CLINICAL TRIAL PROTOCOL

Drug developer:	Federal Government Budgetary Institution N. F. Gamaleya National Research Center of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation (FSBI N. F. Gamaleya National Research Center of Epidemiology and Microbiology of the Ministry of Health of Russia) **Legal address:** **18 Gamalei Street, Moscow, Russia 123098** **Tel.: 8 (499) 193-30-01, Fax: 8 (499) 193-61-83** **E-mail: info@gamaleya.org.**
Protocol number:	**No. 06 - Sputnik Light - 2020**
Medicinal drug:	An open study on the safety, tolerability, and immunogenicity of the medicinal drug "Sputnik Light" to help prevent the coronavirus infection caused by the SARS-CoV-2 virus

Contents

LIST OF ABBREVIATIONS

ABP	Arterial blood pressure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BBA	Biochemical blood analysis
EVD	Ebola virus disease
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
CEP	Chicken Egg Protein
IB	Investigator’s Brochure
PFU	Plaque-forming units
VAS	Visual Analogue Scale
RIUL	Reference interval upper limit
IM	Intramuscular
HIV	Human immunodeficiency virus
VNA	Virus neutralizing antibodies
v. p.	Viral particles
WHO	World Health Organization
DTH	Delayed-type hypersensitivity
Russian Pharmacopoeia	State Pharmacopoeia of the Russian Federation
VHI	Voluntary health insurance
RF	Respiratory failure
DNA	Deoxyribonucleic acid
HID	Human immunizing dose
BMI	Body mass index
INF	Interferon
CRF	Case report form
IC	Informed consent

EIA	Enzyme immunoassay test
IFN	Interferon
CS	clinical trials
CT	computed tomography scan
LD50	50% lethal dose
LDH	Lactate dehydrogenase
MD	Medicinal drug
MP	Medicinal preparation
LEC	Local Ethics Committee
MID	Medicinal immunological drugs
INN	International non-proprietary name
RILL	Reference interval lower limit
RI	Research institute
RW	Research work
NSAID	Non-steroidal anti-inflammatory drugs
ADR / UADR	Adverse drug reaction /unexpected adverse drug reaction
SCEEMP	Scientific Center for Expert Review on Medical Products
IEC	Independent Ethics Committee
AE / SAE	Adverse event / Serious adverse event
BPCD	Biological and process control department (division)
CBC	Complete blood count
ARF	Acute respiratory failure
ARI	Acute respiratory infection
RNA	Ribonucleic acid
CPE Dept	Geometric mean titer
SAR	Serious adverse reaction
SAE	Serious adverse event
ESR	Erythrocyte sedimentation rate

CRP	C-reactive protein
Ultrasonic	Ultrasonic examination
FSBI	Federal State Budgetary Institution
FZ	Federal Law
CNS	Central nervous system
HR	Heart rate
RR	Respiratory rate
ALP	Alkaline phosphatase
ED	Effective dose
EID	Equivalent immunizing dose
EDTA	Ethylenediaminotetraacetic acid
ECG	Electrocardiogram
IRB	Institutional review board
ADE	Antibody-dependent enhancement
Ad5	Human adenovirus 5
Ad26	Human adenovirus 26
COVID-19	an infectious disease caused by new SARS-CoV-2
GCP	Good clinical practice
HEK293	Human Embryonic Kidney 293 – a cell line obtained from adrenal cell of aborted human embryo
ICH	International Conference on Harmonization
InfA	Interferon-alfa
IgM, IgG, IgA, IgE	Immunoglobulins M, G, A and E, respectively
LASV	Lassa virus
MARV	Marburg virus
MVA	Modified Vaccinia Ankara
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
RBD	Receptor-binding domain

RSV	Respiratory syncytial virus
RVF	Rift Valley fever
S	Glycoprotein S
SARS	Severe acute respiratory syndrome
SARS-CoV-2	New coronavirus which caused an infection outbreak in 2019-2020
Vs	Versus
VEE	Venezuelan equine encephalitis virus
VLP	Virus-like particles

1. GENERAL INFORMATION

Developer of the medicinal product under trial and the organizer of the trial:	Federal State Budgetary Institution N. F. Gamaleya National Research Center of Epidemiology and Microbiology, Ministry of Health of the Russian Federation (FSBI N. F. Gamaleya NRCEM of the Ministry of Health of Russia) Registered / location address: 18 Gamalei street, Moscow, Russia 123098 Tel: +7 (499) 193-30-01 e-mail: info@gamaleya.org

Name and position of the person authorized to sign the Protocol and amendments thereto on behalf of the Developer

Director of FSBI N. F. Gamaleya National Research Center of Epidemiology and Microbiology, Ministry of Health of the Russian Federation A.L. _____ Gkintsburg

LIST OF CHANGES VS THE PREVIOUS VERSION

Version	Date	List of changes
1.0	30.12.2020	Not applicable (primary application on receiving RCCT)
1.1	11 January 2021	Editorial changes, criteria detailing of inclusion in investigation
1.2	02.02.2021	Information volume is updated for including in an interim report on the results of the safety and immunogenicity assessment that will be drawn up on the basis of the results obtained on the 28th day of the study to help make a decision on the registering the drug in accordance with Russian Federation government Resolution No. 441 dated April 3, 2020 "On the Specifics of Handling Human Medicinal Drugs Intended for Use During the Threat of or an Actual Emergency Situation, and Emergency Response, and for Arranging Medical Assistance to Persons Affected by Emergency Situations, Preventing Emergency Situations, Preventing and Treating Diseases That Pose a Serious Hazard to the Public, Diseases and Injuries Resulting from Adverse Chemical, Biological, and Radiation Factors"

1.1. Administrative structure of the study

Pharmacovigilance Officer	Marina Yuryevna Chernukha, *Head of Biological and Technical Control Department, Pharmacovigilance Officer*	Registered / location address: 18 Gamalei street, Moscow, Russia 123098 Tel.: 8 (499) 193-30-01 Fax: 8 (499) 193-61-83 E-mail: info@gamaleya.org
Drug development group (experts)	Denis Yurievich Logunov, *Deputy Director for Scientific Research, Doctor of Biology, Corresponding Member of the Russian Academy of Sciences* Inna Vadimovna Dolzhikova, *Head of State Virus Collection Lab, PhD in Biology*	Registered / location address: 18 Gamalei street, Moscow, Russia 123098 Tel.: 8 (499) 193-30-01 Fax: 8 (499) 193-61-83 E-mail: info@gamaleya.org
Medical expert of the organization responsible for clinical trial management	Lyudmila Vasilievna Kolobukhina *Head of Viral Hepatitis and Clinical Virology Department, Professor, Doctor of Medicine*	Registered / location address: 18 Gamalei street, Moscow, Russia 123098 Tel.: 8 (499) 193-30-01 Fax: 8 (499) 193-61-83 E-mail: info@gamaleya.org
Person responsible for medical decision-making in the Research Center	Principal investigator	According to the address specified in the clinical trial authorization
Names and addresses of clinical laboratories participating in the clinical trial	**Efficacy assessment**	
	Cell Microbiology Laboratory *Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation* (efficacy assessment)	Registered / location address: 18 Gamalei street, Moscow, Russia 123098 Tel.: 8 (499) 193-30-01 Fax: 8 (499) 193-61-83 E-mail: info@gamaleya.org
	Safety assessment	
	Laboratory study of safety: Research Center Laboratory	According to the address specified in the clinical trial authorization

1.2. Signature page(s) for Research Centers

I have read and understood the Clinical Trial Protocol. Having read and understood Clinical Trial Protocol No. 06-Sputnik Light-2020, I hereby confirm my consent to:

- the performance of this clinical trial in accordance with this Protocol, international rules of good clinical practice, and requirements of regulatory bodies;
- provision of direct access to initial data/documents (validation of initial documents);
- ensuring the right for monitoring and audit of clinical trials, IRB/IEC expert evaluation, and inspection by regulatory bodies;
- use of the clinical trial materials, including medicinal drugs, only in accordance with this Protocol;
- informing the person responsible for clinical safety within 24 hours of any serious adverse event, whether related to the studied therapy or not;
- signing this Protocol before formal commencement of the trial.

I understand that:

- any changes to this Protocol must be executed as an amendment to be approved by the Sponsor in writing before being given effect;
- the contents of this Protocol is confidential and must not be copied;
- any violation of this Protocol may lead to early suspension of the Research Center from the trial.

Principal investigator _____ _____

FULL NAME Signature

_____ _____ 2020

1.3. PROTOCOL SYNOPSIS

Protocol code	No. 06 - Sputnik Light - 2020
Study title	An open study on the safety, tolerability, and immunogenicity of the medicinal drug "Sputnik Light" to help prevent the coronavirus infection caused by the SARS-CoV-2 virus
Trial phase	I-II
Medicinal drug developer	Federal Government Budgetary Institution N. F. Gamaleya National Research Center of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation (FSBI N. F. Gamaleya National Research Center of Epidemiology and Microbiology of the Ministry of Health of Russia)
Drug information	*Study drug*: "Sputnik Light combined vector vaccine to help prevent the SARS-CoV-2-induced coronavirus infection" International nonproprietary or generic or chemical name: Vaccine to help prevent the newly discovered coronavirus infection (COVID-19) Dosage form: solution for intramuscular injection Composition for 1 dose (0.5 ml): Active substance: recombinant serotype 26 adenoviral particles, containing the SARS-CoV-2 protein S gene, in the amount of (1.0±0.5) x 10^{11} particles per dose. Excipients: Tris-(hydroxymethyl)aminomethane – 1,21 mg, sodium chloride – 2,19 mg, sucrose – 25.0 mg, magnesium chloride hexahydrate – 102,0 μg, EDTA-disodium salt dihydrate – 19,0 μg, polysorbate 80–0 μg, ethanol 250% – 95 μl, water for injections – 2.5 mL or less. The vaccine has been produced using biotechnological methods, without the use of the SARS-CoV-2 virus, a human pathogen. The preparation contains a recombinant adenoviral vector based on the human adenovirus serotype 26, which carries the SARS-CoV-2 virus S protein gene. The vaccine induces humoral and cellular immunity towards the coronavirus infection caused by the SARS-CoV-2 virus. The immunological properties and safety of the vaccine were studied during a clinical Trial conducted on healthy, adult volunteers from both genders, ranging in age from 18 to 60. Nine volunteers received component I of the Gam-COVID-Vac combination vaccine. Immunogenicity was assessed by the level of specific IgG antibodies for the SARS-CoV-2 coronavirus S protein and virus neutralizing antibodies, as well as by the formation of specific T helper (CD4 +) and T cytotoxic (CD8 +) lymphocytes. The safety of the vaccine was confirmed in the trials 02-Gam-COVID-Vac -2020, 03-Gam-COVID-Vac -2020, 04-Gam-COVID-Vac - 2020, 05-Gam-COVID-Vac -2020. The drug (component I of the Gam-Covid-Vac combination vaccine) has been given to more than 33,000 volunteers in clinical trials, and has demonstrated a favorable safety profile.
Trial goal	The purpose of this trial is to assess the safety, tolerability, and

	immunogenicity of Sputnik Light, a solution for intramuscular injection, at various intervals after vaccinations are administered to adult volunteers
Trial objectives	1. Assess security and tolerability of the medicinal drug Sputnik Light, a solution for intramuscular injections, after immunizing adult volunteers with the vaccine *The assessment of safety and tolerability included data collection throughout the entire observation period by studying the drug's influence on vital signs (systolic and diastolic blood pressure, heart rate, body temperature) and laboratory indicator values in volunteers, and by the presence of general and localized post-vaccination reactions in comparison with background values (before administering the drug).* 2. Assess post-immunization immunity at various intervals after vaccinating the volunteers by: – *determining the titer of specific antibodies in blood serum by enzyme-linked immunosorbent assay as compared to background values before immunization, and on days 10, 28, 42, 90, and 180 after immunization;* – *assessing the viral neutralization activity before administering the vaccine and on days 28 and 42 after immunization* – *assessing antigen-specific cell-mediated immune response (specific T-cell response) before administering the vaccine, and on day 10 from the start of vaccinations, as compared to the background values before vaccination.* assessing the epidemiological efficacy of vaccination may be based on the information obtained concerning morbidity in vaccinated individuals (in the framework of subsequent phase III clinical trials).
Design of the trial	Phase I open prospective, non-randomized study in adult volunteers. Screening Period = up to 7 days. All screening procedures must be carried out within the shortest possible time before the scheduled date of Visit 1 (drug injection). The laboratory and instrumental examination data obtained within 14 days before the screening will be recorded as the screening data. The trial will include 110 volunteers that will be administered the study drug. Follow-up will take place in the course of 4 visits, i. e. on the 10th, 28th and 42nd day upon injection. Trial coordinator must minimize the risks for volunteers and researches in the context of pandemic (letter of the Ministry of Health of the Russia Federation No. 20-1/I-2-3651 dated 27.03.2020 On the Issues of Clinical Trials of Medicinal Drugs during COVID-19 Pandemic). An interim report can be prepared at the initiative of the developer at any point in the study to assess safety and / or immunogenicity. Upon reaching the primary points involved in immunogenicity assessment described in the Protocol, a report on the results of the safety and immunogenicity assessment will be drawn up on the basis of the results

