after prolonged therapy with immunosuppressants,
- lung tuberculosis.

In children of 6 month and older in complex therapy of:

- acute and exacerbated chronic viral, bacterial, or fungal infections (including otorhinolaryngologic diseases such as sinusitis, rhinitis, adenoiditis, pharyngeal tonsil hypertrophy, ARVIs),
- acute allergic and toxico-allergic conditions complicated by a bacterial, viral, or fungal infection,
- bronchial asthma complicated with chronic infections of respiratory tract,
- atopic dermatitis complicated with purulent infection,
- intestinal dysbiosis (together with specific therapy),

For prevention (as monotherapy) in children of 6 month and older and in adults:

- influenza and ARVIs,
- infectious postoperative complications.

Posology and mode of administration (according to the instructions for use):

Posology and mode of administration in adults

Parenteral administration (intramuscular or intravenous): 6–12 mg once daily every day, every other day, or 1–2 times a week depending on the diagnosis and severity of the disease.

In patients with acute viral and bacterial infections of ENT organs and upper respiratory tract, gynaecological and urological diseases: 6 mg every day for 3 days, then every other day (10 injections in total).

In patients with chronic recurrent infective and inflammatory diseases of various location and of bacterial, viral, and fungal nature during recurrence and remission: 6 mg every other day (5 injections), then 2 times a week (10 injections in total).

In patients with acute and chronic allergic disorders (including pollinosis, bronchial asthma, atopic dermatitis) complicated with chronic recurrent bacterial, viral, or fungal infection: 6–12 mg, 5 injections.

In patients with rheumatoid arthritis that is complicated with bacterial, viral, or fungal infection, after prolonged therapy with immunosuppressants: 6 mg every other day (5 injections), then 2 times a week (10 injections in total).

In patients with generalized chronic infections: 6 mg daily for 3 days, then every other day (10 injections in total).

For activation of regeneration processes (in patients with fractures, burns, trophic ulcers): 6 mg daily for 3 days, then every other day (10 injections in total).

For prevention of postoperative infectious complications: 6 mg every other day (5 injections).

In patients with lung tuberculosis: 6 mg 2 times a week (20 injections in total).

In cancer patients:

- before and during chemotherapy to decrease immunosuppressive, hepato- and nephrotoxic effects of chemotherapeutic agents: 6 mg every other day (10 injections); the attending doctor will choose the further administration mode depending on the tolerability and duration or chemo- and radiotherapy,
- for prevention of immunosuppressant effect of the tumour, for treatment of immunodeficiency after chemo- and radiotherapy, after surgical tumour resection: Polyoxidonium® is used for a long period of time (from 2–3 months to 1 year) in the dose of 6 mg 1–2 times a week. No cumulation, toxicity, or habituation was reported during the long-term treatment.

The drug product is administered intranasally in the daily dose of 6 mg (3 drops in each nostril 3 times a day for 10 days):

- to treat acute and recurrent chronic infections of ENT-organs,
- to reinforce regeneration of mucous membranes,
- to prevent complications and recurrence of chronic diseases,
- to prevent influenza and ARVIs.

Contraindications:

- Hypersensitivity
- Pregnancy and lactation
- Children younger than 6 months old
- Acute renal impairment

Use with care:

Chronic renal insufficiency (the drug product should be administered with an interval of at least 2 times a week).

Side effects:

The following systemic and local reactions were reported during administration of Polyoxidonium®:

During parenteral administration: Uncommon (≥1/1000 to <1/100): tenderness, redness, and skin induration in the site of injection.

During parenteral administration and topical application: Very rare (≥1/10000): fever, mild anxiety, chills, hypersensitivity to components of the drug (allergic reactions).

Drug interactions

Azoximer bromide dose not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 isoforms of cytochrome P-450 and therefore is compatible with many drug products, including antibiotics, antivirals, antifungal and antihistamine agents, broncholytic agents, glucocorticoids, and cytostatic agents.

Special warnings:

In case of allergic reactions and hypersensitivity to Polyoxidonium® discontinue the treatment and contact a doctor.

Polyoxidonium® can be discontinued at once, without decreasing the dose gradually.

If a dose was missed, continue the administration according to the prescription or these instructions for use. Do not take double dose to compensate for the missed dose.

Do not use the drug product that looks like unsuitable for use (packaging defect, odd colour of the powder).

Effects on ability to drive and use machines

Polyoxidonium® does not influence the ability to any potentially hazardous activities that require close attention and quick psychomotor reactions (including driving and operating machines).

Overdose

No cases of overdose were reported. Contact a doctor immediately in case of unintended overdosage.

In this study, the study drug will be administered in the dose of 12 mg once daily IV for 3 days, then every other day IM on days 5–17 (the total treatment course is 10 injections).

For intramuscular injection: Dissolve Polyoxidonium® (6 mg of the active substance) in 2 mL of water for injection or 0.9% sodium chloride solution. Leave the dissolved product for 2–3 minutes to swell, then mix by swirling, but not shaking.

For intravenous drip injection: Dissolve Polyoxidonium® (6 mg of the active substance) in 2 mL of sterile 0.9% sodium chloride solution. Leave the dissolved product for 2–3 minutes to swell, then mix by swirling. Transfer the calculated patient dose into a bag/vial with 0.9% sodium chloride in sterile conditions.

2.3. Results of preclinical and clinical studies

2.3.1. Results of preclinical studies

Pharmacokinetic properties

After subcutaneous and intramuscular administration, absorption of azoximer bromide from the injection site is prolonged. The average absorption time after intramuscular injection was 7 hours in *in vivo* experiments. It has been shown that about 90% of azoximer bromide binds to blood plasma proteins, and 7.5–10% of the drug binds to blood cells. Increased absorption of azoximer bromide was shown in liver, kidneys, heart, lungs, pituitary gland, spinal cord, adrenal glands, thyroid gland, spleen, ovaries, pancreas, mesenteric lymph node, inguinal lymph node, stomach, small intestine, and skin. Azoximer bromide can penetrate the blood-brain and blood-ocular barriers and does not have a cumulative effect. The drug is excreted in two phases mainly by the kidneys. *In vivo* experiments showed that $t_{1/2}$ of the fast phase is about 1.5 hours, and $t_{1/2}$ of the slow phase is about 84 hours. About 45% of the labelled dose is excreted with urine in 24 hours after administration. Not more than 3% is excreted with faeces [Nekrasov A.V. Et al., 2000; Ivanova A.S. et al, 2015; Preclinical study of the pharmacokinetics of the substance 3H-Polyoxidonium with intravenous and intramuscular administration to rabbits, 2013].

Toxicity

Acute toxicity

A.S. Ivanova et al. (2015) studied the toxicity of a single injection of Polyoxidonium® in the department of drug pharmacology and toxicology of NPO Petrovax Pharm LLC. The study used 55 mice (males and females, 8–9 weeks old), the first generation from mating CBA and C57BL/6 mice, 30 female Wistar rats (9–11 weeks old), 32 guinea pigs (males and females) and 12 males of Soviet Chinchilla rabbits. Rodents received a single intraperitoneal dose of azoximer bromide: 500, 1000, 1500, 2000 or 2500 mg/kg for the mice and rats, 200, 400 or 800 mg/kg for the guinea pigs. Rabbits received a single intravenous dose of 500 or 1000 mg/kg of azoximer bromide. Animals from the control group were injected with saline. The animals were observed within 14 days after the dosing. The intraperitoneal LD_{50} was 1458 mg/kg for male mice and 1490 mg/kg for female mice, and 1270 mg/kg for female rats. The intraperitoneal absolute lethal dose (lethal dose 100%, LD100) in guinea pigs was 800 mg/kg. A histopathological examination revealed that single intraperitoneal injections of high doses of azoximer bromide (1500 and 2000 mg/kg) had a significant toxic effect on the kidneys, liver, heart, lungs, thymus, spleen, adrenal glands, and brain. No pronounced dystrophic, necrobiotic or inflammatory processes were seen in other organs and tissues. The authors concluded that Polyoxidonium® is almost non-toxic (toxicity class V) [Ivanova A.S. et al, 2015].

Koryakova A.G. et al. (2015) investigated the cytotoxicity of azoximer bromide. Cellular toxicity of the drug was determined in vitro by the effect on the survival of human embryonic epithelial cells of the human kidney (HEK293). The cells were incubated with azoximer bromide at each test concentration (0.1, 1.0, 10, 100, 1000 μg/ml) for 24 hours. The content of living cells was evaluated. The investigators found that azoximer bromide (Polyoxidonium®) did not affect HEK293 cell viability in the tested concentration range. The authors concluded

that the drug product is characterised by a low risk of cytotoxicity [Cytotoxicity study of drug products manufactured by NPO Petrovax Pharm LLC, 2015].

Murashev A.N. et al. (2015) evaluated the local irritant effect of Polyoxidonium® with its multiple intramuscular administration. The study is described in detail in the Investigator's Brochure. Histological examination revealed signs of a nonspecific inflammatory reaction involving fibroblast-like and mononuclear cells at the injection site and surrounding connective tissues in one control animal and in almost all animals that received the maximum dose of Polyoxidonium® [Murashev A.N., Rzhevskiy D.I., 2015].

The allergenic effect of Polyoxidonium (PO-100) was evaluated via the reaction of leucocytosis. Guinea pigs (6–7 animals in each experimental group) were sensitized using PO-100 at doses of 0.05 μg/kg or 50 μg/kg three times (the drug was administered subcutaneously for the first time and then intramuscularly) with 1-day intervals. Blood samples were taken from the heart in 21 days after the end of the experiment. A suspension of cells was isolated from the blood samples and incubated with PO-100 at a concentration of 100 μg/ml or 500 μg/ml for 2 hours at 37 ºC. The number of leukocytes and the number of agglomerates per 500 leukocytes were counted after the erythrocyte lysis. The reaction index was calculated as the ratio of the number of leukocytes without the drug to the number of leukocytes incubated with the drug. The leukocytolysis indices in the experimental groups did not significantly differ from the indices of the control group, which indicated the absence of allergic reactions to PO-100 [An experimental study of the specific (immunomodulating) and general pharmacological activity of Polyoxidonium and its dosage form, 1994].

Pharmacological effects

R.V. Petrov el al. (2000) showed that Polyoxidonium® (azoximer bromide, NPO Petrovax Pharm LLC) stimulates resistance to infections. Preventative administration of Polyoxidonium® for 48, 72 or 96 hours leads to a significant increase in animal resistance to infection with several absolute lethal doses (dosis certe fetalis, DCL) of *S. typimurium*. 85–95% of the mice treated with Polyoxidonium® survived for 10–12 days after the contamination, while 100% mice died in the control group that did not receive the drug. Polyoxidonium® had a pronounced ability to stimulate a humoral immune response in normal and immunodeficient mice of various strains *in vivo*. Administration of Polyoxidonium® to animals together with low doses of antigen contributed to an increase in antibody production by 5–10 times compared with the value in animals that received only the antigen. A similar increase in antibody formation was detected only in old mice with reduced immune response. The immune response to sheep erythrocytes was restored when Polyoxidonium® was administered to mice of the C57Bl/6 line with a genetically determined low response to the T-dependent antigen - sheep erythrocytes, as well as to B-mice, the blood of which contains almost no T-cells [Petrov R.V. Et al, 2000].

A.S. Ivanova et al. (2015) studied how Polyoxidonium® (azoximer bromide, NPO Petrovax Pharm LLC) increases the number of antibody-producing cells (APC) in mice spleen. The investigators found that intraperitoneal administration of Polyoxidonium® to mice at a dose of 10, 100 or 1000 μg/mL increases the number of APCs in the spleen of mice by 3–6 times in comparison with mice that did not receive the drug. Subcutaneous injection of Polyoxidonium® led to increase in the number of APCs in the spleen of mice by 2–4 times in comparison with mice that did not receive the drug. The authors found that the intraperitoneal administration of Polyoxidonium® at a dose of 1 mg led to more than 3-fold increase in the number of antibody-producing cells in 16-month-old CBA mice. The results of the study by A.S. Ivanova et al. (2015) that assessed stimulation of the immune response to sheep erythrocytes in CBA mice with modelled congenital immunodeficiency were comparable with data from an earlier study by R.V. Petrov et al. (2000) [Ivanova A.S. et al., 2015; Petrov R.V. et al., 2000].