	obtained on the 28th day of the study to help make a decision on the registering the drug in accordance with Russian Federation government Resolution No. 441 dated April 3, 2020 "On the Specifics of Handling Human Medicinal Drugs Intended for Use During the Threat of or an Actual Emergency Situation, and Emergency Response, and for Arranging Medical Assistance to Persons Affected by Emergency Situations, Preventing Emergency Situations, Preventing and Treating Diseases That Pose a Serious Hazard to the Public, Diseases and Injuries Resulting from Adverse Chemical, Biological, and Radiation Factors". This report will include the results of assessing the immunogenicity for not less than 50 participants at the 28-day point. Along with that, the study will be continued in accordance with the Protocol, accompanied by all the prescribed procedures and visits up to 180 days of observation. Visit 0: screening (as an outpatient). Visit No. 1 vaccination (outpatient) Visits No. 2, 3, 4, 5, and 8: follow-up on days 10, 28, 42, 90, and 180 after vaccination (outpatient). On days 120 and 150, visits 6 and 7 will be accomplished by telephone contact / telemedicine conference or, if necessary, in the form of an in-person visit. Any volunteer who received a dose of the study drug will be registered as a trial participant, and his/her data will be used to help assess the drug's safety and tolerability.
Number of volunteers	The trial will include 110 volunteers The screening procedures will be done with 150 volunteers participating
Inclusion criteria	1. The subject's written informed consent to participate in the trial; 2. Males or females 18 years old or older; 3. No history of COVID-2019: negative SARS CoV2 IgM and IgG EIA test (at most 14 days prior to enrollment); 4. Negative COVID-2019 PCR test result at the screening visit 5. No contact with COVID-2019 persons within at least 14 days before the enrollment (by the subject's account); 6. Negative HIV and hepatitis test results; 7. Consent to use effective contraception methods during the trial; 8. Negative drugs or psychostimulants urine test at the screening visit; 9. Negative alcohol test at the screening visit; 10. Negative pregnancy test (women of reproductive potential) 11. No evident post-vaccinal reactions or complications after receiving immunobiological drugs in the medical history 12. No acute infectious and/ or respiratory diseases within at least 14 days before the enrollment.
Exclusion criteria	1. Any vaccination / immunization performed within 14 days prior to enrollment in the study, or a planned vaccination within 14 days after being administered the study drug; 2. Steroid therapy (except hormonal contraceptives or drugs used as hormone replacement therapy for menopause) that has not been

	completed 30 days before enrollment 3. Therapy with immunoglobulins or other blood products not completed 30 days before enrollment in the trial; 4. Immunosuppressor therapy that was completed within 3 months before being included in the trial; 5. A vaccination against COVID-2019 using any other drugs, including in the course of other clinical trials 6. Female subjects during pregnancy or breastfeeding (for women with preserved reproductive potential); 7. Acute coronary syndrome or stroke suffered less than one year before enrolling in the trial; 8. Tuberculosis, chronic systemic infections; 9. Medical history with aggravated allergies (severe life-threatening allergic reactions), hypersensitivity or allergic reactions to immunobiological drugs, known allergic reactions to the drug's components, exacerbation of allergic diseases occurs on the day of inclusion in the study; 10. Neoplasms in a person's medical history (ICD codes C00-D09); 11. Donated blood or plasma (450+ ml) within 2 months before enrollment; 12. Splenectomy in the medical history; 13. Neutropenia (decrease in the absolute neutrophil less than 1000 mm_3), agranulocytosis, significant blood loss, severe anemia (hemoglobin <80 g/L), immunodeficiency disorder in a person's medical history within 6 months before enrollment; 14. Active form of a disease caused by the human immunodeficiency virus, syphilis, hepatitis B or C; 15. Anorexia, protein deficiency of any origin; 16. Large tattoos at the injection site (deltoid muscle area), which does not allow the localized response to administering the study drug to be assessed; 17. Alcohol and drug addiction in a person's medical background; 18. Registered psychiatric patient; 19. Participation in any other interventional clinical trial within 90 days before the start of this trial; 20. Any other condition that the researching physician considers to be a hindrance to completing the trial as per the protocol; 21. Research facility staff and other employees directly involved in the trial (research team members) and their families. 22. Any related conditions that, in the opinion of the study physician, could be a hindrance to participating in the trial.
Key assessment and analysis criteria	***Safety*** assessment will be based on recording adverse events during the trial (Appendix 1 Evaluation scale for the vaccination's adverse effects). In order to prevent from development of vaccine-associated reactions and complications screening of volunteers was carried out for identification of the initial body state parameters. In addition, the volunteers undergo medical examinations. All the background parameter values (examinations before

administering the drug) are entered into the volunteer's Case Report Form.

For the entire period of hospital observation, information on safety will be collected using the following parameters:

- Development, intensity, and relation to Sputnik Light of all the adverse events (AEs) for the whole period of the study;
- frequency and intensity of local signs and symptoms, relatedness of general signs and symptoms to the study product, after administration of the drug;
- Data obtained from physical, laboratory, and instrumental examinations;
- reactogenicity for the vaccine is assessed based on localized (drug administration site) and general (body reactions to product administration) reactions.

Local reactions are assessed according to the following parameters:

- hyperemia in the drug administration area;
- edema (infiltrate);
- regional lymph node hyperplasia;
- changes in mucous membranes, presence of a papule, vesicule or erosion.

General reactions associated with the vaccine include: a rise in body temperature, a decrease in wellbeing, a headache, dizziness, poor appetite, insomnia, nausea, vomiting, dyspepsia, faintness, sweatiness, joint and abdominal pain, convulsions, etc. Allergic reactions are also possible. Local and general reactions were recorded by the researching physician based on measurements taken for body temperature, examinations, and interviewing the volunteers in accordance with the schedule for the visits and the procedures for the study.

Changes in the in laboratory parameter values (complete blood count and biochemical blood assay), and dynamics for the vital signs (ABP, HR, body temperature) will also be analyzed.

During the investigation, it is worth keeping in mind that there are no pathognomonic symptoms that could unequivocally signify that each specific adverse event is related to the vaccination. Clinical symptoms such as intoxication, high temperature, neurologic symptoms, and various allergic reactions, including immediate allergic reactions, may not be due to the immunization but may be caused by a disease that developed at the time of vaccination.

That is why each incident involving a serious disease that develops in the post-vaccination period requires thorough differential diagnostics for both infectious and non-infectious diseases using instrumental and laboratory examination methods, based on the clinical symptoms of the disease.

One of the criteria is the time that it arises. As a rule, immunization reactions occur within 48 hours; more than 72 hours of fever or occurrence of fever after 72 hours may be indicative of an possible intercurrent infection. It is recommended using the Naranjo algorithm to assess an association with the drug.

<table>
<tr><td></td><td>
Blood samples will be taken from trial subjects during the following visits to assess the immunogenicity parameters listed below:
<table>
<tr><th>Immunogenicity assessment parameter</th><th>B1[1]
D1[2]</th><th>B2
D10±1</th><th>B3
D28±2</th><th>B4
D42±2</th><th>B5
D90±7</th><th>B8
D180±14</th></tr>
<tr><td>Virus-neutralizing activity (110 subjects)</td><td>×[3]</td><td></td><td>×</td><td>×</td><td></td><td></td></tr>
<tr><td>Determination of the expression of interferon gamma during antigenic restimulation (at least 30 subjects)</td><td>×[3]</td><td>×</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Determining lymphoproliferative response during antigen restimulation (at least 30 subjects)</td><td>×[3]</td><td>×</td><td></td><td></td><td></td><td></td></tr>
<tr><td>SARS-CoV-2 glycoprotein-specific antibody titer (at least 90 subjects)</td><td>×[3]</td><td>×[4]</td><td>×</td><td>×</td><td>×</td><td>×</td></tr>
</table>
1 V = visit
2 D = day
3 Blood sampling is performed on the day of injecting the first dose of the study drug immediately prior to administering the study drug
4 Blood sampling is performed on the day of injecting the second dose of the study drug immediately prior to administering the study drug
</td></tr>
<tr><td>Statistical analysis</td><td>Statistical data processing will be based on the STATISTICA application package or equivalent. Statistical data resulting from the trial will be subject to analysis.
The trial sponsor will analyze the data after the trial is completed. For purposes of statistical programming analysis, STATISTICA and/or other statistical software will be used, if required.
The conclusion about immunogenicity, or the presence or absence of adverse events, is given based on all the objective and subjective data, and laboratory and instrumental examination results obtained in the course of the study, and is described in compliance with the Protocol. Data on all the volunteers initially included in the study is subject to statistical processing, i. e. the volunteers excluded from the study for medical reasons will be taken into account for the safety analysis purposes.
The statistical analysis of the key parameters of efficacy will include all the volunteers who have completed the trials as per the Protocol.</td></tr>
<tr><td>Concomitant therapy: dose / administration route / introducing scheme</td><td>If a concomitant disease or adverse conditions arise that require the use of any medicinal drugs, the entire scope of therapy will be recorded in the CRF and primary documentation on the volunteer.
If adverse events arise in volunteers that require medical therapy, the corresponding concomitant therapy drugs will be administered in compliance with the ratified instructions for use for the medicinal product.
Medicinal drugs used for concomitant therapy purposes must be approved for use in the Russian Federation, and be used only in compliance with the officially approved patient information leaflet. Administering these drugs does not constitute grounds for barring a volunteer from the trial.
Prohibited therapy that does constitute grounds for barring a volunteer from the trial will include the administration of immunoglobulins or blood products,</td></tr>
</table>

	immunosuppressive agents, and X-ray therapy throughout the study until the end of the follow-up period. Donating blood is prohibited during the study. If such drugs have to be administered to a volunteer for medical reasons, the volunteer will have be subject to drop-out and follow-up in accordance with the drop-out procedures specified in the Protocol. No vaccination against COVID-2019 with any other drugs, including over the course of other clinical trials, is allowed. All the therapy will be recorded in the CRF and primary documentation on the volunteer. In the course of observation period after administering the study drug, the volunteers are obliged to inform the researchers about any medical drugs taken during the course of study. Administering any concomitant drugs should be recorded in the Case Report Form, which specifies the active substance, dosage, timing, and reasons for using the drug. The medical institution that performs the clinical trial should have all the necessary first-aid equipment. If first aid is required, all the measures taken and the drugs necessary for use must be recorded in the primary documentation and CRF.

2. RATIONALE OF THE STUDY

2.1. Introduction

Coronaviruses (Coronaviridae) is a large family of RNA viruses that can infect humans and some animals. In humans, coronaviruses can cause a whole range of diseases, from mild forms of acute respiratory infections to severe acute respiratory syndrome (SARS). Currently, four circulating coronaviruses (HCoV-229E, -OC43, -NL63 and -HKU1) have been known to cause common cold throughout the year with mild to moderate upper respiratory tract symptoms.

Drawing on the results of serological and phylogenetic analysis, coronaviruses can be divided into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. The natural hosts for most currently known coronaviruses are mammals.

Before 2002, coronaviruses were considered as agents that cause non-severe upper respiratory tract diseases (with very few lethal cases). In late 2002, SARS-CoV emerged, causind atypical pneumonia and leading to severe acute respiratory syndrome in humans. This virus belongs to Betacoronaviruses. Bats are a natural reservoir for SARS-CoV, while camels and Himalayan palm civets are its intermediate hosts. A total of more than 8,000 confirmed cases in 37 countries were reported during the epidemic; 774 of them resulted in fatalities. Since 2004, no new cases involving atypical pneumonia caused by SARS-CoV have been registered.

In 2012, the world faced a new MERS-CoV, which causes the Middle East respiratory syndrome, and also belongs to the Betacoronavirus species. The main natural reservoir for MERS-CoV is the one-hump camel (dromedary). From 2012 to 31 January 2020, 2,519 confirmed cases of coronavirus infection caused by MERS-CoV were reported; 866 of them with lethal outcome. All cases are geographically associated with the Arabian peninsula (Saudi Arabia accounting for 82% of all cases). Currently, the MERS-CoV continues to circulate and cause new cases of diseases.

On December 31, 2019, the World Health Organization (WHO) received reports of a cluster of viral pneumonia cases of unknown cause in Wuhan, Hubei (China). On January 7, 2020, the Chinese authorities found that this disease was caused by a coronavirus related to SARS-CoV, and on February 11, 2020, WHO named it COVID-19, i. e. Coronavirus disease 2019. On 11 February 2020, the International Committee on Taxonomy of Viruses assigned an official name to the infectious agent — SARS-CoV-2.[1]

The new SARS-CoV-2 coronavirus is a single-stranded RNA virus that belongs to the Coronaviridae virus and Beta-CoV B lineage. The virus also falls under group II in terms of pathogenicity, just like some other representatives from this family (the SARS-CoV and MERS-CoV viruses).

The points of entry for the pathogen is upper respiratory airway epithelium, and gastrointestinal epitheliocytes. The beginning stage of affliction is when SARS-CoV-2 INFILTRATES target cells that have angiotensin-converting enzyme 2 (ACE2) receptors. ACE2 receptors are present in the cells of the respiratory tract, kidneys, esophagus, urinary bladder, ileum, heart, and the central nervous system. However, the main target – and the one that is easiest to access – are alveolar type II (AT2) cells in the lungs, and this is why pneumonia may develop. In addition, the role CD147 plays as a route for SARS-CoV-2 cell invasion is under debate.

SARS-CoV-2 dissemination from systemic blood or through Lamina cribrosa may result in brain damage.

The most common symptoms of COVID-19 include fever, fatigue, and dry cough. Some patients may have different pain, nasal congestion, running nose, pharyngitis or diarrhea. As a rule, such

[1] 1Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2)https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the- coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

symptoms develop gradually and are mild in nature. Some infected people may not develop any symptoms at all or feeling unwell. Most people (~80%) recover completely without any specific remedial actions required. Approximately one in six COVID-19 patients develops severe symptoms with respiratory insufficiency. In elderly people, and people with certain medical conditions, such as arterial hypertension, heart disorders, or diabetes, the risk of developing a severe case of the disease is higher. According to most estimates, the typical COVID-19 incubation period ranges from 1 to 14 days, and most often is about five days long.

A person may contract COVID-19 from other people if they are infected with the virus. COVID-19 can spread from person to person via small droplets expelled from an infected person's nose or mouth when coughing or sneezing.

Since the end of January 2020, COVID-19 cases had been reported worldwide, most of them related to travel to China. In late February 2020, the epidemiologic situation in South Korea, Iran, and Italy became more complicated thus leading to a significant growth in other countries of COVID-19 cases related to travel to those countries. On March 11, 2020, WHO declared the COVID-19 outbreak a pandemic.

As part of WHO's response to the outbreak, arrangements were made to speed up the implementation of it research and development program (RDP) that included an accelerated development of diagnostic tools, vaccines and medicines aimed at fighting the novel coronavirus. With WHO's coordinating role, a coalition of experts from different fields have contributed to the development of vaccines to prevent COVID-19.

The key aim of worldwide R&D is to fast-track the availability of a universally available, safe and effective vaccine.

Table 1. Target product profiles recommended by the WHO[2]

Candidate characteristics	Preferable	Critical / minimal
Indications and usage	For active immunization of risk groups, individuals in the ongoing SARS-CoV-2 outbreak area to prevent infection; for use in combination with other control measures to reduce or stop the outbreak. Note: for active immunization against COVID-19 of individuals susceptible to higher risks	For active immunization of individuals in the ongoing COVID-19 outbreak area to prevent infection; for use in combination with other control measures to reduce or stop the outbreak.
Contraindications	No	Some contraindications (i. e. for people with compromised immunity) may be acceptable

[2] WHO Target Product Profiles for COVID-19 Vaccines. 9 April 2020

Target population	All ages (as herd immunity and transmission blocking will depend on extensive immunization likely to involve children). Suitable for pregnant and nursing women.	Adults, including elderly people
Safety /reactogenicity	Safety and reactogenicity adequate for a favorable safety profile and risk to benefit ratio in the context of the observed vaccine efficacy; only mild and transient adverse events related to vaccination, and no serious adverse events.	Safety and reactogenicity at which vaccine benefit exceeds safety risks. The risk to benefit ratio may depend on the age or other factors. Assessment of the risk to benefit ratio must take into consideration the potential for aggravation of the disease. Safety and reactogenicity adequate for a favorable risk to benefit ratio in the context of the observed vaccine efficacy; only mild and transient adverse events related to vaccination.
Efficacy	Efficacy of at least 70% (in a population with steady results in elderly people) *Minimum limit of efficacy estimate reliability may be lower* The endpoint may be assessed by incidence, severe cases, and/or spread of infection. Rapid onset of protection (less than 2 weeks). Note: rapid onset of protection is less important	Visible demonstration of efficacy (in the population), ideally of ~ 50% *Minimum limit of efficacy estimate reliability may be lower* The endpoint may be assessed by incidence, severe cases, and/or spread of infection. If the regulatory approvals were obtained in the context of incomplete clinical efficacy data, the efficacy data must be obtained during use

Dosing schedule	Single-dose initial vaccination Lower frequency (annually or less often) of booster doses is preferable	Maximum two doses Booster doses are allowed
Administration route	Non-parenteral administration is preferable Comment: any route of administration is acceptable	Any route of administration is acceptable if the vaccine is safe and effective.
Protection length	Offers at least 1 year of protection.	Offers at least 6 months of protection. This may not be demonstrated during the initial clinical trials, but may be confirmed by other trials in animals, other data etc.
Stability and storage conditions	Higher storage temperatures and higher thermal stability will significantly improve distribution and availability of the vaccine, and thus are highly preferable.	Useful life is at least 12 months at minus 60-70 °C; demonstration of stability for at least 2 weeks at 2–8 ° C. Storage at -20 ° C or higher
Co-administration with other vaccines	Stand-alone product Comment: co-administration with other vaccines (e. g. against influenza, polio, measles, pneumococcus) is more preferable	Standalone product
Dispensing	Maximum parenteral dose: 0.5 ml	Maximum parenteral dose: 1 ml

2.2. Experience of study drug use in humans, as well as experience of similar vaccine use

Based on vector data from the National Research Center for Epidemiology and Microbiology named after N.F. Gamaleya of the Ministry of Health of Russia, total 8 vaccines have been developed, including three vaccines for prevention of Ebola fever registered in Russia in 2015-2019 and experimental vaccines for MERS and pandemic influenza.

The Gam-COVID-Vac vaccine has been made based on recombinant adenoviral vectors in FSBI National Research Center for Epidemiology and Microbiology named after N.F. Gamaleya, Ministry of Health of Russia; and it develops both antibody and cell immunity to the COVID-19 pathogen.

This study implies administration of the first component of Gam-COVID-Vac, marketed product

in the Russian Federation (as well as the product Gam-COVID-Vac-Lyo, similar by its active substances in the formula, in the lyophilised form for making solutions for intramuscular injection. Clinical trials of two formulations of the vaccine on 76 participants were performed in June-August, 2020, in the First Moscow State I.M. Sechenov Medical University and FSBI Main Military N.N. Burdenko Clinical Hospital of the Ministry of Defense of Russia (Clinical Trial Permits of the Ministry of Health of Russia No. 241, 242 dated 16.06.2020, clinicaltrials.gov: NCT04437875, NCT04436471).
Both vaccines showed a favorable safety profile: the study participants showed short-time (1-2 days), general (short flu-like syndrome characterized by chills, increased body temperature, arthralgia, myalgia, asthenia, general malaise, headache) and local (pain at the injection site, hyperemia, swelling) side effects specific for vaccines based on the recombinant viral vectors. No serious, unexpected adverse events and events that had not been described before were observed.
Adverse reactions observed in the course of study are generally specific to any vaccination and can be stabilized with antifebrile medicines and NSAIDs, when needed, which does not impact the efficacy of immunization.
See the Investigator's Brochure for the detailed results of the relevant clinical trials.

The list of vaccines developed by the Russian Ministry of Healthcare FGBU N.F. Gamaleye Scientific Research Center of Epidemiology and Microbiology using adenovirus vectors as a platform is given below in Table 2.

Table 2 Vaccines developed by FSBI N. F. Gamaleya National Research Center of Epidemiology and Microbiology, Ministry of Health of the Russian Federation, based on adenoviral vectors

Drug	**Presentation**	**Number of subjects**	**Doses studied during clinical trials**	**Current status**
GamEvac, vector vaccine against Ebola fever	solution for intramuscular injection 0.5 ml/dose 0.5 ml x 2	92 healthy volunteers	½ of the expected clinical dose and a full vaccine dose	Registration LP-003389 on 28/12/2015
GamEvac-Combi, combination vector vaccine against Ebola	solution for intramuscular injection, dose/0.5 ml	10 healthy volunteers (Russian Federation) 2,000 healthy volunteers (Guinea)	½ of the expected clinical dose and a full vaccine dose	Registration LP-003390 on 28.12.2015 NCT03072030

Drug	**Presentation**	**Number of subjects**	**Doses studied during clinical trials**	**Current status**
GamEvac-Lyo, a combined vector vaccine to prevent Ebola	lyophilizate for intramuscular injections [component A (vial)(1 dose) + component B (vial) (1 dose)]	260 healthy volunteers	full vaccine dose	Registration LP-006175 on 17/04/2020
GamEvac (Vector vaccine against Ebola fever)	solution for intramuscular injection 0.5 ml/dose	60 healthy volunteers	½ of the expected clinical dose and a full vaccine dose	RCCT No. 435 (24/08/2018) CSP, IV
GamFluVac (Vector Vaccine Against for prevention of Influenza A (recombinant)	nasal drops dose/0.5 ml	60 healthy volunteers	½ of the expected clinical dose and a full vaccine dose	RCCT No. 393 (22/07/2019) clinical trial, II continued
GamFluVac (Vector Vaccine Against for prevention of Influenza A (recombinant)	nasal drops dose/0.5 ml	300 healthy volunteers	full vaccine dose	RCCT No. 393 (22/07/2019) clinical trial, II continued
MERS-GamVac (vector vaccine against MERS)	lyophilizate for intramuscular injections	194 healthy volunteers	½ of the expected clinical dose and a full vaccine dose	RCS No. 506 (09/09/2019) clinical trial, I-II continued
MERS-GamVac-Combi (combined vector vaccine against MERS)	lyophilizate for intramuscular injections	291 healthy volunteers	½ of the expected clinical dose and a full vaccine dose	RCCT No. 507 (09/09/2019) clinical trial, I-II Ongoing

Drug	**Presentation**	**Number of subjects**	**Doses studied during clinical trials**	**Current status**
Gam-COVID-Vac, combined vector vaccine for prevention of coronaviral infection induced by SARS-CoV-2 virus	Solution for intramuscular injection	43 healthy volunteers	full vaccine dose	RCCT No. 241 (16/06/2020) drug is registered 11/08/2020 (LP-006395) The observation is ongoing (telephone contact on days 90 and 180)
Gam-COVID-Vac, combined vector vaccine for prevention of coronaviral infection induced by SARS-CoV-2 virus	solution for intramuscular injection	40,000 volunteers Russian Federation 100 volunteers – Republic of Belarus	full vaccine dose	RF: RCS No. 450 (25/08/2020) is being conducted RB: Order MZ RB from 21/09/2020 No. 954
Gam-COVID-Vac Lio combined vector vaccine against the SARS-CoV-2-induced coronavirus infection	lyophilizate for intramuscular injections	43 healthy volunteers	full vaccine dose	RCCT No.242 (16/06/2020) drug is registered on 25/08/2020 (LP-006423) The observation is ongoing (telephone contact on days 90 and 180)

Drug	**Presentation**	**Number of subjects**	**Doses studied during clinical trials**	**Current status**
Gam-COVID-Vac, combined vector vaccine for prevention of coronaviral infection induced by SARS-CoV-2 virus	solution for intramuscular injection	150 volunteers	full vaccine dose	RCS No.566 (13.10.2020) The observation is ongoing (telephone contact on days 90 and 180)

The clinical trial results for other drugs to help prevent COVID-19, developed worldwide, using adenovirus vectors as a platform

Worldwide clinical trials took place for drugs engineered with similar vectors: Ad5 (10,000+ participants) and Ad26 (15,000+ participants).

At present, clinical trials of more than 11 vector vaccines (based on non-replicating viral vectors) to help prevent COVID-19 are in the development stage, presented below in Table 3.

Table 3. Candidate vaccines to help prevent COVID-19

Platform / Candidate type	**Developer**	**Current status**	**Similar platform for non-coronavirus candidates**
adenovirus 5 vector (Ad5)	CanSino Biological Inc./Beijing Institute of Biotechnology	CS (Phase III)	Ebola
ChAdOx1	University of Oxford	Phase III	MERS, flu, tuberculosis, Chikungunya, Zika, MenB, plague
MVA encoded VLP	GeoVax/ BravoVax	Pre-clinical trials	LASV, EBOV, MARV, HIV
26 serotype adenoviral vector (Ad26 monotherapy or under an arrangement for MVA boosting)	Janssen Pharmaceutical Companies	Pre-clinical trials	Ebola, HIV, RSV

Platform / Candidate type	**Developer**	**Current status**	**Similar platform for non-coronavirus candidates**
Replicative defective pseudo-adenovirus particles that code the SARS-CoV-2 S sequence	ReiThera	Pre-clinical trials	-
MVA	DZIF – German Center for Infection Research	Pre-clinical trials	various infections
NasoVAX adenovirus vector	Altimmune	Pre-clinical trials	influenza
Serotype 5 adenoviral vector Ad5 (GREVAX™ platform)	Greffex	Pre-clinical trials	MERS
Oral Vaccine platform	Vaxart	Pre-clinical trials	InfA, CHIKV, LASV, NORV; EBOV, RVF, HBV, VEE
MVA	Centro Nacional Biotecnología (CNB-CSIC), Spain	Pre-clinical trials	HIV, HCV, chikungunya, Ebola, zika, malaria, leishmania
Dendritic cellbased vaccine	University of Manitoba	Pre-clinical trials	-

At present, the following clinical trials are under way: 23 clinical trials of rAd5-based vaccines, 37 trials of rAd26-based vaccines, and 19 trials on ChAdOx-based vaccines against COVID-19. Moreover, Gendicine, the first approved drug for use based on recombinant human adenovirus serotype 5, has been successfully used in China for cancer gene therapy for more than 12 years (2018 Zhang). 12-year Gendicine utilization review demonstrated its absolute safety: throughout the study period, no significant side effect related to the use of this drug was registered.