T.A. Bondareva et al. (2009) studied the efficacy of Polyoxidonium® (azoximer bromide, Immafarma LLC, Russia) for the treatment of plague. The study was conducted on 500 outbred white mice of both sexes (18–20 g body weight). A two-day agar culture of the plague pathogen (Yersinia pestis 231 strain) at a dose of 2000 living microbial cells was injected subcutaneously into the inner thigh to simulate the plague. Gentamicin (an antibacterial drug) was used as an aetiotropic therapy, which was administered intramuscularly into the inner thigh 3 times a day for 10 days starting from 48 hours after the pathogen infection. The daily dose of gentamicin was 1.2 mg. The mice were randomized into 6 groups before any study procedures. The animals from the first group were injected 32 μg of Polyoxidonium® once in 24 hours before the pathogen infection and were treated with gentamicin according to the described scheme. The mice from the second group were injected 32 μg of Polyoxidonium® once in 1 hour after the pathogen infection and were treated with gentamicin. The animals from the third group were injected 32 μg of Polyoxidonium® once in 48 hours after the pathogen infection and were treated with gentamicin. The mice from the fourth group were injected 32 μg/day of Polyoxidonium® for 5 days, starting from 48 after the infection and were treated with gentamicin. Animals from the fifth group received only gentamicin. Mice from the sixth group received no treatment. The animals were followed up for 30 days. The average time of death (mean ± standard deviation), as well as the number of surviving animals were used as criteria for evaluating the efficacy of various treatment regimens. In the first group, 30 animals survived in 30 days after the start of the experiment; the average death time was 5.6 ± 1.1 days. In the second group, 58 animals survived, and the average death time was 5.6 ± 0.9 days. In the third group, 26 animals survived, and the average death time was 4.8 ± 0.8 days. In the fourth group, 54 animals survived, and the average death time was 5.4 ± 0.6 days. In the fifth group, 8 animals survived, and the average death time was 4.6 ± 0.6 days. All mice in the sixth group died within 30 days, and the average death time was 3.7 ± 0.3 days. The investigators concluded that the addition of Polyoxidonium® to the therapeutic regimens increased the significantly survival in the experimental group, which received this drug along with the antibiotic, when compared with the survival rate of animals from the control group that were given only the antibiotic. According to the authors, the efficacy of Polyoxidonium® was based on its immunomodulating, detoxifying, and antioxidant properties [Bondareva T.A. et al, 2009].

I.V. Zarubina et al. (2005) investigated the immunotropic effect of Polyoxidonium® using an experimental model of bronchopneumonia. The study used male Wistar rats weighing 200–250 g (the number of animals that were administered Polyoxidonium® was not indicated). Acute bronchopulmonary inflammation was induced by injecting 0.1 ml of gum turpentine into the trachea. 0.75 mg/kg of Polyoxidonium was administered intraperitoneally to the animals of the main group for 5 days after the surgery. The control group was not administered Polyoxidonium®. On day 5, all animals were decapitated. The lung tissue and blood samples were taken for further studies. An increase in the phagocytic activity of lymphocytes, inhibition of T-lymphocytic function and activity of oxygen-independent microbicidal systems of phagocytes were noted in animals from the main group when compared to animals from the control group. The authors concluded that Polyoxidonium® restored immunobiological parameters to levels characteristic of intact animals [Zarubina I.V. et al. 2005].

2.3.2. Results of clinical studies

Polyoxidonium® (azoximer bromide) is rapidly absorbed after parenteral, intranasal, or sublingual administration. T_{max} of azoximer bromide in the blood was 40 minutes after intramuscular injection of Polyoxidonium®. Polyoxidonium® is rapidly distributed throughout all organs and tissues of the body and penetrates the blood-brain and blood-ocular barrier. The effects are not cumulative [IHU].

Monakhov A.S. et al. (2010) studied the efficacy of adjuvant immunotherapy with

Polyoxidonium® in patients with skin melanoma. The study involved 70 patients with a morphologically verified diagnosis of stage I – IV skin melanoma. Group A consisted of 30 patients (11 men and 19 women) who underwent only surgical treatment. Group B included 40 patients (17 men and 23 women) who had immunotherapy with intramuscular injections of Polyoxidonium® at a dose of 6-12 mg every other day for 3 months (1 course of treatment) after the surgery. The dose Polyoxidonium® was based on body weight and results of the previous cytogenetic examination. The treatment was started immediately after healing of the surgical wound, and only 3 courses of treatment were carried out with 1-month intervals in the first year after the surgery. Cytogenetic studies of peripheral blood lymphocytes were performed before therapy, during treatment, and after its completion. Based on the presence and nature of chromosomal abnormalities assessed in a cytogenetic study, we determined the risk of developing a malignant process, the likelihood of metastases and the development of metachronous multiple primary malignant tumours (MMPMT), relapse or remission of the disease, as well as the effectiveness of the therapy. All 70 patients showed cytogenetic signs of metastasis: hyperaneuploid cells and / or cells with chromosomal markers (double mini chromosomes) at baseline. During treatment and after each treatment course, early and long-term prognoses (signs of remission or relapse, as well as the likelihood of secondary tumours) were determined based on the change in the number of cells with stable cytogenetic disorders. Signs of relapses after completion of the treatment were noted in 28 patients of group A and in 19 patients of group B. Clear signs of the remission were recorded in 1 patient from group A and in 19 patients from group B. A trend towards remission was noted in 1 patient from group A and in 1 patient from Group B. Cells with new stable chromosomal abnormalities (signs of the development of MMPMT) were found in 16 patients of group A and 10 patients in group B. Efficacy assessment showed that the number of cells with both stable and unstable chromosomal abnormalities (including signs of the development of MMPMT) increased by 2–5 times in 1–2 months after the surgery in comparison with these parameters immediately after the surgery in all patients of group A. In contrast, a decrease in the number of peripheral blood lymphocytes with cytogenetic disorders by 2–5 times, as well as an improvement in clinical indicators, were observed in 37 patients of group B. A significant increase in the number of peripheral blood cells with cytogenetic disorders was revealed in 3 patients of group B who started taking Polyoxidonium® at a late (IV) stage of the disease, which indicated the tumour relapse. The three-year survival rate was 13.3 and 92.5% in group A and group B, respectively. Three patients from group B with stage IV melanoma died because of brain metastases. The investigators concluded that it is advisable to use Polyoxidonium® as an adjuvant therapy. This drug product contributes to a more rapid remission and increases the life expectancy up to 3-5 years or more in patients with skin melanoma after surgery [Monakhov A.S. et al., 2010].

S.M. Harit et al. (2017) confirmed the efficacy and safety of the sublingual use of Polyoxidonium® (azoximer bromide) in the treatment of upper respiratory tract acute respiratory infections in children (3–14 years) with normalization of T-cell indices and phagocytic activity of neutrophils based on the results of double-blind, placebo-controlled, randomized phase II and III clinical trials. These trials included a total of 228 patients aged 3 to 14 years who were diagnosed with ‘ARI of the upper respiratory tract’ or ‘influenza’, based on the clinical and laboratory data. Patients were randomized into two groups in each trial. The main group of the phase II study included 52 children (28 children aged 3–9 years and 24 children aged 10–14 years); the control group included 46 children (24 children aged 3–9 years and 22 children aged 10–14 years). The main group of the phase III study included 65 children (42 children aged 3–9 years and 23 children aged 10–14 years); the control group included 65 children (41 children aged 3–9 years and 24 children aged 10–14 years). In both studies, patients of the main and control groups were prescribed subliminal tablets of Polyoxidonium® or placebo for 7 days, 2 times a day, at a dose of 6 mg (children 3–9 years

old) and 12 mg (children 10-14 years old) as part of the ARI complex therapy. In the phase II study, the mean duration of fever and intoxication was 2.6 ± 0.2 days in children from the main group and 3.2 ± 0.2 days in the control group ($p < 0.05$). The phase III study showed that the time to normal body temperature was statistically significantly ($p = 0.00004$) shorter in patients from the main group (80.13 h) as compared to the control group (100.99 h). In a phase II study, laboratory blood parameters were evaluated in 10 days after the start of therapy. A statistically significant ($p \leq 0.001$) change in the T-cell parameters (CD3 +, CD4 +, CD8 +) and the phagocytic activity of neutrophils was showed in the main group compared to baseline. No statistically significant ($p > 0.05$) deviations of the immunogram parameters were found in the control group [Kharit S.M., Galustyan A.N. 2017].

M.V. Skachkov (2007) published the results of a 10-day open-label controlled randomized study on the effectiveness of the sublingual use of Polyoxidonium® for prevention of acute respiratory infections, that were comparable with the data of S. M. Harit et al. (2017). The study involved 360 patients (ages 18 to 60) who often have acute respiratory infections. The patients were randomized into 4 groups of 90 people. Three experimental groups received Polyoxidonium® sublingually for 10 days at a dose of 24 mg/day, 36 mg/day or 48 mg/day. Patients from the control group received vitamin therapy for 10 days. After the end of therapy, the patients were followed for 8–10 days and all cases of ARI symptoms were recorded during the follow-up. The authors found that all studied doses of Polyoxidonium® increased the effectiveness of ARI prophylaxis in patients who often become ill as compared with multivitamin therapy. According to investigators, the highest prophylactic efficacy of Polyoxidonium® was reported at 24 mg/day [Skachkov M.V., 2007].

S.M. Harit et al. (2017) evaluated the safety of sublingual use of the drug Polyoxidonium® in the treatment of upper respiratory tract acute respiratory infections in children aged 3–14 years in double-blind, placebo-controlled, randomized phase II and II clinical studies which are described in detail in the Investigator's Brochure.

In both studies, the main group was administered Polyoxidonium® tablets sublingually for 7 days, 2 times a day, at a dose of 6 mg (children 3–9 years old) and 12 mg (children 10–14 years old) as part of the ARI complex therapy; the control group received placebo. No AEs were reported neither in the main group, nor in the control group in the phase II study. No negative changes in the clinical status of the patients were seen in the main group within the 6 months of follow-up. 4 AEs were reported in the phase III study: one AE in a patient from the placebo group (mild acute catarrhal otitis media on the right) and 3 AEs in patients of the main group (moderate acute enteritis, moderate acute gastroenteritis, and mild gastroenteritis of unspecified etiology). In all cases, all registered AEs were resolved with the appropriate therapy until the end of the patients' participation in the study. The relationship with the study drug was identified as doubtful for all registered AEs. The authors did not reveal statistically significant differences ($p > 0.05$) in the incidence of AE between the main group and the control group [Kharit S.M., Galustyan A.N. 2017].

More detailed information on the results of experimental and clinical studies is presented in the Investigator's Brochure.

2.4. Benefit/risk ratio for the study subjects

2.4.1. Potential benefit for the patients

Benefit for patients participating in this observational study is being provided with the study drug for free.

Hospitalized adult patients with COVID-19 who will be administered Polyoxidonium® are expected to recuperate and recover more quickly and have milder symptoms.

Polyoxidonium® may or may not improve clinical outcome of an individual adult subject with COVID-19 who participates in this study. However, their participation in this study may be beneficial for the society because of the insights gained about the study therapeutic agents

as well as the natural history of the disease. While there may not be benefits for an individual subject, there may be benefits to society if a safe, efficacious therapeutic agent is identified during the global COVID-19 outbreak.

2.4.2. Known risks

Subjects of this clinical study might incur the risks related to administration of the products, study procedures and the risks that are inherent to the experimental nature of this research study. The potential risks of participating in this study are those associated with blood sampling, the intravenous (IV) catherization, possible reactions to investigational product and breach of confidentiality.

The design of the study meets the definition and all criteria of a non-interventional study. The latter are defined in the Good Clinical Practice of the Eurasian Economic Union, approved by the Council of the Eurasian Economic Union on November 3, 2016. The study will be conducted in accordance with generally acknowledged current routine clinical practice; the study protocol; provisions for non-interventional studies set forth in the Decision of the Eurasian Economic Commission No. 87 dated November 3, 2016 'On the Approval of the Rules for Good Clinical Practice of Pharmacovigilance of the Eurasian Economic Union'; as well as in compliance with the operational procedures of the Sponsor. The Sponsor will also follow the recommendations regarding non-interventional studies defined in the 'Code of Practice of the Association of International Pharmaceutical Manufacturers (2015)', approved at the AIPM General Meeting of November 30, 015, as well as in the Good Clinical Practice of the Eurasian Economic Union that was approved by the Eurasian Economic Commission Council Resolution No. 79 dated November 3, 2016.

The personal data will be collected and processed during this study in accordance with applicable local legislation (in particular, in accordance with Federal Law No. 152-FZ 'On Personal Data' dated July 27, 2006 in Russia).

The ethical assessment will be carried out by the Institutional Review Board (IRB), which specializes in evaluating non-interventional studies. The conduct of this non-interventional study is regulated by the current applicable legislation (152-FZ 'On Personal Data', 61-FZ 'On Drug Circulation', EAEU GVP 2016) and ethical requirements (Nuremberg Code, Helsinki Declaration), codes (AIPM Code), high international scientific standards of quality, transparency, as well as principles, best practices (GVP, GRP, GPP, GEP, GCP, Good Practice for RWD) and international experience in this field.

This study is based on medical research goals. Data on treatment received by patients in routine clinical practice will be collected and analysed using epidemiological methods. Patient management, including diagnosis and monitoring of ongoing therapy, will be carried out within the routine clinical practice only. The study does not use unapproved drugs. The drug products will be administered according to the approved instructions for human use and in accordance with generally recognized current routine clinical practice. Compliance with the generally acknowledged current routine medical practice mitigates any additional risks. Thus, participation in this non-interventional study does not expose patients to any additional risks.

Risks related to administration of the investigational product

The following systemic and local adverse reactions are identified in the instructions for human use of Polyoxidonium®: parenteral use: uncommon (≥1/1000 to <1/100): tenderness, redness, and skin induration in the site of injection; very rare (≥1/10000): fever, mild anxiety, chills, hypersensitivity to components of the drug (allergic reactions) [IHU].

Additional measures will be taken during screening to ensure safety of the study subjects. The protocol specifies constant medical surveillance over the patients which includes recording and evaluation of adverse events and which will minimise the risks associated with participation in this study.

In case of a known adverse reaction to the drug product, the investigator will take all the

necessary actions, including discontinuation of the drug product. Besides, unknown and unexpected adverse reactions to the investigational product are possible.

This study includes administration of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (OOO NPO Petrovax Pharm, Russia) in dose of 12 mg once daily intravenously (IV) for 3 days, then every other day intramuscularly (IM) on days 5–17 (the total treatment course is 10 injections).

This dosage regimen is thought to be associated will low probability of adverse events.

Based on the facts described above, the benefit outweighs the potential risks for the patient in the active treatment group.

Risks associated with diagnostic procedures

Blood sampling may cause transient discomfort and fainting. Fainting is usually transient and managed by putting the subject in the supine position and elevating his/her legs. Bruising at the blood sample site may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. Intravenous catheterization may cause insertion site pain, phlebitis, haematoma, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or at catheter site less likely.

The risks associated with the diagnostic procedures do not exceed similar risks in the routine clinical practice.

Qualified personnel will perform the study diagnostic procedures. The patients will receive accurate information about their health that was collected in the result of these procedures.

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study files will be kept according to the requirements for confidentiality. Electronic files will be password protected. Only the people involved in conduction, surveillance, monitoring, or audit of this study will have access to the collected medical data. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy study records maintained at the participating centre for quality assurance and data analysis include Sponsor, ethics committees, and the pertinent regulatory authorities.

Based on the above, benefits from participation in this study outweigh risks for patients of both groups, so the risk/benefit ratio is ethically acceptable.

2.5. Description and justification of the mode of administration, dose, and dosage regimen

According to the legal and regulatory basis, the study will use samples of the investigational product and the comparator provided by the Sponsor.

The study will include evaluation of the efficacy and safety of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in patients with COVID-19.

In this study, the investigational product will be administered to hospitalized adult patients with COVID-19:

All patients will be administered Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in dose of 12 mg after reconstitution once daily intravenously (IV) for 3 days, then every other day intramuscularly (IM) on days 5–17 (the total treatment course is 10 injections).

Polyoxidonium® was shown to be effective in the treatment of infectious diseases, in particular, acute respiratory infections in the previous clinical trials and clinical practice [Pružinec P., Chirun N., Sveikata A., 2018; Harit S.M. et al., 2017]. Polyoxidonium® as an adjunct to traditional therapy in both children and adult patients leads to the normalization of

T-cell parameters and the phagocytic activity of neutrophils in the treatment of infectious diseases of various etiology. Polyoxidonium® reduces the duration of the inflammatory process and prevents relapse. The highest prophylactic effectiveness of the Polyoxidonium® was with the dose of 24 mg/day [Kharit S.M., Galustyan A.N., 2017; Skachkov M.V., 2007]. Based on the available efficacy data, Polyoxidonium® should be considered for evaluation in clinical studies as a treatment of COVID-19.

According to the Instructions for human use of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia), the drug is administered parenterally in doses of 6-12 mg once a day, every other day, or 1-2 times a week, depending on the diagnosis and severity of the disease. In patients with acute viral and bacterial infections of ENT organs and upper respiratory tract, the dose of 6 mg is administered every day for 3 days, then every other day (10 injections in total). In addition, the dose of 12 mg is allowed for use in complicated diseases, for example, acute and chronic allergic diseases complicated by bacterial, viral, or fungal infection [IHU].

The drug was administered parenterally in the dose of 12 mg in patients with breast cancer and skin melanoma in clinical trials [Monakhov A.S. et al., 2010; Shamilov F.A. et al., 2013].

Based on the clinical studies and the post-marketing experience, Polyoxidonium® has a favourable safety profile. The general tolerability of the drug was evaluated as follows in a large post-marketing study by the investigators and patients: 75.3% of patients and 79.7% of doctors rated the tolerance of the oral dosage form as ‘very good’, 21.1% of patients and 19.3% of doctors rated the tolerance as ‘good’. Treatment of acute respiratory infections was also investigated in the clinical studies in the paediatric population at various dosages. No statistically significant difference ($p > 0.05$) was found in the incidence of AE between the main group and the control group [Shirokova I., 2017; Kharit S.M., Galustyan A.N., 2017].

Thus, taking into account the severity of the disease, pronounced symptoms, in particular, severe acute respiratory syndrome, it is planned to evaluate the effectiveness of IP in the maximum dose and in the dosage regimen for acute viral infections of the respiratory tract. Given the favourable safety profile of IP, increasing the dose per treatment course is not likely to increase the risks for patients. It is expected that this approach will achieve the most profound therapeutic effect with a low risk of adverse events.

The risk to subjects can be minimized by excluding those with significant underlying severe renal disease, and appropriate monitoring during the study.

To date, there is no evidence of the effectiveness of any drug against 2019-nCoV. The disease should be treated according to the existing international and national recommendations in force at the time of the study. Patients infected with 2019-nCoV should receive supportive symptomatic therapy. The comorbid conditions and complications should be treated in accordance with clinical guidelines, standards of medical care for these diseases, conditions[1], and complications in force in the relevant country at the time of the planned clinical trial.

If the concomitant condition is not an inclusion/exclusion criterion, the treatment of such condition within this protocol should follow the standard of care. The concomitant medications should not be prohibited by this protocol.

The enrolled patients will receive full treatment in accordance with the standards of supportive treatment.

[1] Temporary guidelines. Prevention, diagnosis, and treatment of the novel coronavirus infection (2019-nCoV). Version 2 (02/03/2020). Electronic source Free access: https ://static-1.rosminzdrav.ru/system/attachments/attaches/000/049/329/original/%D0%92%D1%80%D0%B5%D0%BC%D0% B5%D0%BD%D0%BD%D1%8B%D0%B5 %D0%9C%D0%A0 2019-nCov_03.02.2020_%28%D0%B2%D0%B5%D1%80%D1%81%D0%B8%D1%8F_2%29_fiml.pdf?1580748451. Access date: March 16, 2020.

2.6. Statement on quality of the study

The observational study will be conducted according to the current version of the study protocol and routine practice of the health care institution. The Protocol with any amendments as well as the Patient Information Leaflet and the Informed Consent Form should be approved by the local ethics committee and should not contradict the routine clinical practice.

This is a non-interventional study protocol. The study will be conducted in accordance with the principles of the Helsinki Declaration of the WMA (adopted at the 18th Assembly of the WMA in Helsinki in June 1964; the latest edition was approved at the 64th Assembly in Fortaleza in October 2013) and is regulated by the current legislation of the EAEU and the Russian Federation. The definition of 'non-interventional study' is given in Good Clinical Practice of the Eurasian Economic Union that was approved by the Eurasian Economic Commission Council Resolution dated November 3, 2016, No. 79. Features of a non-interventional study are presented in the Decision of the Eurasian Economic Commission No. 87 dated November 3, 2016 'On the Approval of Good Clinical Practice of Pharmacovigilance of the Eurasian Economic Union'. According to this document, a non-interventional study should meet the following conditions:

- a drug is prescribed in accordance with the summary of product characteristics,
- the decision to prescribe a specific treatment to the patient is not made in compliance with the routine clinical practice, rather than the study protocol, and the prescription is clearly separated from the decision to include the patient in the study,
- no additional diagnostic or control procedures are applied to patients, and epidemiological methods are used to analyse the collected data.

Non-interventional studies are defined by the methodological approach and not by scientific objectives. Recommendations regarding non-interventional studies are given in the Code of Practice for the Association of International Pharmaceutical Manufacturers (2015), as well as in the Good Clinical Practice of the Eurasian Economic Union.

The personal data will be collected and processed during this study in accordance with applicable local legislation (in particular, in accordance with Federal Law No. 152-FZ 'On Personal Data' dated July 27, 2006 in Russia).

2.7. Study Population

The patient inclusion criteria were validated scientifically. The main inclusion criterion is a confirmed diagnosis of COVID-19.

Standard case of the novel 2019-nCoV coronavirus infection [Temporary guidelines, 2020]

Suspected 2019-nCoV infection:

- clinical manifestations of an acute respiratory infection, bronchitis, pneumonia in combination with the following epidemiological history:
- a visit to the epidemiologically unfavourable for 2019-nCoV countries and regions (mainly Wuhan, China) in the last 14 days before the onset of symptoms,
- close contacts over the past 14 days with persons under surveillance for the novel coronavirus 2019-nCoV infection, who subsequently became ill,
- close contacts over the past 14 days with people who had their 2019-nCoV diagnosis confirmed by laboratory testing.

Probable 2019-nCoV infection:

- clinical manifestations of severe pneumonia, ARDS, sepsis in combination with relevant epidemiological history (see above).