2.3. Name and description of study drugs

Invented name: Sputnik Light vector vaccine for the prevention of SARS-CoV-2-induced coronavirus infection

International non-proprietary or generic or chemical name:

A vaccine to help prevent the novel coronavirus infection (COVID-19).

Dosage form: a solution for intramuscular injection.

Composition per dose (0.5 ml):
Active substance: recombinant serotype 26 adenoviral particles, containing the SARS-CoV-2 protein S gene, in the amount of (1.0±0.5) x 10^{11} particles per dose.

Excipients: Tris-(hydroxymethyl)aminomethane – 1.21 mg, sodium chloride – 2,19 mg, sucrose – 25.0 mg, magnesium chloride hexahydrate – 102.0 μg, EDTA-disodium salt dihydrate – 19.0 μg, polysorbate 80–250 μg, ethanol 95% – 2.5 μl, water for injections – 0.5 mL or less.

Description:

A frozen solution. A dense, solidified mass whitish in color. After thawing: a homogeneous solution, colorless or with yellowish hue, slightly opalescent.

Characteristics: the vaccine is derived using biotechnology, and without using the SARS-CoV-2 virus, which is pathogenic in humans. The preparation contains a recombinant adenoviral vector based on the human adenovirus serotype 26, which carries the SARS-CoV-2 virus S protein gene.

Pharmacotherapeutic group: medical immunobiological vaccine.

ATC code: J07B

Pharmacological properties

The vaccine induces humoral and cellular immunity towards the coronavirus infection caused by the SARS-CoV-2 virus.

Immunological efficacy

The vaccine induces humoral and cellular immunity towards the coronavirus infection caused by the SARS-CoV-2 virus.
Immunological efficacy
The immunological properties and safety of the vaccine have been studied in various clinical trials in adult volunteers of both sexes over the age of 18.

The protective antibody titer is currently unknown. Duration of protection is not known. clinical trials on epidemiological efficacy were not conducted.

Indications for medical use:

The prevention of the novel coronavirus infection (COVID-19) in adults aged over 18.

Contraindications:

- Hypersensitivity to any component of the vaccine, or a vaccine that contains similar components;
- Severe allergic reactions in the medical history;
- Acute infectious and non-infectious diseases, acute exacerbations of chronic diseases –

vaccination is administered 2-4 weeks after recovery or remission. In cases of non-severe ARVI, acute gastrointestinal infections — the vaccination is administered after body temperature normalizes;

- pregnancy and breastfeeding period;
- age under 18 (due to lack of data on safety and efficacy)

With caution: the vaccine should be used with caution in cases of chronic liver and kidney diseases, endocrine diseases (apparent thyroid function abnormalities and diabetes mellitus in decompensation stage), serious diseases of the hematopoietic system, epilepsy and other CNS diseases, acute coronary syndrome and acute cerebrovascular event, myocarditis, endocarditis, pericarditis.

Due to lack of data, vaccination may be a risk for the following groups of patients:

- with autoimmune diseases (stimulation of the immune system can lead to an exacerbation of the disease, special caution should be exercised with patients with an autoimmune disorder that tend to lead to severe and life-threatening conditions) development of severe and life-threatening states)
- with malignant neoplasms

The decision to vaccinate should be based on the assessment of a benefit/risk ratio in each specific situation.

Side effects

Adverse reactions specific to the use of the vaccine, revealed in clinical trials and studies of other vaccines based on a similar technological platform, are predominantly of mild or medium severity, and may develop during the first or second day following vaccination and usually abate within 3 subsequent days. The most common include short-term general (a brief flu-like syndrome characterized by chills, fever, arthralgia, myalgia, asthenia, general discomfort, headache) or local (injection site tenderness, hyperemia, swelling) reactions. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended in case of post-vaccination fever and antihistamines for expressed local reactions.

Less common ones are nausea, dyspepsia, loss of appetite, occasionally – enlarged regional lymph nodes. Some patients may develop allergic reactions, short-term elevated liver transaminase levels, elevated serum creatinine and creatine phosphokinase levels.

Within the Gam-COVID-Vac safety, tolerability, and immunogenicity clinical trials conducted to date the following AEs have been registered:

“General injection site disorders and reactions”: hyperthermia, vaccination site tenderness, edema and pruritus, asthenia, pain, malaise, pyrexia, increased vaccination site skin temperature, decreased appetite. Incidence rate – very common and common.

“Respiratory, chest, and mediastinal disorders”: oropharyngeal pain, nasal congestion, sore throat, rhinorrhea. Incidence rate – common.

“Nervous system disorders”: common – headache; rare – dizziness, syncope.

“Gastrointestinal disorders”: nausea, vomiting, dyspepsia – common.

“Laboratory and instrumental data”: divergent abnormalities of immunological status indicators: increased count of T-lymphocytes, increase in the percentage of lymphocytes, decreased count of natural killer cells, increased count of CD4-lymphocytes, decreased count of CD4-lymphocytes, increased count of B-lymphocytes, decreased count of B-lymphocytes, increased count of natural killer cells, increased count of CD8 lymphocytes, increased level of immunoglobulin E (IgE) in

the blood, increase in the CD4/CD8 ratio, decrease in the CD4/CD8 ratio, increased level of immunoglobulin A (IgA) in the blood, decrease in the percentage of CD8 lymphocytes. Abnormalities in the complete blood count: increase in the percentage of lymphocytes, decrease in the hematocrit, increased count of lymphocytes, increase in the erythrocyte sedimentation rate, increased leukocyte count, increased count of monocytes, increased platelet count, decreased count of neutrophils, decreased platelet count. Abnormalities in common urine analysis: erythrocytes in the urine.
Most AEs ended in complete recovery, with no consequences. Lab test deviations were not of clinical significance (did not require additional diagnostics or therapy).

2.4. Summary of the results of the pre-clinical trials for the product relevant for this study
Previously developed medicinal products against EBHF, influenza and MERS were studied in the course of pre-clinical trials and demonstrated a favorable safety profile. Effect of products on animals was studied in a wide range of doses, including doses exceeding the therapeutic dose 1,000 times. There were no animal death cases or significant toxicity; deviations in laboratory and physiological parameters were not clinically significant; no significant pathologic processes in the animal organism or local irritation was observed; allergenic or immunotoxic effect was not revealed; reproductive toxicity was not revealed (no reproductive toxicity in males and females, embryotoxic and fetotoxic action recorded throughout pregnancy, anomalies or delays in embryo development, embryotoxic or teratogenic action during the antenatal life were revealed). The safety profiles for the various vaccines that use adenoviruses developed by the Russian Federation Ministry of Healthcare Gamaleya Research Institute of Epidemiology and Microbiology are comparable, and do not differ significantly across those vaccines or in respect to the information found in literature for similar drugs).

Previously developed drugs for the diseases caused by the Ebola virus (EVD), influenza, and the Middle East respiratory syndrome (MERS) were studied during preclinical trials, and demonstrated a favorable safety profile. Effect of products on animals was studied in a wide range of doses, including doses exceeding the therapeutic dose 1,000 times. There were no animal death cases or significant toxicity; deviations in laboratory and physiological parameters were not clinically significant; no significant pathologic processes in the animal organism or local irritation was observed; allergenic or immunotoxic effect was not revealed; reproductive toxicity was not revealed (no reproductive toxicity in males and females, embryotoxic and fetotoxic action recorded throughout pregnancy, anomalies or delays in embryo development, embryotoxic or teratogenic action during the antenatal life were revealed). The safety profiles for the various vaccines that use adenoviruses developed by the Russian Federation Ministry of Healthcare Gamaleya Research Institute of Epidemiology and Microbiology are comparable, and do not differ significantly across those vaccines or in respect to the information found in literature for similar drugs).

Preclinical safety (toxicity) trials
The full extent of toxicity studies was completed on the vaccine to help prevent SARS-CoV-2 (Component I, active ingredients of which are recombinant adenoviral vectors that use serotype 26 human adenovirus carrying the SARS-CoV-2 S protein gene, and Component II, active ingredients of which are recombinant adenoviral vectors that use serotype 5 human adenovirus carrying the SARS-CoV-2 S protein gene).
See the Investigator’s Brochure for detailed results of pre-clinical trials.

Research on mice, guinea pigs, and rabbits
The research program on toxicity in rodents (mice, rabbits, guinea pigs) was done on the premises

of the FGAOU VO Ministry of Healthcare I.M. Sechenov Moscow State Medical University (Sechenov University).

A toxicity study was done by giving a single dose of each component separately on sexually mature outbred mice and rabbits of both sexes. A total of 400 mice (200 males and 200 females) and 24 rabbits (12 males and 12 females) were used in a single-dose toxicity study. The vaccine was administered to mice intramuscularly and intravenously in increasing doses: 10^8 v.p., 10^9 v.p., 10^{10} v.p., 10^{11} v.p. During the experiment, no animal fatalities were recorded, and no symptoms of intoxication occurred. Autopsies carried out 14 days after the vector vaccine was administered showed no deviations in the structure of the internal organs of mice. The experiment on the drug being studied did not show local irritations that arose due to intravenous and intramuscular administration.

A toxicity study was carried out that involved a single injection of component 1, and then component 2 (in the mode stipulated for clinical use) on sexually mature rabbits of both sexes. A total of 24 rabbits (12 males and 12 females) were used in a single-dose toxicity study. The vaccine was administered to mice intramuscularly in increasing doses: 10^{10}d.u. and 10^{11}d.u. During the experiment, no animal fatalities were recorded, and no symptoms of intoxication manifested themselves. Autopsies carried out 14 days after the vector vaccine was administered showed no deviations in the structure of the internal organs of mice. According to the data obtained, no toxic effects from the vaccine on the condition of internal organs and body systems were discovered, using biochemical, hematological, coagulometric, physiological, and pathomorphological research methods. The experiment did not show any localized irritations resulting from the drug that is being studied.

Allergenic properties for components 1 and 2 of the vector vaccine against SARS-CoV-2 among guinea pigs at doses of 10^9 d.u. and 10^{10} d.u. in general anaphylaxis tests, and conjunctival allergen provocation tests, were not detected.

While studying the immunotoxicity properties, no effects from components 1 and 2 of the vector vaccine on the immune system of mice in reaction to delayed-type hypersensitivity at doses of 10^8 v.p. and 10^9 v.p. were found. There was also no effect on the activity of peritoneal macrophages and the formation of antibodies in the hemagglutination reaction. There was no impact discovered on the weight and cellularity of immunocompetent organs. These studies attest to the absence of immunotoxicity properties for components 1 and 2 of the vector vaccine to help prevent SARS-CoV-2.

Protectivity studies on sensitive animals

Lethal model in Syrian hamsters

Administering the vaccine allows generating a protective immune response that protects 100% of the animals (Syrian hamsters with induced immunodeficiency) from a lethal infection caused by the SARS-CoV-2 virus. Analyzing the viral burden in the lungs of infected hamsters showed a verifiable decrease in the viral burden for the group of vaccinated animals at 6, 8, and 10 days after infection. Damage in the lungs in the group of vaccinated animals is significantly less than in unvaccinated animals, both in terms of pathomorphological and histological data. The antibody-dependent enhancement effect (ADE) was not revealed.

Research on primates

A study on acute toxicity and the ADE effect in primates after intramuscular injection, with an interim report on day 28 in the observation period, on-site at FGBU Central Scientific Research Institute No. 48 of the Russian Ministry of Defense.

The total number of animals used in the work is 17: 11 in the experimental group and 6 in the

control group. During 20 days of observation toxic events were not recorded.
Results of daily monitoring the rhesus monkeys' body weight and temperature, examining their physical condition (behavior, appearance, and physiological functions), and monitoring the general symptoms of intoxication in the monkeys, localized reactions, and changes in the laboratory indicators for those vaccinated with the vector vaccine against COVID-19 based on recombinant adenoviruses expressing the SARS-CoV-2 S protein gene, attest to the safety of the studied vaccine when administered intramuscularly in primates in a clinical dose appropriate for humans in a prime-boost mode.
Research done on severe toxicity by the Russian Academy of Sciences FGBNU Federal Research Center for Research and Development of Immunobiological Drugs conducted in common marmosets (Callithrix jacchus) species with a confirmed health status, born and raised in isolation in a vivarium, certified for work with hazard group III–IV pathogens. The total number of animals studied was 18 (16 males and two females), their age was 2 to 5 years: 12 monkeys in the experimental group (10 males and 2 females) and 6 in the control group (6 males). During 20 days of observation toxic events were not recorded.