Confirmed case of 2019-nCoV1 infection[1]:

[1] Temporary guidelines. Prevention, diagnosis, and treatment of the novel coronavirus infection (2019-nCoV). Version 2 (02/03/2020). Electronic source. Free access: https ://static - 1.rosminzdrav.ru/system/attachments/attaches/000/049/329/original/%D0%92%D1%80%D0%B5%D0%BC%D

1. Clinical manifestations of an acute respiratory infection, bronchitis, pneumonia in combination with the epidemiological history.
2. Positive laboratory test results for 2019-nCoV RNA by polymerase chain reaction (PCR).

2.8 References to relevant literature

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3. AIM AND OBJECTIVES OF THE STUDY

3.1. Study Aim

To evaluate safety and efficacy of Polyoxidonium® (azoximer bromide) as an addition to complex treatment of hospitalized patients with COVID-19.

3.2. Study Objectives

1. To evaluate clinical efficacy of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in hospitalized adult patients with COVID-19.
2. To evaluate safety of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in hospitalized adult patients with COVID-19.

4. STUDY DESIGN

4.1. Primary and Secondary Outcomes

According to the aim and objectives of this study, safety and efficacy of Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) will be evaluated in hospitalized patients with coronavirus disease (COVID-19).

Efficacy outcomes

Primary efficacy outcome

Subject clinical status using the WHO 7-point ordinal scale on day 15 as compared to baseline.

1. Not hospitalized, no limitations on activities.
2. Not hospitalized, limitation on activities.
3. Hospitalized, not requiring supplemental oxygen.
4. Hospitalized, requiring supplemental oxygen.
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices.
6. Hospitalized, on invasive mechanical ventilation or ECMO.
7. Death.

Secondary efficacy outcomes

Clinical severity assessed by scales

1. Subject clinical status using the WHO 7-point ordinal scale

- Time to improvement of each parameter of the primary scale from admission.

- Subject clinical status at days 3, 5, 8, 11, and 29.
- Average change in the clinical status at days 3, 5, 8, 11, 15, and 29 as compared to baseline.

2. The NEWS Score (National Early Warning Score)
describes the vital signs (pulse rate, breathing rate, temperature, blood pressure etc.) and its deviation from the reference ranges): is evaluated daily and on day 15.

- The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
- Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS.

3. *Oxygenation, including mechanical ventilation:*
   - Change (day by day) in the need for oxygenation in the first 28 days (up to day 29).
4. *Hospitalization*
   - Duration of hospitalization (days).
5. *Mortality (date, cause)*
   - 28-day mortality.
6. *SOFA scale (evaluation of organ failure associated with sepsis):* is evaluated daily and on day 15.
   - Change from baseline to days 3, 5, 8, 11, 15, and 29 in SOFA.

Safety outcomes
Safety outcomes

- Cumulative incidence of serious adverse events/reactions (SAEs, SARs)
- Cumulative incidence of adverse events/reaction (AEs, ARs)
- Permanent or temporary discontinuation of infusions/injections (by any cause)
- Clinically significant changes in the levels of leukocytes, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, CRP, and other parameters.

The safety of the investigational product will be evaluated based on statistical analysis of the specified parameters.

4.2. Type/design of the study

This study is an open multi-centre observational study evaluating the efficacy and safety of a non-interventional drug.

The design of a non-invasive non-interventional study was chosen to evaluate the efficacy of the drug in routine clinical practice. Since this study will be non-interventional, all procedures will be carried out in strict accordance with the standards of routine clinical practice and meet the non-interventional criteria set by the Good Pharmacovigilance Practice of the Eurasian Economic Union [approved by the decision of the Council of the Eurasian Economic Commission dated 03.11.2016 No. 87].

No	CRITERION	CONTENT
1	Object, MA	Drug products approved for human use; with a valid marketing authorization
2	Rationale for prescription	As judged by the doctor within the routine clinical practice
3	Time of prescription	Prior to inclusion in the study and regardless of the decision to participate
4	Requirements to the prescription	According to the approved therapeutic indications (therapeutic indications, dosage, etc.)
		According to the current routine practice, up-to-date and widely accepted

5	Patient management	clinical guidelines and guides According to the protocol, however, the intervention in the routine management of the patient is minimal
6	Randomization, blinding	Not applicable

The clinical efficacy will be assessed by changes in the patient's clinical status, duration of hospitalization, oxygenation/mechanical ventilation. The clinical examination will include clinical, laboratory, and instrumental investigations according to the current guidelines on treatment of COVID-19 in the Russian Federation. No additional procedures, except for the special scales (non-invasive), will be carried out during the planned non-interventional study.

The overall objective of the study is to evaluate the clinical efficacy of the investigational product in adult patients hospitalized with COVID-19. The primary endpoint is the patient's clinical status (in a 7-point ordinal school) on day 15 in accordance with the WHO Master Protocol[1].

The study will be conducted in the clinical centre during hospitalization and outpatient visits of patients to the clinical centre, if necessary.

Patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be included in a single study group, that will receive Polyoxidonium®, lyophilizate for solution for injections and topical application, 6 mg (NPO Petrovax Pharm LLC, Russia) in dose of 12 mg once daily intravenously (IV) for 3 days, then every other day intramuscularly (IM) on days 5–17 (the total treatment course is 10 injections).

The data collected in this observational program should help doctors find more effective therapy for other patients with COVID-19.

The study will include the following periods:

- **Treatment period** (17 days in total, days 1...17, if the study criteria are met) with administration of the investigational product (IP) (intravenous injections for 3 days, then intramuscular injections for 14 days), assessment of the clinical status, recording of AEs.
- **Follow-up period** (days 18...29±3)

Figure 4.1 shows the study flow chart.

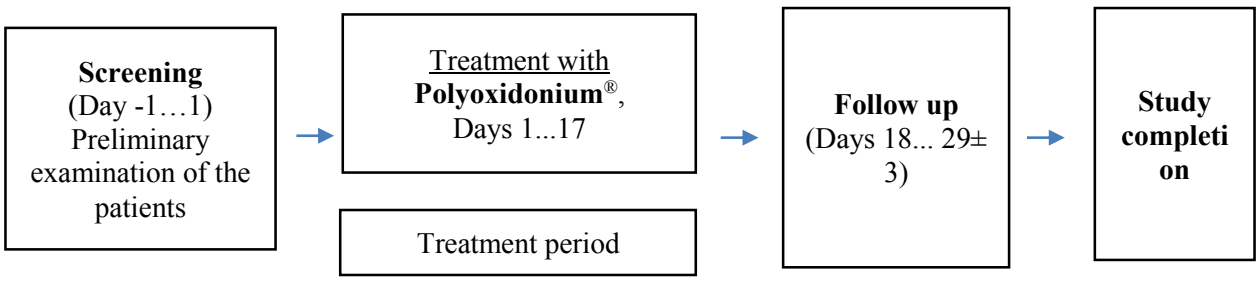

Figure 4.1. Study flow chart

[1] MASTER PROTOCOL. A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. Electronic source Free access: https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf. Access date: March 13, 2020

4.3 Measures that minimise/eliminate subjectivity during the study

The study limitations are typical for an observational study. The inclusion criteria were set so that the analysed population is representative of the target group of patients and allows to generalize the findings. Such design should prevent a systematic selection error that may occur if the patients are enrolled depending on a recorded outcome. The study plans to include a relatively large number of centres in various countries. Such international multicentre studies have the advantage of being able to generalize the results to a population of interest. All the necessary data will be collected at the enrolment visit and all subsequent visits to minimize errors associated with missing data. Also, such prospective observational study might include a systematic error related to patient withdrawal. However, all possible latest data and the reason for the discontinuation will be collected in case of a patient discontinuation.

4.3.1. Blinding

In contrast to interventional clinical trials, the design of non-interventional trials does not involve randomization and blinding. In accordance with the non-intervention principle, the doctor's decision to prescribe a therapy is made before the patient is included in the study as part of routine clinical practice and in no way can be associated with the possibility of the patient participating in this study. As a result, blinding is impossible. The procedures will be carried out within the current routine clinical practice in the presence of relevant therapeutic indications.

4.3.2. Randomization

Not applicable.

4.4 Expected duration of a patient's participation in the study

The total duration of a patient's participation in this study will not exceed 32 days.

The study will include the following periods:

- **Treatment period** – administration of IP, evaluation of the clinical status, recording of AEs.
- **Follow-up period** – evaluation of the clinical status, recording of AEs.

4.5. Suspension, termination of the study, withdrawal of the study subjects

The Sponsor may suspend the study at any time based on any reasons that include, but are not limited to, safety, ethics, or administrative issues.

The Sponsor can terminate the study at any time if the aim and objectives of the study are not met.

The Sponsor should inform the investigator or the leadership of the study centre about the study suspension or termination in writing.

If the study is suspended or terminated because of a safety issue, the Sponsor shall notify the Investigator, regulatory authorities, and the ethics committees immediately.

The Investigator can withdraw a subject from the study if any of the withdrawal criteria is met.

Patients are free to withdraw from the study at any time upon request, without any consequence. Patients should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the investigators to make efforts to continue to obtain their outcome data. Every effort should be made to encourage patients to remain in the study for their planned outcome assessments. The patients should be told that their data are important for the scientific research even after they discontinue the drug product. If a patient is lost to follow-up, attempts to contact the patient should be made and documented in the patient's medical records.

4.6. Accountability of the investigational product

The investigator is responsible for complying with the routine rules for handling drug products in the healthcare institution.

4.7. Storage and disclosure of randomization / screening numbers

Not applicable.

4.8. The list of all data that are recorded directly in the CRF and considered primary

In this study, all data will be recorded in the primary documentation before entry into the CRF.

All information that is recorded in the CRF is first entered into the patient's primary medical documentation — the patient's medical record, laboratory analysis forms, etc. An electronic data collection system can also be used to collect primary data (for example, the results of filling in specialized scales).

5. SCREENING AND WITHDRAWAL OF THE SUBJECTS

5.1. Inclusion criteria

1. The patient is already receiving, or the patient have been prescribed therapy with Polyoxidonium® in accordance with the approved labelling in combination with COVID-19 therapy recommended by the Ministry of Health of the Russian Federation.
2. Verified diagnosis: COVID-19.
3. Severity of the disease at hospitalization:

- severe disease: requiring mechanical ventilation or oxygen, a $SpO_2 \leq 94\%$ on room air or tachypnoea (respiratory rate ≥ 24 breaths/min).
- mild-moderate disease: $SpO_2 \geq 94\%$ and respiratory rate ≤ 24 breaths/min without supplemental oxygen.

4. Patients who signed the informed consent.
5. Understands and agrees to comply with planned study procedures.
6. Age ≥18 years old at the enrolment.
7. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen prior to the enrolment.

5.2. Exclusion criteria

1. Pregnancy and lactation.
2. Pathological conditions that make participation in the study impossible for the patient (as judged by the investigator).
3. Participation in any other clinical study during this study, including participation in a clinical study within 30 days before the informed consent.
4. Increased sensitivity to any component of the investigational product.
5. Acute or chronic renal failure.

5.3 Withdrawal criteria

1. The investigator decided that withdrawal from the study is in the patient's interests.
2. Withdrawal of the informed consent (the patient does not want to continue participation in the study).
3. Serious deviation from the study protocol.
4. Idiosyncrasy to the investigational products that developed during the treatment period.
5. AE/SAE that requires an examination and/or treatment that would affect the study procedures significantly.
6. Patient non-compliance.
7. The patient was enrolled by mistake.
8. The patient receives/needs an additional treatment that could affects result of the study or the patient safety.
9. Other conditions or events that require patient withdrawal, as judged by the study

doctor.

The subjects that were withdrawn from the study because of an AE/SAE will be followed until the AE/SAE is resolved or the patient is stabilized.

A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment and cannot be contacted with good effort. These efforts will be documented in the subject's record.

5.4. Patient withdrawal

If the patient was not administered at least one dose of the investigational product and left the study for any reason, then further monitoring is not carried out, and data of this patients are not included in the statistical analysis.

Unless the patient withdraws consent, those who discontinue study drug early should remain in the study, if possible, for further acquisition of endpoint measurements. The reason for patient discontinuation of study drug should be documented in the case report form.

The investigator submits the data on the patients excluded from the study to the Sponsor and the monitor of the study within 24 hours in the form of a report that includes the patient's status at the end of the study.

Patient status at the end of the study:

1. *Completed the study.*
2. *Did not complete the study because of:*
    - The investigator's mistake.
    - Adverse events.
    - Serious adverse events.
    - Pregnancy.
    - Protocol violations.
    - The patient's wish to leave the study.
    - The patient did not show up for a visit.
    - Other reasons (specify).

5.5. Replacement of the subjects

This study does not provide for the replacement of withdrawn study participants.

5.6. Follow up of the withdrawn patients

The subjects that were withdrawn from the study because of an AE/SAE will be followed until the AE/SAE is resolved or the patient is stabilized.

5.7. Strategies for Recruitment and Retention

5.7.1. Screening

It is anticipated that patients with COVID-19 will present to participating hospitals, and that no other efforts to recruit potential subjects are needed. Recruitment efforts may also include spreading information about this study among other medical professionals / hospitals.

Patients that are confirmed to have SARS-CoV-2 will be assessed for eligibility.

Some patients will not be included in the study based on demographic data and medical history, namely, due to pregnancy, age under 18 years, and so on. Potential participants will be told about the study and asked questions to determine if they can be included in the study. The study procedures can begin only after informed consent is obtained.

5.7.2. Retention

Participating subjects will be reminded of subsequent visits.

6. STUDY PLAN

6.1 Schedule of the study visits and procedures

The study will be conducted in the clinical centre during hospitalization and outpatient visits of patients who were discharged by their attending physician according to routine clinical

practice.

The study will include the following periods:

Treatment period (17 days in total, days 1...17) with administration of the investigational product (intravenous injections for 3 days, then intramuscular injections for 14 days), assessment of the clinical status, recording of AEs.

Follow-up period (days 18...29±3)

Additional visits can be performed if judged necessary by the study doctor. The study doctor will define the scope of assessments and procedures for the additional visits individually, based on the patient's needs.

The Early Termination Visit is performed if the patient is withdrawn from the study. The scope of activities and procedures carried out at the visit is similar to the activities and procedures carried out at the visit on Day 29.

Schedule of the study procedures is included in the Appendix 1.

6.2. Description of the visits

A comprehensive description of visits (by days) is provided in Appendix 1. All procedures described below should be carried out as part of the routine practice of the health care institution.

Preliminary evaluation of the inclusion/exclusion criteria

(Before the study initiation)

Full list of the procedures is provided in Appendix 1.

- Signing of informed consent.
- Confirmation of the positive test for SARS-CoV-2[1].
- Collection of patient history, demographics, and anthropometric data.
- Collection of information about previous/concomitant treatments.
- Physical examination (including lung auscultation).
- Evaluation of chest X-ray or CT scans[2].
- Laboratory test[3]: haematology, biochemistry, urinalysis.
- Oxygen saturation (SpO2).
- Evaluation of the eligibility.

Treatment period

Day 1 - enrolment, initiation of the treatment

Full list of the procedures is provided in Appendix 1.

- Evaluation of measures of clinical support.
- Assessment of the clinical status according to the 7-point ordinal scale.
- Assessment of the clinical status according to the NEWS scale and SOFA scale.
- Oropharyngeal/nasal (OP/N) sample.
- Haematology (only if this test was not performed at the screening).
- Blood chemistry (only if this test was not performed at the screening).
- Urinalysis (only if this test was not performed at the screening).
- Administration of the investigational product
- Physical examination (including lung auscultation).
- Collection of the efficacy data (oxygenation, mechanical ventilation, prolongation of

[1] Data obtained not later than 48 hours before signing the informed consent may be used.

[2] Recent chest X-ray/CT scans can be used, if the scans were obtained after the coronavirus disease (COVID-19) was diagnosed.

[3] If the patient has results of laboratory tests that were performed within 48 before the enrolment, these results can be used to assess the clinical status and eligibility. These data can be used only if they are complete and include all parameters specified in the Protocol. Repeated laboratory tests on Visit 0 are not required in this case.

hospitalization).
- Recording of AEs.

Days 2...18

Full list of the procedures is provided in Appendix 1.

The visits are performed in the in-patient settings. If the patient is discharged before Day 17, the procedures will be performed at the outpatient visits to the clinic.

Visits to the clinic are preferred after discharge, but the quarantine or other reasonable factors can limit this opportunity. The visits could be performed in a form of phone call or with other remote communication technologies. Some data will not be collected by obvious reasons.

- Evaluation of the measures of clinical support.
- Assessment of the clinical status according to the 7-point ordinal scale — every day during hospitalization up to and including Day 17.
- Assessment of the clinical status according to the NEWS scale and SOFA scale.
- Oropharyngeal/nasal (OP/N) sample.
- Haematology.
- Blood chemistry.
- Urinalysis.
- Administration of the investigational product.
- Physical examination (including lung auscultation).
- Collection of the efficacy data (oxygenation, mechanical ventilation, prolongation of hospitalization).
- Collection of information about concomitant treatments.
- Recording of AEs.

Follow-up period
(Day 29±3)

Full list of the procedures is provided in Appendix 1.

The visits are performed in the in-patient settings. If the patient is discharged earlier, the procedures will be performed within the outpatient visits to the clinic (if possible).

- Evaluation of the measures of clinical support — only if the hospitalization is prolonged.
- Assessment of the clinical status according to the 7-point ordinal scale.
- Assessment of the clinical status according to the NEWS scale and SOFA scale.
- Oropharyngeal/nasal (OP/N) sample.
- Haematology.
- Blood chemistry.
- Urinalysis.
- Collection of the efficacy data (oxygenation, mechanical ventilation, prolongation of hospitalization).
- Collection of information about concomitant treatments.
- Physical examination (including lung auscultation).
- Recording of AEs.

6.3. Study procedures

6.3.1. Written informed consent

The patient should sign two copies of the Patient Information Leaflet and the Informed Consent Form for participation in this study before any initiation of any study procedures.

The patient should receive the written information about:

1. The drug product for human use and nature of this observational study.
2. Safety of the drug product for human use and risks for the patient.

3. Terms of participation in the observational study of the drug product for human use.
4. Aim, objectives, and duration of the observational study of the drug product for human use.
5. Patient actions in case of unexpected effects of the drug product for human use on the patient's health.
6. Confidentiality statement in relation to participation in the clinical study of the drug product for human use.

The Investigator should also sign and date the Patient Information Leaflet and the Informed Consent Form and hereby confirm that the study was discussed with the patient and the patient gave his/her consent, that the patient had the opportunity to ask questions and received full answers to all questions.

The patient will receive one copy of the Patient Information Leaflet and the Informed Consent Form. The second copy will be kept by the investigator in the study centre together will the other clinical study records.

6.3.2. Collection of the patient history

During the screening, the patient's detailed medical history will be collected, in particular, diseases transferred over the last year, concomitant diseases, previous surgery, previous (over the last 4 weeks) and concomitant therapy, history of alcohol, drugs and / or drugs addictions, information about bad habits (smoking and drinking), including the following:

- Day of onset of COVID-19 symptoms
- History of chronic medical conditions related to inclusion and exclusion criteria
- Medication allergies
- List of medications and therapies for this current illness

6.3.3. Collection of demographic and anthropometric data

Demographic and anthropometric data (date of birth, gender, race) will be collected during the enrolment.

6.3.4. Physical examination

The physical examination will be carried out by the study doctor in accordance with the schedule of the study procedures outlined in Appendix 1.

The examination includes[1]:

- Lung auscultation and percussion.
- Assessment of the visible mucous membranes of the upper respiratory tract.
- Palpation of lymph nodes.
- Examination of the abdominal organs and size of the liver and spleen (without instrumental investigation, by palpation; criteria for assessing the size of the liver and spleen: increased / not increased).
- Measurement of the body temperature.

6.3.5. Laboratory tests

The schedule of laboratory tests is included in description of the study parts and in the schedule of the study procedures.

List of the evaluated laboratory parameters

[1] Temporary guidelines. Prevention, diagnosis, and treatment of the novel coronavirus infection (2019-nCoV). Version 2 (02/03/2020). Electronic source with free access: https://static-i.rosminzdrav.ru/system/attachments/attaches/000/049/329/origmal/%D0%92%D1%80%D0%B5%D0%BC%D0% B5%D0%BD%D0%BD%D1%8B%D0%B5 %D0%9C%D0%A0 2019-nCov 03.02.2020 %28%D0%B2%D0%B5%D1%80%D1%81%D0%B8%D1%8F 2%29 final.pdf?1580748451.
Access date: March 16, 2020.

Haematology
Red blood cells, haematocrit, white blood cells, platelets, neutrophils, eosinophils, basophils, monocytes, lymphocytes
The volume of the blood sample is approximately 5 mL.

Blood chemistry
Urea, creatinine, Na+, K+, bilirubin, glucose, ALT, AST, albumin, pH, bicarbonates, lactate, coagulogram with prothrombin time, coagulogram with international normalized ratio and activated partial thromboplastin time, CRP. The blood sample volume is approximately 5 mL.
If indicated: PaO_2, FiO_2 , $PaCO_2$

Urinalysis
According to routine practice of the centre.

Test for SARS-CoV-2
The test is performed at the screening to assess the eligibility. Data obtained not later than 48 hours before signing the informed consent may be used.

Oropharyngeal/nasal (OP/N) sample
Oropharyngeal/nasal samples will be taken in accordance with the routine practice of the health care institution.

6.3.6. Evaluation of chest X-ray or CT scans

The scans are evaluated before the enrolment[1]. Recent chest X-ray/CT scans (frontal view and lateral view) will be used, if the scans were obtained after the coronavirus disease (COVID-19) was diagnosed.

6.3.7. Oxygen saturation (SpO_2)

This assessment is performed before the enrolment according to the schedule of study procedures.

6.3.8. Collection of efficacy data

The efficacy data (the need for oxygenation, the need for mechanical ventilation, continued hospitalization) will be collected daily during the study to assess the effectiveness of therapy during hospitalization. The selected scales are recommended for efficacy assessment by WHO[2].

The patient status will also be assessed using the following questionnaires/scales in accordance with the description of the study periods and the schedule of the study procedures.

Examples of the scales used in the study

[1] Temporary guidelines. Prevention, diagnosis, and treatment of the novel coronavirus infection (2019-nCoV). Version 2 (02/03/2020). Electronic source with free access: https://static-i.rosminzdrav.ru/system/attachments/attaches/000/049/329/original/%D0%92%D1%80%D0%B5%D0%BC%D0% B5%D0%BD%D0%BD%D1%8B%D0%B5 %D0%9C%D0%A0 2019-nCov 03.02.2020 %28%D0%B2%D0%B5%D1%80%D1%81%D0%B8%D1%8F 2%29 final.pdf?1580748451. Access date: March 16, 2020.

[2] MASTER PROTOCOL. A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. Electronic source with free access: https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf. Access date: March 13, 2020

Measures of clinical support

The following measures of clinical support will be evaluated on each day of hospitalization up to day 17:

- Hospitalization
- Oxygen requirement
- Non-invasive mechanical ventilation (via mask)
- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
- ECMO requirement

7-point ordinal scale

Recommended by WHO as the primary endpoint for evaluating the efficacy of coronavirus infection therapy[1].

The 7-point ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. For example, on day 3, day 2 score is obtained and recorded as day 2. The scale is as follows:

1. Not hospitalized, no limitations on activities.
2. Not hospitalized, limitation on activities.
3. Hospitalized, not requiring supplemental oxygen.
4. Hospitalized, requiring supplemental oxygen.
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices.
6. Hospitalized, on invasive mechanical ventilation or ECMO.
7. Death.