Conclusion on the results of preclinical trials
The findings demonstrated the non-toxicity of the vaccine in different laboratory animals across a broad range of doses. The safety level demonstrated by pre-clinical trials enable clinical trials in healthy volunteers.
See the Investigator's Brochure for the detailed results of the relevant clinical trials of other vaccines based on adenovirus vectors.

2.5. Experience of using on humans the Gam-COVID-Vac combined vector vaccine against the SARS-CoV-2-induced coronavirus infection, whose Component I corresponds to the drug Sputnik Light

Study name: Open study on the safety, tolerability, and immunogenicity of the drug Gam-COVID-Vac, a solution for intramuscular injection, in healthy volunteers.
Protocol number: 02-Gam-COVID-Vac-2020.

Study site and principal investigator:
Federal State Budgetary Institution N.N. Burdenko Main Military Clinical Hospital N.N. Burdenko Main Military Clinical Hospital, branch No. 7
Legal address: 3 Gospitalnaya Square, Moscow, Russia 105229
Actual address: 4 Novaya St., Sergiyev-Posad 6, Moscow Region, Russia 141306 Principal investigator: Irina Viktorovna Gagarina, infectious disease doctor of infection unit, candidate of medicine.

First participant screening: 17-Jun-2020
Stage I beginning: 17-Jun-2020
Stage II beginning: 19-Jun-2020
Completion of the 28th day of observation: 20-Jul-2020
Completion of the 42th day ob observation: 03-Aug-2020
A total of 43 volunteers have been screened; as a result, 18 volunteers (+2 backups) have been included in the first stage and 20 volunteers (+3 backups) have been included in the second stage. Participation by the backups was not needed. This means that 38 healthy volunteers took part in

the study, and received the study drug: 18 volunteers in stage 1 (9 volunteers received component I and 9 volunteers– component II) and 20 volunteers in stage 2. All 38 volunteers completed the study according to the protocol.
Stage 1 involved only men (n=18), all Caucasian, with the mean volunteer age (average (standard deviation, SD)) at 26.6 (5.60) years. Body mass index (mean (SD)) was 25.7 (2.75) kg/m^2.
Stage 2 involved 14 men and 6 women, all Caucasian, with the mean volunteer age (average (standard deviation, SD)) at 26.4 (4.36) years. Body weight index (average (SD)) was 24.4 (3.11) years.
There was nothing significant in their medical histories that could have prevented them from participating in the study. 1 volunteer for stage 1 had an appendectomy present in the medical records, and 2 volunteers in stage 2 had appendectomies (n=1) and removal of the meniscus (n=1). Physical examination results at screening detected no pathologies. Test results for HIV, syphilis, hepatitis B and C were negative in all the volunteers. There were no other vaccinations 30 days prior to screening. No IgM and IgG antibodies to SARS-CoV-2 (based on the qualitative analysis results) were detected. Other screening studies complied with the criteria for inclusion/exclusion.
All 38 volunteers were administered the drug being studied as per the protocol, without deviating from the scheduled regimen.

Results of the analysis of immunological efficacy

The efficacy analysis included all volunteers who completed the study in accordance with the Protocol — 38 volunteers (18 at the first stage and 20 at the second stage).
The data obtained make it possible to confirm the hypothesis put forward by the study that administering the developed vaccine induces the formation of an intense immune response to the SARS-CoV-2 virus, and involves both humoral and cellular immunity.
Results of the safety analysis

The safety analysis included 38 volunteers (all volunteers who received the dose of the drug being studied) (18 volunteers at the first stage and 20 volunteers at the second stage of the study).

Frequency of development for any adverse events

A total of 295 AEs were recorded during this study. 120 AEs were registered in volunteers during the first phase study, of which 73 AEs occurred in volunteers that received the first component of the drug (60.1%), and 47 AEs in volunteers that received the second component of the drug (39.9%). 175 AEs were reported in the volunteers who participated in the second phase study. AEs have been registered in every single volunteer who has taken part in the study (in both phases).

Frequency of development for serious adverse events

During the study, no serious adverse events (SAE) have been recorded.

Causality relationship with the study drug

During the first stage of the study, 119 AEs have been registered, which have at least a potential relation to the study product (i.e. a certain, potential or probable relation). These AEs were observed in all 9 volunteers in the group that received the first component of the drug (72 events) and in all volunteers that received the second component of the drug (47 events). One AE in a volunteer from the group that received Component I was considered as being doubtfully related to the drug.
Based on their connection to the study drug, the AEs were classified as follows. A total of 12 (Component I) and 7 (Component II) AEs considered to be certainly associated with the study

product were recorded, another 18 (Component I) and 5 (Component II) were considered as possibly associated with the study drug, 42 (Component I) and 35 (Component II) AEs were considered as likely associated with the study drug, and 1 (Component I) AE was considered to have a doubtful relationship with the study product.
At the second stage of the study, 164 AEs were recorded that had at least a possible association with the studied drug (i.e. definite, possible, or probable). Four AEs were assessed as having a doubtful relationship with the drug, 2 AEs were assessed as having a conditional relationship with the drug, and in 4 AEs researcher regarded the relationship as "unassessable."

The severity of adverse events

At the first stage, mild AEs prevailed in terms of severity (73 AEs in the group that received the first component of the drug and 45 AEs in the group that received the second component of the drug); 2 moderate AEs were registered in the group that received the second component of the drug (increased AST levels and hyperthermia in different volunteers).
At the second stage, mild AEs prevailed in terms of severity (169 AEs); 6 moderate AEs were registered, associated with asthenia -
2 cases, pain (this MedDRA term means body aches accompanied by arthralgia) – 1 case, hyperthermia (increased body temperature reaching 38.7 C – 1 case), headache – 2 cases.
Severe AEs were not reported during the study.

Outcomes of adverse events

None of the AEs in the either first or second phase led to the withdrawal of a volunteer from the study or cancellation of the study drug.
Most AEs ended in complete recovery, with no consequences.
At the first stage of the study, the following AEs ended in recovery without consequences: 44 AEs in the group that received the first component of the drug, and 21 AEs in the group that received the second component of the drug. The outcomes of 29 and 26 AEs, respectively, on Day 42 of the study were unknown, and the volunteers continue to be followed up until Day 180.
During the second stage of the study, 144 AEs recovered without any consequences. On Day 42 of the study, the outcome was unknown for 27 AEs, and a recovery process was ongoing for 4 AEs. Pursuant to the protocol, the volunteers will be followed up till Day 180.

AE description

At the first stage, the most frequent adverse reactions were deviations from the laboratory and instrumental parameters (SOC “Laboratory and instrumental data”) and “General disorders and reactions at the injection site”.
AEs in the category "*Laboratory and instrumental data*" included:

- Abnormalities in immunological status: increased count of T-lymphocytes, decreased count of natural killer cells, increased count of B-lymphocytes, increased count of CD4-lymphocytes, increased count of CD8-lymphocytes, increased level of immunoglobulin E (IgE) in the blood, increased count of natural killer cells, decrease in the CD4/CD8 ratio, increased level of immunoglobulin M (IgM) in the blood, decreased count of CD4-lymphocytes, decreased count of CD8-lymphocytes, decreased level of immunoglobulin M (IgM) in the blood, decreased count of T-lymphocytes, increase in the CD4/CD8 ratio.
- Abnormalities in the complete blood count (CBC): increased count of monocytes, decrease in the percentage of lymphocytes, increase in the erythrocyte sedimentation rate, increased count of leukocytes,increased count of platelets, increase in the

percentage of lymphocytes.

- Abnormalities in the biochemical blood assay (BBA): increased level of aspartate aminotransferase, increased level of lactate dehydrogenase in the blood, increased level of cholesterol in the blood.
- Elevated or reduced blood pressure (BP).

AEs in the category "*General disorders and reactions at the injection site*" were represented by such reactions as pain at the vaccination site, hyperthermia, asthenia, pain (this MedDRA term means body aches accompanied by arthralgia), decreased appetite, itching at the injection site.
The following AEs were less common: headache, palpitations (increased heart beat), diarrhea, oropharyngeal pain, and urticaria (this allergic reaction occurred in one volunteer who received Component I).
At the second stage, AEs in the system organ class category of the MedDRA dictionary "Laboratory and instrumental data" were most frequently noted. The second common were AEs in the General Injection Site Disorders and Reactions category. Other AEs were rarer.
AEs in the category "*General disorders and reactions at the injection site*" included: hyperthermia, pain at the vaccination site, asthenia, pain, malaise, pyrexia, increased skin temperature at the vaccination site, edema at the vaccination site.

AEs in the category "*Laboratory and instrumental data*" included:

- Abnormalities in immunological status: increased count of T-lymphocytes, increase in the percentage of lymphocytes, decreased count of natural killer cells, increased count of CD4-lymphocytes, decreased count of CD4-lymphocytes, increased count of B-lymphocytes, decreased count of B-lymphocytes, increased count of natural killer cells, increased count of CD8 lymphocytes, increased level of immunoglobulin E (IgE) in the blood, increase in the CD4/CD8 ratio, decrease in the CD4/CD8 ratio, increased level of immunoglobulin A (IgA) in the blood, decrease in the percentage of CD8 lymphocytes.
- Abnormalities in the CBC: increase in the percentage of lymphocytes, decrease in the hematocrit, increased count of lymphocytes, increase in the erythrocyte sedimentation rate, increased count of leukocytes, increased count of monocytes, increased count of platelets, decreased count of neutrophils, decreased count of platelets.
- Abnormalities in clinical urine analysis: Erythrocytes in the urine.

Other, more rare AEs were as follows: headache, diarrhea, pain in the oropharynx, nasal congestion, sore throat, rhinorrhea.

In general, it can be said that the AEs identified during the first and the second phase study are characteristic of most vaccine drugs. No severe AEs were recorded.
Main vital sign indicators
The average values for the main vital signs in the volunteers (body temperature, systolic and diastolic blood pressure, heart rate, respiration rate) obtained at the visits as per the schedule of protocol procedures did not change significantly. Individual cases involving an increase in body temperature, or fluctuations in blood pressure, were recorded accordingly as AEs.
Laboratory indicators
Isolated instances of clinically significant deviations from the standard on the part of laboratory test findings were recorded, which were recorded as adverse events of the category of system-organ class of the MedDRA Laboratory and Instrumental Data dictionary.
12-lead electrocardiogram

There were no clinically significant deviations from the normal values in the 12-lead ECG indicators during the first and second stages.

Conclusions

Both a single-dose immunization with component I or II of the drug Gam-COVID-Vac, and a dual-dose immunization in prime-boost mode with Gam-COVID-Vac, can lead to the formation of antigen-specific IgG antibodies in 100% of volunteers by day 21 after immunization. In case of dual prime-boost vaccinations with the Gam-COVID-Vac drug, the maximum titers for the antibodies were shown to develop by Day 42 after first immunization.

Dual prime-boost vaccination with Gam-COVID-Vac drug results in statistically higher values of titers of antigen-specific IgG antibodies compared to single vaccination with components I or II of Gam-COVID-Vac, which demonstrates the advantages of the booster vaccination scheme, and gives grounds to recommend it for further clinical practice.

When the titer values for antigen-specific IgG antibodies were compared in the vaccinated volunteers on Day 28 after the start of vaccination with the titer values for antigen-specific IgG antibodies in patients recuperating after the COVID-19 infection (patients convalescing with a mild or moderate form of disease, one month after complete recovery), it was shown that for a single-dose administration the titers are comparable, and for a prime-boost vaccination the titers in the vaccinated volunteers exceed the titers in convalescing patients one month after recovery.

After injecting Component I of the vaccine, on Day 14 volunteers demonstrated a statistically significant increase in VNA for SARS-CoV-2 ($p=0.0002$). In the blood serum of volunteers that were injected with both components of the vaccine (Component I and Component II, 21 days apart), on Day 28 after starting the vaccination VNA to SARS-CoV-2 were detected with a mean titer value of 16.3 (a 95% confidence interval 10.4–25.4), and the seroconversion rate was 95%. On Day 42 after the commencement of vaccination, in the blood serum of volunteers VNA to SARS-CoV-2 were detected with a mean titer of 49.3 (95% confidence interval 33.2 – 73.1), and the seroconversion rate was 100%.

Administration of GamCovidVac vaccine based on the full scheme (component 1 and component 2 with an interval of 3 weeks) allows induction of VNA in 95% of volunteers already on day 7 after booster immunization (28 days from the start of immunization). On day 21 after the booster immunization (day 42 after the start of immunization) VNA was detected in the blood serum of 100% of volunteers at the level detected in patients convalescing after the COVID-19 coronavirus infection (people convalescing after a mild or moderate severity for how their diseases developed, one month after complete recovery), which attests to the vaccine's high efficacy.

Both single vaccination with Components I or II of Gam-COVID-Vac and dual prime-boost vaccination with Gam-COVID-Vac may result in the development of solid antigen-specific cellular component of anti-infection immunity, which is confirmed by the high degree of statistical reliability of the measured parameters before and after the vaccination.

Both single-dose immunization with the component I or II of Gam-COVID-Vac, and dual-dose immunization with Gam-COVID-Vac in the prime-boost mode is capable of forming antigen-specific cells of both populations of T lymphocytes: T helpers (CD4+) and T killers (CD8+).