NEWS Score

This score is based on 7 clinical parameters. The NEWS scale is used to evaluate efficacy and is recommended by WHO[2].

Literature shows that the NEWS score allows discriminating patients at risk of adverse outcomes [Smith et al., 2016].

This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. For example, on Day 3, Day 3 score is obtained and recorded as Day 3.

Physiological parameters	3	2	1	0	1	2	3
Respiration rate	≤8		9–11	12-20		21 -24	≥25
Oxygen saturation	≤91	92-93	94-95	≥96			

[1] WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Electronic source with free access: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19 Treatment Trial Design Master Protocol synopsis Final 18022020.pdf. Access date: March 20, 2020.

[2] MASTER PROTOCOL. A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. Electronic source with free access: https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf. Access date: March 13, 2020

Physiological parameters	3	2	1	0	1	2	3
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
Systolic BP	≤90	91-100	101–110	111-219			≥220
Heart Rate	≤40		41-50	51-90	91-110	111-130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).

SOFA Score
The SOFA scale is used to evaluate the clinical state and is recommended by WHO. Moreover, the SOFA scale was chosen because it is widely known, simple and applicable to most hospital settings. It was developed by the Sepsis Task Force of the European Society of Critical Medicine.
SOFA Organ Deficiency Assessment (Sepsis-related Organ Failure) is a point scale for assessing multiple organ failure in patients with septic syndrome who are in intensive care. This scale was created to quickly calculate and describe a number of complications in critically ill patients. The scale is intended rather for quick scoring and description of a number of complications than for predicting the outcome.

6.3.9. Recording of Adverse Events

Adverse events (AEs) will be recorded by the study doctor during the study in accordance with the Section 8.

6.4. Concomitant therapy

Standard therapy for coronavirus infection (COVID-19, SARS-CoV-2) will be used in accordance with international and national guidelines that will be in force at the time of the study. The patient's status should be monitored during medical care to identify signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and to prescribe relevant treatment. Patients infected with 2019-nCoV should receive supportive symptomatic therapy[1]. The comorbid conditions and complications should be treated in accordance with clinical guidelines, standards of medical care for these diseases, conditions, and complications in force in the relevant country at the time of the planned study.

If the concomitant condition is not an inclusion/exclusion criterion, the treatment of such condition within this protocol should follow the standard of care.

[1] Temporary guidelines. Prevention, diagnosis, and treatment of the novel coronavirus infection (2019-nCoV). Version 2 (02/03/2020). Electronic source Access: https ://static - 1.rosminzdrav.ru/system/attachments/attaches/000/049/329/original/%D0%92%D1%80%D0%B5%D0%BC%D0%B5%D0%BD%D0%BD%D1%8B%D0%B5_%D0%9C%D0%A0_2019-nCov_03.02.2020_%28%D0%B2%D0%B5%D1%80%D1%81%D0%B8%D1%8F_2%29_final.pdf?1580748451, free. Access date: March 16, 2020.

7. ASSESSMENT OF EFFICACY AND PHARMACODYNAMIC EFFECTS

7.1. Efficacy outcomes

According to WHO Master Protocol, the primary endpoint will be evaluated on day 15 of the first part of the study. The day of the primary endpoint may be modified based on a blinded evaluation of various days because there is uncertainty about the clinical course and potential different trajectories according to baseline disease severity[1].

Efficacy outcomes

Primary efficacy outcome

Subject clinical status using the WHO 7-point ordinal scale on day 15 as compared to baseline.

6. Not hospitalized, no limitations on activities.
7. Not hospitalized, limitation on activities.
8. Hospitalized, not requiring supplemental oxygen.
9. Hospitalized, requiring supplemental oxygen.
10. Hospitalized, on non-invasive ventilation or high flow oxygen devices.
11. Hospitalized, on invasive mechanical ventilation or ECMO.
12. Death.

Secondary efficacy outcomes

Clinical severity assessed on scales

1. Subject clinical status using the WHO 7-point ordinal scale

- Time to improvement of each parameter of the primary scale from admission.
- Subject clinical status at days 3, 5, 8, 11, and 29.
- Average change in the clinical status at days 3, 5, 8, 11, 15, and 29 as compared to baseline.

2. The NEWS Score (National Early Warning Score) describes the vital signs (pulse rate, breathing rate, temperature, blood pressure etc.) and its deviation from the reference ranges): is evaluated daily and on day 15.

- The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
- Change from baseline to days 3, 5, 8, 11, 15, and 29 in NEWS.

3. Oxygenation, including mechanical ventilation:

- Change (day by day) in the need for oxygenation in the first 28 days (up to day 29).

4. Hospitalization

- Duration of hospitalization (days).

5. Mortality (date, cause)

- 28-day mortality.

6. SOFA scale (evaluation of organ failure associated with sepsis): is evaluated daily and on day 15.

- Change from baseline to days 3, 5, 8, 11, 15, and 29 in SOFA.

7.2. Methods for evaluating, recording, and analysing efficacy outcomes

Efficacy of the study therapy will be evaluated in accordance with the schedule of the study procedures and description of the study parts.

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[1] MASTER PROTOCOL. A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. Electronic source Free access: https://www.who.int/blueprint/priority-diseases/key- action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf. Access date: March 13, 2020

8. ASSESSMENT OF SAFETY

8.1. Safety outcomes

The safety will be evaluated throughout the study (from signing the informed consent to the study completion visit) based on the following:

Safety outcomes

Safety parameters

- Cumulative incidence of serious adverse events/reactions (SAEs, SARs)
- Cumulative incidence of adverse events/reaction (AEs, ARs)
- Permanent or temporary discontinuation of infusions/injections (by any cause)
- Clinically significant changes in the levels of leukocytes, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, CRP, and other parameters.

The safety of the investigational product will be evaluated based on statistical analysis of the specified parameters.

The investigator is responsible for notifying the Sponsor of any event that seems unusual, including the deviation of the patient's test results from normal values, even if this event can be considered as an unforeseen benefit for the patient.

8.2. Methods and deadlines for assessing, recording, and analysing safety and tolerability outcomes

Surveys related to safety assessment are carried out in accordance with the schedule of the study procedures and a description of the study parts.

8.3. Recording and reporting of adverse events

8.3.1. Definition of Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention related or not. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vitals and laboratory. All Grade 3 and 4 AEs will be captured as AEs in this study.

8.3.2. Definition of Serious Adverse Event (SAE)

SAE is defined as an AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

'Life-threatening' refers to an AE that at occurrence represents an immediate risk of death

to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the appropriate SAE CRF.

All SAEs will be followed through resolution or stabilization by a licensed study physician.

All SAEs will be reviewed and evaluated and will be sent to the SMC (for periodic review), and the IRB/IEC.

8.3.3. Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

8.3.4. Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Severity of adverse events

All AEs and SAEs will be assessed for severity, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, version 2.1 (July 2017).

The following guidelines can be used to determine the severity of AE.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Severe (Grade 4): Events that are potentially life threatening.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop duration of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

Relationship to Study Intervention

For each reported adverse reaction, the Principal Investigator or designee must assess the relationship of the event to the study product using the following guideline (according to the WHO Master Protocol[1]):

- Related - The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship

[1] MASTER PROTOCOL. A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. Electronic source with free access: https://www.who.mt/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf. Access date: March 13, 2020.

between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- Not Related - There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate aetiology has been established.

8.3.5. Time Period and Frequency for Event Assessment and Follow-Up

For this study, all Grade 3 and 4 AEs and all SAEs occurring from the time the informed consent is signed through the study completion (end of study) visit will be documented, recorded, and reported.

Investigators Reporting of AEs

Information on all AEs should be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.3.6. Serious Adverse Event Reporting

Investigators Reporting of SAE s

Any AE that meets a protocol-defined criterion as a SAE must be submitted immediately (within 24 hours of the centre awareness) on an SAE form to the designated Pharmacovigilance Group, at the following address:

NAME	Jeffrey Poplavskiy
POSITION	Pharmacovigilance manager
COMPANY	NPO Petrovax Pharm LLC
ADDRESS	123112, Moscow; Sosnovaya ul. 1, s. Pokrov, Podolsk, Moscow Oblast, 142143 Russia
TELEPHONE	8-800-234-44-80
EMAIL	adr@petrovax.ru

Other supporting documentation of the event may be requested by the designated Pharmacovigilance manager and should be provided as soon as possible. The designated Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the centre PI or appropriate study doctor becomes aware of an SAE, they will report the event to the designated Pharmacovigilance Group.

Reporting SAEs to regulatory authorities

Following notification from the centre PI or appropriate sub-investigator, the Sponsor will report any SUSAR in an IND safety report to the regulatory authority and will notify all PIs of the participating centres as soon as possible. Any unexpected fatal or life-threatening suspected adverse reaction will be reported to the regulatory authority as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting. Relevant follow up information to an IND safety report will be submitted as soon as the information is available.

Upon request from regulatory authority, the sponsor will submit any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not SUSARs will be reported to the regulatory authority at least annually in a summary format which includes all SAEs.

Centres may have additional local reporting requirements (to the IRB and/or national regulatory authority).

8.3.7. Reporting Events to Subjects

Subjects will be informed of any severe AEs or SAEs that occur as part of their participation in this study.

8.3.8. Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the sponsor and recorded on the appropriate CRF. Pregnancy should be followed to the outcome.

8.4. Unanticipated Problems

8.4.1. Definition of Unanticipated Problems

An Unanticipated Problem is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the approved study protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ('possibly related' means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2. Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, unanticipated problems (UP) will be reported using the following timeline:

- UPs that are SAEs will be reported to the Statistical and Data Coordinating Centre (SDCC)/study sponsor and the ethics committee within 24 hours of the investigator becoming aware of the event per the above describe SAE reporting process.
- Any other UP will be reported to the SDCC/study sponsor and the ethics committee within 3 days of the investigator becoming aware of the problem.

8.4.3. Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this study.

9. STATISTICS

9.1. Statistical analysis

Analysis of the primary endpoint

The primary efficacy outcome for the first part of the study is 'Clinical status of the patient (according to 7-point ordinal scale) on day 15 as compared to baseline'.

Analysis of the secondary endpoints

The interval (quantitative) data will be described with arithmetic mean, standard deviation, median, lower quartile (25%) and higher quartile (75%), minimum, maximum, coefficient of variation, and 95% confidence interval for the mean. The categorical (qualitative) data will be described with incidences, percentage, or proportions, and 95% confidence interval for percentage or proportions.

The time to event data will be processed via survival analysis with the use of Kaplan-Meier curves and 95% confidence intervals.

The following standard parametric tests are planned for comparison of quantitative data with normal distribution: Student t-test, analysis of variance (ANOVA) for repeated measurements.

The following standard non-parametric tests are planned for comparison of quantitative data with distribution other than normal: Mann-Whitney U-test, Wilcoxon T-test, Friedman test.

Shapiro-Wilk test will be used to test normality of the distribution.

The incidences will be compared with Pearson's $\chi 2$-test or Fischer's exact test.

9.2. Software for statistical analysis

Statistical analysis of the data collected during the study will be performed with the use of programming language R for statistical computing (version 3.6.0 or higher), statistical software SAS (version 9.4 or higher) or other special software that ensures adequate quality of the results.

9.3. Review of violations from the protocol and plan of analysis

Statistical methods could be replaced if it contributes to a more correct and informative analysis. Any changes will be described and justified in the final study report.

9.4. Drop-outs, withdrawn patients, and missing data

No missing data will be substituted. The missing/omitted data will not be considered during statistical analysis.

9.5. Outliers

Identification of doubtful data and data not suitable to analysis can be performed by visual analysis of dispersion diagrams, boxplots, etc.

9.6. Population for analysis

The following populations will be used for analysis:

1. All enrolled patients (Intent-to-treat, ITT).
2. Safety population: Patients who received at least one infusion, according to the prescribed treatment.

9.7. Statistical methods

The methods of statistical analysis will depend on the type of source data and the type of distribution. The possibility of using a number of statistical methods will be evaluated after collection of the data, since the nature of distribution, homogeneity of the sample, and other parameters are unknown at the beginning of the study.

The list of methods may be expanded during the analysis for high-quality data processing.

9.7.1. Assessment of demographic indicators and baseline data

The categorical (qualitative) data will be described with incidences, percentage, or proportions, and 95% confidence interval for percentage or proportions.

The interval (quantitative) data will be described with arithmetic mean, standard deviation, median, minimum, maximum, lower quartile (25%) and higher quartile (75%), coefficient of variation, and 95% confidence interval for the mean.

Shapiro-Wilk test will be used to test normality of the distribution.

9.7.2. Statistical methods for efficacy analysis

ITT will be the main population for efficacy analysis.

9.7.2.1. Analysis of the Primary Efficacy Endpoint

The primary efficacy outcome for the first part of the study is 'Clinical status of the patient (according to 7-point ordinal scale) on day 15'. Because there is uncertainty about the clinical course and potential different trajectories according to baseline disease severity, the day of the primary endpoint may be modified based on a blinded evaluation of various timepoints (e.g., days 7-17). Analyses will be evaluated by baseline severity (mild/moderate vs severe). For example, in mild disease, recovery may occur rapidly such that all patients with mild disease have resumed normal activities by Day 15. Hence, the final timepoint selected may vary accordingly.

9.7.2.2. Analysis of the secondary efficacy endpoints

The interval (quantitative) data will be described with arithmetic mean, standard deviation, median, lower quartile (25%) and higher quartile (75%), minimum, maximum, coefficient of variation, and 95% confidence interval for the mean. The categorical (qualitative) data will be described with incidences, percentage, or proportions, and 95% confidence interval for percentage or proportions.

The time to event data will be processed via survival analysis with the use of Kaplan-Meier curves and 95% confidence intervals.

The following standard parametric tests are planned for comparison of quantitative data with normal distribution: Student t-test for dependent/independent samples, analysis of variance (ANOVA) for repeated measurements.

The following standard non-parametric tests are planned for comparison of quantitative data with distribution other than normal: Mann-Whitney U-test, Wilcoxon T-test, Friedman test.

Shapiro-Wilk test will be used to test normality of the distribution.

The incidences will be compared between the treatment groups with Pearson's $\chi 2$-test or Fischer's exact test.

9.7.3. Statistical methods for analysis of safety of the investigational product

Safety analysis will be performed in the safety population. Regardless of the reason for the completion of the study, the data of all patients who received at least one infusion according to the assignments will be included in the safety analysis.

Safety data will be analysed using the methods chosen for efficacy analysis.

Incidences of adverse events/serious adverse events will be calculated for assessment of AEs. Incidences of adverse events reported during the study will be presented as number of patients with AE in total and in each treatment group. Also, number of AEs per each severity category and per causal relationship with the study drug will be presented.

9.8. Level of significance

The significance level will be 0.05 (5%).

9.9. Subgroup analyses

Subgroup analyses for the primary outcomes may evaluate the treatment effect across the following subgroups: geographic region, duration of symptoms prior to enrolment, age, and

sex. Subgroup analyses might include additional interaction tests to determine whether the effect of treatment varies by subgroup.

9.10. Procedures that increase accuracy of the statistical analysis

Monitors will check the case report forms for missing data during monitoring visits to the centre. If any data are absent in the CRF and are present in the source records, relevant inquiries and instructions for the corrective actions will be sent to the study doctors.

The statistician and the Principal Investigator will review the database for any doubtful, missing, and non-analysable data. Inquiries will be sent to the investigators in case of any findings.

If necessary, the study doctors will correct the errors in CRFs and inform the Principal Investigator and the monitors about the corrective actions. If the identified errors in the data cannot be corrected after the completion of the subjects' participation in the study, sensitivity of the resulting parameters to questionable data will be performed as part of the statistical analysis. Information about any missing, doubtful, and non-analysable data will be presented in the Clinical Study Report.

10. DIRECT ACCESS TO THE SOURCE DATA/SOURCE RECORDS

Source data is the information contained in the original medical records and their certified copies that describe the results of clinical observations, examinations and other activities and allow reproducing the course of a clinical study and evaluate its quality. Source data is entered to the source records (originals or their certified copies) and to electronic form if an electronic data collection system is used.

The study doctor has to authorize monitoring of the study (by the authorized representative of the Sponsor), audits (by the authorized representative of the Sponsor or the company authorized by the Sponsor to conduct audits of the study centre) and inspections by the regulatory authorities with direct access to source data and source records.

11. QUALITY CONTROL AND ASSURANCE

11.1. General information on quality assurance and quality control

The sponsor must provide an appropriate quality assurance and quality control system for the conduct of this clinical study in accordance with the Study Protocol, Good Clinical Practice, and other regulatory requirements that are applicable to non-interventional studies.

The study doctor and members of the study team must strictly follow the study procedures specified in the Protocol.

11.2. Risk management

The methods used to ensure and control the quality of the study should be correlated with the risks inherent to all parts of the observational study and importance of the data obtained during the study. The quality management system should use a risk-based approach.

In accordance with the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency[1], the study procedures will be conducted with respect for the rights of the subjects, ensuring their security, as well as taking into account national and international regulatory requirements for managing and controlling the spreading of COVID-19, including quarantine measures.

The Sponsor is responsible for composing the risk management plan for the clinical study. The risk management plan is part of the clinical study project.

11.3. Clinical study monitor

Sponsor or the designated vendor will monitor the clinical study to:

- ensure protection of the rights and health of the patients,
- review the accuracy and reliability of the data entered in the CRFs and the source records,
- verify that the study doctor and members of the study team follow the procedures of the approved study Protocol, current amendments to the protocol (if applicable), Good Clinical Practice, and applicable regulatory requirements.

Clinical study monitoring is carried out according to the approved plan. Monitor must comply with the written standard operating procedures of the Sponsor/CRO, as well as procedures that were specified by the Sponsor/CRO to monitor this study.

The monitor must ensure that the study is conducted and documented properly. Monitor has the following duties and responsibilities:

- acts as the main link between the Sponsor and the study doctor,
- verifies that the Investigator has the required qualification and sufficient resources, including laboratories, equipment, and personnel throughout the study,
- controls the investigational product (storage terms, shelf life, a sufficient stock of the product in the centre, the correct administration of the investigational product, the accounting),
- verifies that the study doctor complies with the approved Protocol and all approved Amendments to the protocol (if applicable),
- verifies that the Patient Information Sheet and the informed consent form for participation in the clinical study is signed in a timely manner, i.e. before the patient is included in the study,
- ensures that the study doctor has the current version of the study records (protocol, amendments to the protocol (if applicable), investigator's brochure, patient information leaflet and informed consent form for participation in the clinical study),

[1] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. Electronic source. Free access: https://www.fda.gov/media/136238/download. Access date: March 20, 2020.

- provides sufficient information about the study to the study doctor and the study team,
- controls how the study doctor and study team fulfil their duties within the study in accordance with the protocol and other applicable agreements/contracts between the Sponsor and the study doctor/healthcare institution,
- verifies that the study team fulfils their duties independently (that the study doctor duties are not transferred to unauthorized persons),
- monitors how the study doctor complies with the eligibility criteria,
- informs the Sponsor about the enrolment rate,
- verifies the accuracy and completeness of data in the CRF, source records and other study records by comparing them,
- informs the study doctor about any errors, omissions, and illegible entries in the CRF,
- verifies compliance with the adverse events reporting deadlines defined by this Protocol,
- verifies filing of the main study documents by the study doctor,
- informs the study doctor of deviations from the Protocol, SOP, regulatory requirements, and takes the necessary actions to prevent the recurrence of such deviations.

11.4. Audit by Sponsor

The Sponsor's audit is carried out separately and independently of the routine monitoring and quality control of the clinical study. The purpose of the audit is to assess the conformity of the study to the protocol, SOPs, and regulatory requirements.

For the audit, the Sponsor appoints individuals who are not involved in this clinical trial.

The sponsor must make sure that the auditors are qualified to conduct the audit properly. The qualifications of the auditor must be documented.

The sponsor or the designated vendor develop an audit plan and audit procedures for this study.

11.5. Actions of the Sponsor in response to non-compliance with applicable requirements

The Sponsor should take immediate actions in case of any non-compliance with the Protocol, SOPs, and/or related regulatory requirements by the study doctor/study centre, CRO or Sponsor's staff.

If any serious and/or repeated non-compliance with applicable requirements by the study doctor/health care institution/CRO are detected during monitoring or audit, the Sponsor may terminate the participation of the violating party in the study. If participation of the investigator/study centre in the study is terminated because of serious or repeated non-compliance with the applicable requirements, the Sponsor must notify the regulatory authorities.

11.6. Clinical Study Documents

The Sponsor provides the following main documents and materials to the study centre:

- study protocol (with amendments, if any),
- Investigator's Brochure,
- patient information sheet with informed consent form for participation in the observational study,
- investigational product (IP),
- agreement,
- documents required for submission to the local ethics committee.

The study doctor provides the Sponsor with the following key documents before the start of the study:

- a referral letter to the local ethics committee (if any),

- signed confidentiality agreement,
- signed investigator statement of agreement with the protocol,
- approval of the protocol by the local ethics committee,
- list of members of the local ethics committee,
- CVs of all study doctors (signed and dated),
- laboratory reference ranges with the signature and date of the responsible laboratory employee,
- certificates for medical / laboratory equipment.

The study doctor must keep clinical study documents (source records and the investigator file) for 15 years after the completion of the study.

11.7. Amendments to the protocol

Amendment to the Protocol is a written description of the changes or a message about the amendments, or an official explanation of the Protocol.

Amendments to the Protocol are significant if changes to the Protocol affect the safety or physical/mental well-being of the patients, the scientific value of the study, the study procedures, the quality or safety of the investigational product, or if it implies replacement of the responsible study doctor in the centre or inclusion of a new centre in the study.

Any changes or additions to this Protocol require should be issued as written amendments to the protocol and approved before entry into force.

Any changes or additions to this Protocol require should be issued as written amendments to the protocol and approved before entry into force.

Any amendments which affect the safety of patients, conduct or the scientific value of the study should be further approved by the local ethics committee.

Changes to the Protocol that affect only the administrative aspects of the study do not require the approval of the local ethics committee, but the parties should be notified of such amendments in writing.

The final study report should describe frequency and type of Protocol Amendments and explain how the changes affect results of the study.

11.8. Compliance with the protocol

The study doctor conducts the study in accordance with the approved Protocol.

Deviation from the Protocol is any change, inconsistency, or deviation from the study design or the study procedures described in the Protocol.

Any deviation from the Protocol during the clinical study should be recorded and reflected in the study documentation.

All deviations from the Protocol are classified as significant or minor.

A minor deviation from the protocol does not significantly affect the rights, safety and well-being of the patient or completeness, accuracy, and reliability of the study data.

A significant deviation from the protocol (or violation of the protocol) is a deviation that may affect the rights, safety and well-being of the patient or completeness, accuracy, and reliability of the study data.

Examples of significant deviations from the protocol:

- the patient met the withdrawal criteria, but was not excluded from the study,
- the patient was included in the study while not being eligible,
- conducting study procedures without a written informed consent of the patient,
- violations of the procedure for administration of the investigational product,
- lack of discipline of the patient, non-compliance with limitations implied by the study,
- systematic (repeated at least 2 times) negligent loss of data or samples collected for the study in the centre,
- the patient missed a visit.

Significant deviations must be reported to the ethics committee. If significant deviations from the protocol are detected, the patient should be excluded from the final analysis of efficacy data.