Dual prime-boost vaccination with Gam-COVID-Vac (both in terms of the lymphoproliferative response and in terms of growth of IFNɣ concentration) develops higher stress cell-mediated antigen-specific immunity compared to a single-dose vaccination with components I or II of the drug Gam-COVID-Vac.

Single-shot vaccination with Component I or II of Gam-COVID-Vac results in a statistically significant increase in IFNɣ secretion on Day 14 compared to Day 0 of the study (prior to vaccinating volunteers), whereas the values for lymphoproliferative response on Day 14 of the

study do not differ statistically from the respective values on Day 0. A statistically significant difference in the rates of lymphoproliferative response is observed later into the study (day 28).
The findings of the study have shown that no valid correlation exists between the titer of neutralizing antibodies to recombinant viral vectors on day 0 and the titer of RBD-specific IgG in the blood serum of volunteers on days 14, 21, 28 and 42 after the start of vaccination, and consequently the pre-immunity to the components of vaccine vectors does not affect the vaccination's efficacy.
A safety analysis on the study's findings (until day 42 of the observation period) has shown that certain AEs have been identified in all the volunteers that were injected with the study vaccine, during both the first and the second stages of the study.
Most of the detected AEs, both during the first and during the second stage of the study, were mild, and ended in recovery. No severe AEs were recorded.
The AEs detected both during the first and the second stages of the study are typical for most vaccines, and in most cases manifested themselves as deviations from the laboratory indicators or AR category
"General disorders and reactions at the injection site".
During the first and the second stage of the study, no AEs which would require excluding a volunteer from the study, or serious AEs (SAEs), were recorded.

Study name: Open study on the safety, tolerability, and immunogenicity of the drug Gam-COVID-Vac, a solution for intramuscular injection, in healthy volunteers over the age of 60.
Protocol number: 05-Gam-COVID-Vac-2020
The goal of the study: to assess the safety, tolerability and immunogenicity of Gam-COVID-Vac, a solution for intramuscular injection, at various intervals after vaccination in healthy adult volunteers over the age of 60.
Study period (years):
First participant screening (start of the study): October 22, 2020 End of observation of day 28: December 10, 2020

A total of 132 volunteers passed screening, based on the results of which 110 volunteers were enrolled. One volunteer (No.124) exited prior to administering Component I by withdrawing his consent; accordingly, 109 volunteers started study therapy. Another volunteer (No.076) received Component I, but exited before receiving Component II (due to getting COVID-19). Respectively, both vaccine components were received by a total of 108 volunteers.
The final analytical sample (n=109) included 56 (51.4%) males and 53 (48.6%) females, of which 107 (98.2%) volunteers were Caucasian, and 2 (1.8%) Asian; average subject's age (mean (standard deviation, SD)) was 68.2 (5.96) years, age range 60 to 85 years. Body mass index (mean (SD)) was 28,4 (4,11) kg/m^2.
Almost everybody had a history of significant disease, 106 (97.2%) volunteers, which is expected of this age group. The top three common comorbidities were hypertension, obesity, and dyslipidemia. Pathologies diagnosed during a physical exam at the screening visit were assessed as clinically non-significant. Test results for HIV, syphilis, hepatitis B and C were negative in all the volunteers. There were no other vaccinations 30 days prior to screening. IgM and IgG antibodies to SARS-CoV-2 (based on qualitative analysis results) were not detected. Other screening studies complied with the criteria for inclusion/exclusion.
Of 110 enrolled volunteers 108 received the study drug according to protocol, without deviations from the planned scheme, and only one volunteer received only the first component of the vaccine.

IMMUNOLOGICAL EFFICACY ANALYSIS RESULTS:

An efficacy analysis enrolled all the volunteers who had received both vaccine components – 108 subjects.

The data obtained makes it possible to confirm the hypothesis put forward by the study that administering the vaccine to volunteers over the age of 60 induces the formation of an intense immune response to the SARS-CoV-2 virus, and involves both humoral and cellular immunity.

SAFETY ANALYSIS RESULTS:

A safety analysis included 109 volunteers (all volunteers who were administered at least one dose of the study drug).

AE Incidence Rate

A total of 35 AEs (serious and non-serious) were registered in 17 (15.60%) subjects during this study. The AE incidence rate was 34 in 16 (14.68%) subjects.

SAE Incidence Rate

A single AE in one (0.92%) volunteer was assessed as serious (SAE) - atrial fibrillation. This SAE was graded serious against the criterion "requires hospitalization or its extension", the cause-effect relation with the study drug was evaluated as doubtful, the SAE was of moderate severity, and required drug intervention. The SAE developed after injecting both components of the study drug. The SAE ended in complete recovery.

Causality relationship with the study drug

As for their relationship with intake of the study drug, all registered AEs had distributed as follows: 12 AEs – as linked with the drug (definite relation), 9 AEs – probably linked, 4 AEs – as possibly linked, 7 AEs had a doubtful link with the drug and 3 AEs were noted as having an "unknown" link.

AE severity. All non-serious AEs were mild in severity (34 AEs). Only one AE was evaluated as moderate in severity, the above SAE referred to it.

Actions taken in relation to the drug. For 31 AEs it was indicated that drug administration was carried on in accordance with the scheme provided for by the protocol and for 4 AEs this assessment was not applicable since no further drug administration was planned.

AE outcomes. 31 AEs have ended in full recovery, without any consequences, 3 AEs are on the recuperation stage. For one AE the outcome was unknown or not specified. Pursuant to the protocol, the volunteers will be followed up till Day 180.

Required drug correction. In most cases (14 (12.84%) subjects, 28 AEs) drug intervention was not required, and only 4 (3.67%) subjects, 5 AEs, needed it. For the remaining two AEs "not applicable" was indicated.

AE description

AEs of the MedDRA system-organ class category "General disorders and administration site conditions" (28 AEs in 15 (13.76%) subjects) were most frequently noted. Less frequent were AEs "Nervous system disorders" - 2 AEs in 2 (1.83%) subjects, "Cardiac disorders" - 3 AEs in 2 (1.83%) subjects, "Gastrointestinal disorders" and "Laboratory and instrumental data" - 1 AE each in 1 (0.92%) subject.

Of these, **related to to the study drug (i.e. 'possible", "probable" or "definite" relation assessment) were the following AEs**: asthenia, vaccination site tenderness, hyperthermia,

discomfort at vaccination site, joint pain in the vaccination area, reduced appetite; increased erythrocyte sedimentation rate. For the remaining AEs the relation was classified as “doubtful” or “unknown”.

Allergic reactions to the study drug were not recorded.

In general, it can be said that the AEs identified during the study are typical for most vaccine drugs. No severe AEs were recorded.

Main vital sign indicators

The average values for the mains scope of vital signs in the volunteers (body temperature, systolic and diastolic blood pressure, heart rate, respiration rate) obtained during their visits in accordance with the schedule for the protocol procedures did not change significantly. Individual cases of increases in body temperature were registered accordingly as AEs.

Laboratory indicators

Few clinically significant deviations from norm in lab test results were registered. Cholesterol levels were the most frequent deviation from the norm observed.

12-lead ECG

There were no clinically significant deviations from the norm in the 12-lead ECG indicators during the study.

CONCLUSIONS:

- A single-dose immunization with Component I of Gam-COVID-Vac can lead to the formation of antigen-specific IgG antibodies in 53.2% of the subjects over 60 on the 21st day after immunization.
- The immunization of volunteers over the age of 60 by Gam-COVID-Vac can lead to the formation of antigen-specific IgG antibodies in 98.1% volunteers on the 28th day after immunization.
- When immunizing volunteers aged over 60 by Gam-COVID-Vac antibody titers continued to rise until 42nd Day after immunization (which was demonstrated for a subpopulation of the volunteers).
- A twofold immunization of the subjects with Gam-COVID-Vac leads to the formation of both CD4+ and CD8+ antigen-specific T-lymphocytes on the 28th Day after administering Component I of the vaccine. Thus, the median percentage of proliferating CD4+ and CD8+ T-lymphocytes in volunteers over the age of 60 was 0.7 (CI: 0.5-2.2) and 0.8 (CI: 0.3-2.2), respectively. A statistically significant difference in the values of proliferating CD4+ and CD8+ T lymphocytes prior to immunization (day 0) and 28 days after injecting Component I of the vaccine was $p<0.001$. These indicators witness a marked formation of a cell immunity as part of overall adaptive immunity in the volunteers following immunization with Gam-COVID-Vac.
- Twofold prime-boost vaccination with Gam-COVID-Vac can cause the development of an expressed antigen-specific cell-mediated anti-infectious immunity in subjects over 60 (based on lymphoproliferative response data, and gamma interferon secretion), which is confirmed by a high degree of statistical significance of the parameters measured before and after immunization.

- Twofold prime-boost vaccination with Gam-COVID-Vac can cause the forming of a marked quantity of antigen-specific cells of both populations of T lymphocytes: T helpers (CD4+) and T killers (CD8+).
- Twofold prime-boost immunization with Gam-COVID-Vac allows VNA to be formed in 90.2% of subjects aged 60+ as early as day 7 after boost immunization (28th day from the start of immunization)
- A safety analysis of the study findings showed that AEs had been registered in 17 (15.60%) subjects.
- One registered SAE (atrial fibrillation that required hospitalization) was judged not be related to the study drug.
- All non-serious AEs were mild in severity, the only moderate AE was classified as a SAE. No severe AEs were recorded. Most AEs have ended in recuperation.
- The AEs detected during the study are characteristic of most vaccines, and in most cases were represented by AEs belonging in the category General disorders and administration site conditions.

Study title: Randomized, double-blind, placebo-controlled, multi-center, parallel-group clinical study of the efficacy, immunogenicity and safety of the Gam-COVID-Vac combined vector vaccine to prevent coronavirus infection caused by SARS-CoV-2 virus.
Protocol number: 04-Gam-COVID-Vac-2020 (**RESIST**)
The Head of the Expert Group, the Coordinating Investigator: Elena Anatolyevna Smolyarchuk, *Candidate of Medical Science/Clinical Assistant Professor, the Head of the Center of Clinical Investigation of Medicinal drugs of the Sechenov University*
Federal State Autonomous Educational Institution of Higher Education I. M. Sechenov First Moscow State Medical Sechenov, Ministry of Health of the Russian Federation (Sechenov University).
Study methodology:
Randomized, double-blind (blinded both for the study subject and the study physician), placebo controlled, multi-center clinical trial in parallel assignment of efficacy, immunogenicity, and safety of the Gam-COVID-Vac combined vector vaccine against the SARS-CoV-2-induced coronavirus infection in adults in the SARS-CoV-2 infection prophylactic treatment.

SUMMARY – CONCLUSIONS
At present, FSBI N.F. Gamaleya NICEM of the Ministry of Health of Russia is conducting the "Randomized double-blind placebo-controlled multicenter clinical trial of the efficacy, immunogenicity and safety of the combined vector vaccine Gam-COVID-Vac in parallel groups in the prevention of coronavirus infection caused by the SARS-CoV-2 virus" , protocol: No. 04 - Gam-COVID-Vac -2020.
The study is ongoing.
The study product "Gam-COVID-Vac", a solution for intramuscular administration, is a vaccine that induces specific immunity to SARS-CoV-2. The vaccine has been produced using biotechnological methods, without the use of the SARS-CoV-2 virus, a human pathogen.
The vaccine is based on adenoviral vectors, the safety of which has been shown in studies of already registered drugs (three vaccines against the disease caused by Ebola virus (EVD),

registered in the Russian Federation, consisting of recombinant particles based on the vesicular stomatitis virus expressing GP gene of Ebola virus and recombinant pseudo adenovirus particles expressing GP gene of Ebola virus) and drugs at the stage of clinical trials (against Middle East respiratory syndrome (MERS) caused by MERS-CoV, and against pandemic strains of influenza – recombinant pseudo adenovirus particles expressing the gene of nucleoprotein protein and M2 protein of influenza A virus).
The drug contains two components: component I and component II. Component 1 contains a recombinant adenoviral vector based on human adenovirus serotype 26 carrying the S-protein gene of SARS-CoV-2 virus, component 2 includes a recombinant adenoviral vector based on human adenovirus serotype 5 carrying the S-protein gene of SARS virus-CoV-2.
Within this study, a therapeutic dose of $1x10^{11}$ VP (viral particles) was administered intramuscularly into the deltoid muscle of the shoulder twice with an interval of 21 days (Component I first, then Component II) on the second stage of the study.

The analysis covers data from 12,296 subjects vaccinated with two Gam-COVID-Vac components / placebo and whose data were documented as comprehensively as possible using the e-CRF (demographic and anthropometric indices, findings of a physical prior to and after vaccination, etc.).
The study enrolled volunteers 18 to 87 years old. Mean age was 45.5 ± 11.9 years in Group I (IP) and 45.5 ± 11.8 years in Group II (placebo). A total of 7,497 males (5,651 – in the IP group and 1,846 – in the placebo group), and 4,799 females (3,607 - the IP Group, and 1,192 - the placebo group) were included.
Analysis of comorbidity data has shown that 2,360 volunteers (25.9%) in the study drug group and 819 volunteers (27.3%) in the placebo group had comorbidities.
For most of the volunteers the risk of infection in both groups had been assessed as average. However, for 42 volunteers (0.5%) in the study drug group and 15 volunteers (0.5%) in the placebo group the risk had been assessed as high.
A physical examination at the screening visit identified 562 deviations, 30 of which were clinically significant. The bulk of the findings were accounted for by cardiac and vascular system (348 of 562 findings, or 61.9%). Intergroup comparison of these data did not find any statistically significant differences ($p > 0.05$).
No statistically significant differences were found between the groups in distributions by demographic and anthropometric data, comorbidities or COVID-19 infection risk.

SAFETY AND EFFICACY ANALYSIS RESULTS:

Incidence and severity of adverse events experienced by study subjects within 6 months after receiving the first dose of the study drug/placebo.
A safety analysis included 12,296 volunteers (all volunteers who were administered a dose of the study drug).

AE Incidence Rate

A total of 8,704 AEs had been registered during the study in 4,401 volunteers by the time of analysis.

SAE Incidence Rate

A total of 12 SAEs had been described and verified during the study by the time of the analysis. Of these, three SAEs were found in volunteers aged 60 or older (all of them in the IP group): renal colic, deep vein thrombosis, and an abscess in the area of a limb. The SAEs were diagnosed due

to the fact that in each of the three cases the event called for the hospitalization of a study subject. A total of 46 cases of SAE (36 in the IPL group and 10 in the placebo group) in 44 subjects (34 in the IPL group and 10 in the placebo group) were registered and are under observation during the data analysis period. This list of SAEs does not include hospitalizations for SARS-CoV2 infection. During the analyzed period, 13 cases of SAE associated with COVID-19 disease were registered (2 in the IPL group and 11 in the placebo group).

Causality relationship with the study drug

In none of the cases was a link with the using the IP/placebo suspected.

Severity of AEs

Three AEs with a severity rate of 3 or higher were registered in volunteers 60 years of age or older. All of these AEs resolved themselves on their own, without any consequences.

Conclusion

1) The vaccine being studied has a good safety profile
2) The group of patients over 60 did not differ from the overall patient population in terms of safety profile
3) There were no unexpected serious adverse events reported during the study
4) It is generally characteristic of vaccine medications that they bring about adverse events

The data obtained seem to confirm the study hypothesis that administering the developed vaccine induces the formation of a protective immune response to the SARS-CoV-2 virus.

Conclusions

1) Twofold prime boost immunization with the Gam-COVID-Vac drug led to statistically lower morbidity in the Gam-COVID-Vac treatment group than in the placebo group.
2) 95% CI for OR did not fall below a superiority of 0.67 which is evidence of high efficacy (96%) of the study vaccine.
3) Twofold prime boost immunization by the Gam-COVID-Vac drug led to reduced severity of disease cases.
4) Age, gender, and comorbidities did not have a statistically significant correlation with the risk of getting infected. A statistically significant difference was found only in the groups receiving the study drug and placebo, respectively.
5) A single-dose immunization with Component I showed a statistically significant difference in efficacy observed in the period 14 to 21 days. According to the data obtained, the odds ratio is 0.305 (CI 95%) — from 0.191 to 0.486 — which corresponds to ~70% efficacy of reducing the risk of the disease from Day 14 to Day 20 after the Component I was administered. Consequently, a single-component immunization is capable of significantly reducing the risk of disease, even at an early stage after vaccination.

2.6. Justification of calculation of a safe dose for clinical trials in humans

In order to select an effective human immunizing dose, an immunogenicity (humoral immune response stress) study was carried out on golden hamsters using a dose of 10^8 particles.

The therapeutic dose safety has been demonstrated in preclinical trials.

The selection of the proposed effective human immunizing dose (HID) was based on available data of our own studies, references and cumulative results of specific activity studies on golden

hamsters. Consideration was given to the available literature data evidencing that, in primates with protective immunity (after vaccination or infection with SARS-CoV-2), that enables their protection against infection or re-infection with SARS-CoV-2, the titer of glycoprotein-specific IgG antibodies was 1/150-1/1000, and the titer of virus neutralizing antibodies (VNA) was 1/75-1/150. Similar VNA titers are currently detected in former COVID-19 patients[3].
The studies in golden hamsters demonstrated that administration of an effective immunizing dose of vaccine (10^8 v.p. per animal) ensures formation of neutralizing antibodies necessary to protect the animal (at least 1/100) as soon as 1 week after immunization. A study on golden hamsters with induced immunodeficiency also demonstrated that vaccine administration in an effective immunizing dose protects the animals against a lethal infection caused by SARS-CoV-2.
In subsequent potential toxicity studies, Gam-COVID-Vac equi-immunizing doses for laboratory animals were calculated drawing on the calculated human immunizing dose (HID) determined in specific activity studies. **1 HID consisted of: $1x10^{11}$ particles.**
The same dose of a drug with an identical composition that was developed earlier for MERS prevention demonstrated a favorable safety profile. In addition, it should be pointed out that the half-dose and full-dose safety profiles did not differ significantly, but the resulting immune response was more prominent in the full-dose group.
Justification of the selected dose is based on the results of development of other vaccines on the basis of the same technology platform being used.
For example, as part of the clinical study of the MERS-GamVac-Combi vaccine (the same vector constructions in the same doses were used) for prevention of the Middle East respiratory syndrome, two doses of vaccine were studied – a half dose and a full dose (10^{11} v.p./dose). The findings of studies completed to date demonstrated that, at the peak of immune response (35th day after vaccination), the levels of antibodies in the half-dose group was 13,824.8 (with a seroconversion rate of 90%), while in the full-dose group – 18,740.3 (with a seroconversion rate of 100%), which demonstrate that administration of a full dose of the vaccine leads to the formation of a stronger and quicker antibody response in 100% of volunteers.

In this regard, assessing a full therapeutic dose was planned during this study, since safety for the full dose was proven during previous clinical trials on similar vaccines, and the efficacy and speed of immune response development is higher for the full dose.

The dose in question was studied in clinical trials 02-Gam-COVID-Vac-2020, 03-Gam-COVID-Vac-2020, 04-Gam-COVID-Vac-2020, 05-Gam-COVID-Vac-2020.
The drug (component I of the Gam-Covid-Vac combination vaccine) has been given to more than 33,000 volunteers in clinical trials, and has demonstrated a favorable safety profile.

2.7. Brief description of known risks and potential risks and benefits for participants of the study

The available data on the safety and immunogenicity of the study drug Gam-COVID-Vac combined vector vaccine against the SARS-CoV-2-induced coronavirus infection allow to consider the developed vaccine as a drug, the potential benefit of which significantly outweighs the risk.
In an unfavorable epidemiological setting, it is expected that volunteers will clearly benefit from

[3] 10.1126/science.abc6284, 10.1126/science.abc4776, 10.1101/2020.04.15.20065623, 10.1016/j.autrev.2020.102554

participating in the study.

The risk of the disease developing, the clinical evidence, and peculiarities of the progression of the disease

Global statistics as of December 28, 2020 (2020 WHO):

- Confirmed cases – 81,713,263
- Confirmed deaths – 1,783,146

As of December 28, 2020 in the Russian Federation is detected:

- Confirmed disease cases – 3,047,335
- Confirmed deaths – 54,559

To date, there has been limited information on epidemiology, clinical features, prevention and treatment of this disease. It is known that the most common symptom of the novel coronavirus infection is bilateral pneumonia; acute respiratory distress syndrome (ARDS) has also occurred in 3–4% of patients.

The incubation period ranges from 2 to 14 days, 5-7 days on average.

COVID-19 is characterized by clinical symptoms of an acute respiratory viral infection:

- Increased body temperature (>90%);
- Cough (dry or with little phlegm) in 80% of cases;
- Shortness of breath (30%);
- Fatigue (40%);
- Feeling of congestion in the chest (>20%);
- There may also be sore throat, runny nose, decreased sense of smell and taste, signs of conjunctivitis.

The most severe shortness of breath develops by the 6th-8th day after infection. It was also found that the first symptoms may include myalgia (11%), confused mental state (9%), headaches (8%), hemoptysis (2-3%), diarrhea (3%), nausea, vomiting, palpitations. These symptoms at the onset of infection can be observed in the absence of an increase in body temperature.

Clinical variants and manifestations of COVID-19:

- Acute respiratory viral infection (affecting only the upper respiratory tract);
- Pneumonia without respiratory failure;
- Pneumonia with symptoms of acute respiratory failure (ARF);
- ARDS;
- Sepsis;
- Septic (infectious toxic) shock;
- Hypoxemia (a decrease in oxygen saturation below 88%) develops in more than 30% of patients.

On average, 50% of infected persons are asymptomatic. In 80% of patients with clinical manifestations of COVID-19, the disease looks like mild ARVI. The average age of patients in China is 51 years, the most severe forms developed in elderly patients (60 years or more), sick patients often have such concomitant diseases as diabetes mellitus (20%), arterial hypertension (15%), other cardiovascular diseases (15%).

Twenty percent of the confirmed cases reported in China have been classified as severe by health authorities (15% severely ill, 5% critically ill). In severe cases, rapidly progressive lower respiratory tract involvement, pneumonia, ARF, ARDS, sepsis and septic shock were often observed. In the city of Wuhan, almost all patients with a severe course of the disease registered progressive ARF: pneumonia is diagnosed in 100% of patients, and ARDS is diagnosed in more

than 90% of patients.

Adverse events and allergic reactions to vaccine administration

Adverse reactions specific to the use of the vaccine, revealed in clinical trials and studies of other vaccines based on a similar technological platform, are predominantly of mild or medium severity, and may develop during the first or second day following vaccination and usually abate within 3 subsequent days. The most common include short-term general (a brief flu-like syndrome characterized by chills, fever, arthralgia, myalgia, asthenia, general discomfort, headache) or local (injection site tenderness, hyperemia, swelling) reactions. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended in case of post-vaccination fever and antihistamines for expressed local reactions.

Less common ones are nausea, dyspepsia, loss of appetite, occasionally – enlarged regional lymph nodes. Some patients may develop allergic reactions, short-term elevated liver transaminase levels, elevated serum creatinine and creatine phosphokinase levels.

Within the Gam-COVID-Vac safety, tolerability, and immunogenicity clinical trials conducted to date the following AEs have been registered:

"General injection site disorders and reactions": hyperthermia, vaccination site tenderness, edema and pruritus, asthenia, pain, malaise, pyrexia, increased vaccination site skin temperature, decreased appetite. Incidence rate – very common and common.

"Respiratory, chest, and mediastinal disorders": oropharyngeal pain, nasal congestion, sore throat, rhinorrhea. Incidence rate – common

"Nervous system disorders": common – headache; rare – dizziness, syncope.

Gastrointestinal disorders: nausea, vomit, dyspepsia – common

"Laboratory and instrumental data": divergent abnormalities of immunological status indicators: increased count of T-lymphocytes, increase in the percentage of lymphocytes, decreased count of natural killer cells, increased count of CD4-lymphocytes, decreased count of CD4-lymphocytes, increased count of B-lymphocytes, decreased count of B-lymphocytes, increased count of natural killer cells, increased count of CD8 lymphocytes, increased level of immunoglobulin E (IgE) in the blood, increase in the CD4/CD8 ratio, decrease in the CD4/CD8 ratio, increased level of immunoglobulin A (IgA) in the blood, decrease in the percentage of CD8 lymphocytes. Abnormalities in the complete blood count: increase in the percentage of lymphocytes, decrease in the hematocrit, increased count of lymphocytes, increase in the erythrocyte sedimentation rate, increased leukocyte count, increased count of monocytes, increased platelet count, decreased count of neutrophils, decreased platelet count. Abnormalities in common urine analysis: erythrocytes in the urine.

Most AEs ended in complete recovery, with no consequences. Lab test deviations were not of clinical significance (did not require additional diagnostics or therapy).

Pregnancy

In experiments on animals, it was proved that the similar vaccine (developed on the same platform of adeno-viral vectors) does not have a negative effect on the embryonic development of rats in the antenatal and postnatal period of development when the vaccine was administered intramuscularly. However, the risks of using this vaccine for the human fetus are currently unknown. Therefore, pregnant women will not be included in the study. All women of childbearing age will be warned at the informed consent stage to use efficient contraception to minimize any potential risk. Given the theoretical risk, male study participants would also be required to use efficient contraception. In a study of a similar vaccine for the prevention of MERS (which also

consists of two viral vectors Ad26 and Ad5 as well as the study vaccine), it was shown that in doses of 1EIDrats (corresponds to 0.06 HID) and 10 EIDrats (corresponds to 0,6 HID) it does not have a negative effect on the generative function of male rats at an equi-immunizing dose (1 EIDrats), however, morphological parameters revealed an inhibitory effect on spermatogenesis at a tenfold equi-immunizing dose (10 EIDrats). The study vaccine in all parameters had no toxic effect on the gonads of female rats in both tested doses. In this regard, it is necessary to use an efficient method of contraception to reduce the possible risk of the effect of the study drug on the health of the offspring.