If the visit procedures go beyond the time frames specified by the protocol, the Sponsor will consider continued patient participation in the study at the request of the study doctor on an individual basis.

11.9. Final study report

A medical research expert/medical consultant will be involved in preparation of the observational study report. The discussion of the results and conclusions will include a clear conclusion on the safety profile as well as efficacy of the investigational products.

The observational study report will show the number and type of Protocol Amendments (if applicable), the number of violations and deviations from the Protocol found during the study.

The final version of the report will be signed by the ones who prepared it, a medical research expert/medical consultant, the head of this study, and will be approved by the head of the institution and certified with the seal of the institution.

12. REGULATORY AND ETHICAL ASPECTS OF THE STUDY

12.1. Authorization for the study

In the case of a non-interventional study, the Protocol and the Patient Information Sheet with an informed consent form for participation in the observational study must be approved by the local ethics committee (LEC) of the institution before the study.

Patients cannot participate in the study until the study is approved by the Council of Ethics and LEC of the institution.

12.2. Ethical Compliance

The investigators and the study team, CRO (if applicable) employees, the Sponsor, as well as other persons involved in this clinical trial, must follow the ethical principles set forth in the WMA Helsinki Declaration (in the latest edition) and Good Clinical Practice.

12.3. Information for the patient and the consent procedure

The patients are provided with oral information and written materials about the objectives and methods of the study before initiation of any study procedures. They are informed of the expected benefits and possible risks associated with participating in the study. In addition, patients should be informed that participation in the study is voluntary and that they have the right to refuse to participate in the study at any time, and that this refusal will not affect the quality of medical care provided. Patients are not required to report the reasons for withdrawal from study, but the investigator should try to find out these reasons without violating the rights of the patient.

The patient should have enough time to consider participation in the study. The patient should be given the opportunity to ask additional questions.

Voluntary consent to participate in an observational study of a medicinal product for human use is documented in the Patient information sheet with the informed consent form for participation in an observational study by date and personal signature of the patient and the Investigator, thereby proving that voluntary consent has been obtained and the patient had the opportunity to ask questions and received full answers to them. The patient information sheet with the informed consent form for participation in the observational study is issued in 2 copies. The patient keeps one copy. The second copy is kept in the study centre together with the other study records.

12.4. Confidentiality

Personal medical information about the study subjects that was collected during the study is considered confidential and cannot be disclosed to third parties.
Such information may only be transferred to the attending doctor or other healthcare provider upon the patient’s consent.

Each study subject will be assigned a screening number that will be used to maintain the confidentiality of his data when transmitting information about adverse events or other data related to the study procedures.

The investigator must ensure that the patient data are anonymized. The patients are identified only by the assigned numbers in the CRF.

The study doctor will keep full identification information about each patient and must provide it to the auditor, or regulatory authorities upon request. The patient screening numbers should be stored in such a way that secures confidentiality of such information.

All persons involved in the study should treat the patient information as well as information about this study as confidential.

13. DATA HANDLING AND RECORD KEEPING

13.1. General terms

The patient is identified by a screening number in the Case Report Form (CRF). If it becomes necessary to identify the patient for safety or regulatory reasons, the investigator must maintain confidentiality of such information.

13.2. Source Records

The source records are kept in the study centre to confirm the existence of patients and accuracy of the collected data. The source records include original documents related to examinations, treatment, medical history, and description of the patient's condition. For example, such documents include medical history and results of laboratory tests.

The source records are filed according to the approved clinical practice, including registration of source records in the appropriate unit of the study centre. Each examination of the patient is recorded in the source records. The required data are transferred to the CRF within the time agreed upon with the Sponsor.

The investigator must evaluate, date and sign results of laboratory tests and other investigations upon receipt. Reports on laboratory tests and other investigations are considered the source records.

The following information should be included in the source medical records:

- demographic data,
- eligibility,
- participation in the study together with the study number and patient number,
- date and time of all examinations,
- medical history and results of physical examination,
- adverse events,
- previous and concomitant treatment,
- results of the examinations,
- results of the laboratory tests,
- description of the prescribed study treatment,
- reason for withdrawal from the study (if applicable).

All entries in the source records should be made in clear, legible handwriting.

To correct an entry in the source records, cross out the incorrect entry with a single horizontal line, make a correct entry next to it, write the date of the correction and the initials and the signature of the person who made the correction. Destruction of the previous record by any means or making it difficult to read is not allowed.

An electronic data collection system can also be used to collect source data (for example, the results of scoring on specialized scales). If an electronic data collection system is used, the source records are kept in electronic form (electronic database). Similar requirements to filing, corrections, etc. are applicable to such source records.

13.3. Filling in the CRFs

This study uses electronic versions of the CRF (eCRF). The investigator is responsible for keeping correct and accurate data on the progress of the study

All entries in the paper source records should be made in clear, legible handwriting.

To correct an entry in the paper source records, cross out the incorrect entry with a single horizontal line, make a correct entry next to it, write the date of the correction and the initials and the signature of the person who made the correction. Destruction of the previous record by any means or making it difficult to read is not allowed.

Do not leave empty cells in the CRF.

Processing the CRF data can cause additional requests. The investigator shall respond to such requests by confirming or changing the requested data.

eCRFs must be filled in within the time period agreed with the Sponsor.

13.4. Data collection

Data that are collected during the study are recorded in the eCRF.

eCRFs must be filled in within the time period agreed with the Sponsor. If a patient is withdrawn from the study, the eCRF is filled in up to the withdrawal and includes the reason for withdrawal.

The study doctor is responsible for ensuring completeness and accuracy of the data in the eCRF. Data in the eCRF should be confirmed by the source records.

The duties of the Monitor include verifying compliance of the eCRF with the source records. The study doctor shall provide the source records to the Monitor for verification.

The Monitor shall inform the study doctor about any discrepancies in the data. The monitor does not have the right to make corrections to the eCRF.

Corrections to the eCRF are made by the investigator or a member of the study team who has the right to enter data in the CRF in accordance with the relevant instructions.

AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug or ATC, respectively.

13.5. Data Transfer and Processing

Accuracy, consistency, and completeness of the study data will be verified after the database lock.

All missing data and discrepancies will be submitted to the study centre as requests and updated by the responsible investigator. If no further adjustments to the database are needed, it will be declared closed and used for statistical analysis.

Data management will comply with the current standard operating procedures (SOPs) of the Sponsor/CRO.

13.6. Storage and archiving of the study records

By signing this Protocol, the Principal investigator agrees to comply with the procedures for storage and archiving of the study records. The source records and the local investigator file including the subject identification sheet and the correspondence associated with the study are subject to storage. The main documents of the clinical study should be kept at the study centre for at least 15 years after the submission of the final version of the clinical study report to the regulatory authorities.

The sponsor is responsible for archiving the Main Clinical Study File.

If the Sponsor discontinues clinical development of the investigational product, the investigator and regulatory authorities must be notified. The Sponsor must inform the Principal investigator in writing about keeping of the study records.

14. FUNDING AND INSURANCE

14.1. Funding of the study

In accordance with Federal Law of the Russian Federation No. 61-FZ 'On circulation of medicines, this study is funded by the Sponsor in accordance to the agreement between the Sponsor, healthcare institutions (study centres), and clinical diagnostic laboratories.

14.2. Compensation

This Protocol does not provide for any compensation of participation in the study to patients.

14.3. Insurance

Data on treatment received by patients in routine clinical practice will be collected and analysed using epidemiological methods during this study. Patient management, including diagnosis and monitoring of ongoing therapy, will be carried out within the routine clinical practice only. Compliance with current medical practice eliminates any risks in addition to those associated with the standard treatment. Thus, participation in the study will not entail any additional danger to patients. Since there are no risks associated with the study, there is no need to provide additional protection for patients in the form of insurance. The general provisions of medical law, as well as professional liability insurance for study doctors and, accordingly, participating health care institutions, provide sufficient protection for both patients and the study doctors.

15. USE AND PUBLICATION OF STUDY DATA

Information about the investigational product, conduct of this study, and unpublished results of the study are considered confidential.

The Sponsor has the exclusive intellectual property rights for the study results and commercial use of the study data.

The study data can only be transferred to representatives of the regulatory authorities who examine possibility or impossibility of conducting this study and issue authorizations to conduct a study, and to the study subjects on confidential terms. The information cannot be transferred to third parties without a specific written permission of the Sponsor.

The public presentation or publication of the results of this study is considered a joint work of the investigator, Sponsor, and other persons involved in the study.

The investigator must be informed and agree that the Sponsor may use the study results for publication and, thus, make such information publicly available.

Investigator may publish the study results only upon the Sponsor's agreement. The investigator must submit the manuscript of the planned publication to the Sponsor for approval.

The Investigator is informed that the data obtained during the study can be provided to other investigators or government organizations by the Sponsor or persons authorized by the Sponsor

16. APPENDICES

SCHEDULE OF ASSESSMENTS

Table 1. Study plan
(ALL THESE PROCEDURES SHOULD BE CARRIED OUT IN THE FRAMEWORK OF ROUTINE PRACTICE OF THE HEALTH CARE INSTITUTIONS)

Procedure / days	**Study according to the Protocol No. COVID dated March 30, 2020**				
	Day **1**	**Daily** *(up to discharge***)*	Day **3, 5, 7, 11**	Day **15±1**	Day **29±3 or** any other **last day****** of the study
Enrolment criteria	X				
Withdrawal criteria		X	X	X	X
Informed consent, enrolment	X				
Polyoxidonium	10 doses: days 1, 2, 3, 5, 7, 9, 11, 13, 15, 17				
History	X				
Clinical signs and symptoms, physical examination[1]	X	X	X	X	X
Nasopharyngeal and/or oropharyngeal smear	X		X	X	X
Haematology[2]	X**		X	X	X
Blood chemistry[3]	X**		X	X	X
CRP	X**		X	X	X
Urinalysis[4]	X**		X	X	X
Bacteriological inoculation of sputum	If necessary				
Chest X-ray/ CT*	If indicated				
ECG*	If indicated				
SpO2[5]	X	X	X	X	X
Evaluation of need for oxygenation, including mechanical ventilation	X	X	X	X	X
Assessment of the treatment efficacy[6]	X	X	X	X	X
Assessment of safety	X	X	X	X	X
NEWS Score	X	X	X	X	X
SOFA Score	X	X	X	X	X
Clinical status by WHO scale	At admission	X	X	X	X

Notes to Table 1

*- including at admission, before enrolment

**- results of the previous laboratory investigations within 48 hours before enrolment can be used

*** - visits to the clinic are preferred after discharge, but the quarantine or other reasonable factors can limit this opportunity. The visits could be performed in a form of phone call or with other remote communication technologies. Some data will not be collected by obvious reasons.

**** - in case of the patient withdrawal (see the withdrawal criteria)

1 – Clinical signs and symptoms

Weakness, fatigue, cough, shortness of breath, stuffiness in the chest, myalgia, headaches, haemoptysis, palpitations, nasopharyngeal symptoms, diarrhoea, nausea, vomiting; physical

examination: heart rate, blood pressure, respiratory rate, body temperature

2 – Haematology
Red blood cells, haematocrit, white blood cells, platelets, neutrophils, eosinophils, basophils, monocytes, lymphocytes

3 - Blood chemistry
Urea, creatinine, Na+, K+, bilirubin, glucose, ALT, AST, albumin, pH, bicarbonates, lactate, coagulogram with prothrombin time, coagulogram with international normalized ratio and activated partial thromboplastin time, CRP
If indicated: PaO_2, FiO_2, $PaCO_2$

4 – Urinalysis
According to routine practice of the centre

5 - SpO_2
With qualitative assessment of oxygenation, including mechanical ventilation

6 – Assessment of the treatment efficacy
The maximal treatment effect, the treatment effect evaluated by the doctor