Effect on reproductive functions

Potential risks to the reproductive health of the population in a pandemic include the effects of the following factors on the reproductive system and its functioning as well as the development of gametes and embryos:

- Effect of SARS-CoV-2 virus and COVID-19;
- Effect of concomitant diseases;
- Medicines for the prevention and treatment of COVID-19;
- Chemical disinfectants;
- Psychological factors associated with panic during the COVID-19 outbreak;
- Decrease in the quality of life associated with economic factors;
- Decreased physical activity and quality of sex life due to isolation.

It is not anticipated that there is a biologically plausible way in which the vaccine could cause infertility in any woman or man, developmental pathology, or affect offspring, since:

- The vaccine does not use adjuvants;
- Potentially toxic (in rats) excipient (polysorbate 80) used in the vaccine is used in a dose that cannot affect human fertility and reproductive function;
- The vaccine virus does not reproduce itself; after injection, the virus delivers the S-protein gene to the cell and ceases to exist in the human body;
- The gene coding S-protein in the body leads to the production of the viral S-protein and the development of an immune response to it;
- Antibodies to S-protein produced in response to immunization are similar to antibodies produced in response to a disease caused by SARS-CoV-2, therefore, the risk of immunization is not higher than in case of infection;
- Antibodies to adenovirus produced in response to immunization are similar to antibodies to adenoviruses produced in response to a disease caused by adenovirus with a widely spread pathogen; therefore, the risk of immunization is not higher than in case of infection.

In preclinical trials of reproductive toxicity, a similar vaccine developed on the platform of adenoviral vectors types 26 and 5 of identical composition was studied.
No increased risk is expected when the vaccine is administered to study participants under conditions of adherence to the restrictions indicated in the instructions for medical use.
Lactation

There is no data on the excretion of the product into the milk of lactating women, and the risks associated with possible excretion in infants are unknown. Therefore, lactating women will not be included in the study in order to minimize all possible risks.

Venipuncture

During this procedure, you may experience mild pain that is quickly passing and/or a hematoma may form in the area where the needle is inserted. Much less often, a thrombus may form in a vein or an infectious complication may develop. Dizziness and/or weakness may occur during or shortly after taking blood. These risks will be minimized taking into account the involvement of qualified medical personnel to perform this procedure.
In total, blood samples for research will be taken from participants 6 times during the entire period of the study and no more than 155 ml of blood will be taken, which is safe for adult participants in the study (table 4).

Table 4. Blood amount for tests.

days	screening	1	10	28	42	90	180	Total
ml	25	45	15	35	25	5	5	155

Unknown risks
In addition to the risks and discomfort listed above, there may be previously unreported or atypical effects. Adverse events that may occur when people first take the study drug cannot be predicted in advance. Therefore, the possibility of the development of a serious unforeseen adverse event cannot be ruled out. After administration of the drug, the volunteers will be monitored by a physician for 5 days from the administration in order to minimize risks and provide quality medical care in case of any adverse events as promptly as possible.
Medical conditions developed during the course of a clinical trial may lead to the termination of a volunteer's participation in a clinical trial, if it is medically necessary or if the volunteer so desires. The volunteers removed from the study due to AE development will receive the necessary therapy in accordance with the existing clinical standard, and they have to be observed till recuperation or stabilization, or until acceptable explanation of the reason for development of such an event is found.
There are no known risks for the environment. All biohazardous waste will be disposed of in accordance with government regulations.
Taking into account the information provided, it can be concluded that the benefits of participating in this study outweigh the potential risks for its participants.

2.8. Legal and regulatory framework

This study will be conducted with deep respect to its individual participants in accordance with the requirements specified in the clinical trial protocol and the following regulatory documents:

- World Medical Association Declaration of Helsinki.
- Ethical Principles for Medical Research Involving Human Subjects;
- Guidelines of the International Conference on Harmonization (ICH).
- (Good Clinical Practice);
- Federal Law No. 61-FZ dd. April 12, 2010 (rev. dd. December 28, 2017) (in the applicable revision) "On Circulation of Medicines"
- Federal Law of the Russian Federation dated July 27, 2006 No. 152-FZ On Personal Data;

- Federal Law N 323-FZ dd. November 21, 2011 "On the Fundamentals of Health Protection in the Russian Federation";
- Good Clinical Practice GOST;
- Russian Federation Ministry of Healthcare Directive No. 200n dated 1 April 2016 "On Approving Good Clinical Practices";
- Rules for Good Clinical Practice of the Eurasian Economic Union (approved by Resolution of the Council of the Eurasian Economic Commission No. 79 dd. November 3, 2016);
- Roszdravnadzor Directive No. 1071 dated 15 February 2017 "On Approving the Procedure for Pharmacovigilance"

Prior to the start of the study, a written approval of the Protocol and the Informed Consent Form by the Ethics Board of the Ministry of Healthcare.

The Informed Consent Form contains a description of the scheduled and allowable use of, and the procedure for transferring and disclosing, volunteers' personal data, as well as their healthcare records for the purposes of holding the trial. The information for the volunteer and the Informed Consent Form contain description of the study nature, its goals, the potential risk, the requirements to the study participant, and the fact that the volunteer may withdraw his or her informed consent at any time without specifying a reason.

If required, the investigator shall explain in detail all the sections of the Informed Consent form to the volunteers. The volunteers will be provided with sufficient time to clarify any questions they are interested in with regard to the study details and take a decision on participation in the study.

The informed consent shall be received before inclusion in the study, i.e. before any screening procedures under the Protocol. In the primary documentation the Investigator specifies the time and the date of signing the Informed Consent for participation in the study according to Protocol № 06- Gam-COVID-Vac Lyo-2020.

Prior to the start of the study, in the course of the initiating visit, the Research Center personnel will be trained for the Protocol and the key provisions of the law of the Russian Federation, the Rules of Due Clinical Practice, and the Declaration of Helsinki.

2.8.1. **Investigator's responsibility**

The prerequisite for assumption of responsibility for due arrangement of the clinical trial in compliance with the applicable requirements of the regulatory authorities shall be the investigator's relevant education, training, and experience. The investigator's qualification shall be proven (autobiography until present time).

The investigator shall:

– fully understand the procedure for use of the study product, as described in the Protocol and the Investigator Brochure;

– know and observe the Rules for Good Clinical Practice and the applicable requirements of the regulatory authorities;

– allow Sponsor to conduct monitoring and audit and allow the corresponding regulatory authorities to carry out inspections;

– keep the list of the skilled personnel to whom the investigator delegated significant responsibilities in the clinical trial;

– be able to demonstrate the possibility of involvement of the required number of volunteers meeting the inclusion/non-inclusion criteria during the agreed selection period;

– have enough time for due arrangement and completion of the study during the agreed study period;

– have sufficient available skilled personnel and adequate equipment for the assumed study period in order to provide for due arrangement of the study and safety;
– ensure that all the persons assisting to conduct the study have adequate information of the Protocol, the study product and their duties and functions related to conducting studies;
– conduct the study in accordance with the Protocol, as the investigator consents when signing the Protocol;
– document and explain any deviation from the approved Protocol.

During the study and after its completion by a participant, the investigation (medial establishment) shall arrange provision of the required medical care to the participant in case of any adverse events, including clinically relevant changes in the laboratory parameters. The investigator (medical establishment) shall inform the study participant of any intercurrent diseases found by the investigator which required medical assistance.

The investigator shall not apply any deviations from or changes in the Protocol without the Sponsor's consent and until review and documented approval/positive conclusion of the IEC/IRB with regard to the adjustment to the Protocol unless there is an urgent need to immediately reduce risk for the clinical trial volunteers or the changes are related only to logistic or administrative aspects of the study (i.e. changing the monitor or phone number).

2.8.2 Medical assistance provided to volunteers in the course of the clinical study

An experienced medical investigator shall be responsible for taking all the medical decisions in the course of the study.

During a volunteer's participation in the study and afterwards the investigator shall ensure adequate medical care for the volunteer in case of any EA associated with the study. The investigator shall inform the volunteer of medical assistance required for treatment of any concomitant disease(s) of the volunteer found by the investigator.

The investigator is recommended to notify the volunteer that the investigator shall advisably inform his or her attending physician, if any.

Even though the volunteer is not obliged to specify his or here reasons for early withdrawal from the study, the investigator shall take reasonable efforts to find the reasons, subject to full respect of the volunteer's rights.

2.9. Description of the study population

110 healthy volunteers will take part in the study and receive the study drug. The study will enroll volunteers from both genders older than 18 years.

2.10. References to literature and data relevant for the study and used as justification of this study

1. Temporary methodological recommendations The Ministry of Health of Russia for doctorson prevention, diagnosis and treatment of COVID-19
2. https://covid19.rosminzdrav.ru
3. https://stopcoronavirus.rf
4. “Selected practice recommendations for contraceptive use” – 2nd ed., World Health Organization, 2005; ISBN 92 4 156284 6 (NLM classification: WP 630). The document has been translated into Russian by the Reproductive Health and Research Program of the WHO Regional Office for Europe within the framework of the Strategic Cooperation Program of the World Health Organization and the United Nations Population Fund.
5. Thomas F. Babor John C. Higgins-Biddle John B. Saunders Maristela G. Monteiro World Health Organization AUDIT The Alcohol Use Disorders Identification Test

Guidelines for Use in Primary Care Second Edition 2001 /WHO/MSD/MSB/01.6a Original: English Distribution: General Department of Mental Health and Substance Dependence

6. Guidelines on clinical trials of Drugs (Immunobiological Drugs). Part two. – M.: Grif and K., 2012, 212 p.
7. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
8. DRAFT landscape of COVID-19 candidate vaccines – 20 April (https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf)
9. https://www.cochrane.org/ru/coronavirus-covid-19-cochrane-resources-and-news
10. Guidelines for Preparing Core Clinical Safety Information on Drugs – Report of CIOMS Working Group III. Geneva, WHO, 1995, Chapter 5, GoodSafetyInformationPractices
11. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research September 2007
12. CTCAE v5.0 – November 27, 2017

3. GOALS AND OBJECTIVES OF THE STUDY

3.1. Trial goal

The goal of this trial is to assess the safety, tolerability, and immunogenicity of Sputnik Light, a solution for intramuscular injection, at various times after vaccination in adult volunteers.

3.2. Trial objectives

1. Assess security and tolerability of the medicinal drug Sputnik Light, a solution for intramuscular injections, after immunizing adult volunteers with the vaccine

   The assessment of safety and tolerability include data collection throughout the research period to study the drug influence on vitals (systolic and diastolic blood pressure, heart rate, body temperature) and laboratory values in healthy volunteers, and generalized and local vaccinal reactions as compared to baseline values (before vaccination).
2. Assess post-immunization immunity at various intervals after vaccinating the volunteers by:

   – *determining the titer of specific antibodies in blood serum by enzyme-linked immunosorbent assay as compared to background values before immunization, and on days 10, 28, 42, 90, and 180 after immunization;*
   – *assessing the viral neutralization activity before administering the vaccine and on days 28 and 42 after immunization*
   – *assessing antigen-specific cell-mediated immune response (specific T-cell response) before administering the vaccine, and on day 10 from the start of vaccinations, as compared to the background values before vaccination.*

assessing the epidemiological efficacy of vaccination may be based on the information obtained concerning morbidity in vaccinated individuals (in the framework of subsequent phase III clinical trials).

3.3. Design of the trial

Phase I open prospective, non-randomized study in adult volunteers.

3.4. Indication of the main and additional (if any) studied parameters to be assessed during the study

In the course of the study of Sputnik Light, solution for intramuscular injection, combination vector vaccine for COVID-19 prevention basic assessment was carried out to determine:

– safety and tolerability of the vaccine
– immunogenicity (humoral immunity)

The following parameters will be studied as secondary indicators

– cell immunity
– serum neutralizing activity.

3.5. Indication of primary and additional endpoints

When studying immunological efficiency, the following possible marker indicators will be identified:

– after vaccination the volunteers were to be detected a relevant increase in the glycoprotein-specific antibodies titer on days 28 and 42, which will be taken as a primary endpoint;

– T-cell immunity stress (antigen restimulated IFN-gamma expression, antigen restimulation lymphoproliferative response) and blood serum neutralizing activity can be used as additional efficacy criteria (secondary endpoints).
– The length of immune response on day 90 and 180 will be evaluated as part of the study.

3.6. Description of study design

This is an open study of the safety, tolerability, and immunogenicity of Sputnik Light, a solution for intramuscular injection, in adult volunteers.

Screening Period = up to 7 days. All screening procedures must be carried out within the shortest possible time before the scheduled date of Visit 1 (drug injection). The laboratory and instrumental examination data obtained within 14 days before the screening will be recorded as the screening data.
The trial will include 110 volunteers that will be administered the study drug. An outpatient follow-up included 5 in-person visits: on the 10th, 28th, 42nd, 90th and 180th day after vaccination.

Trial coordinator must minimize the risks for volunteers and researches in the context of pandemic (letter of the Ministry of Health of the Russia Federation No. 20-1/I-2- 3651 dated 27/03/2020 On the Issues of Clinical Trials of Medicinal Drugs during COVID-19 Pandemic).
An interim report can be prepared at the initiative of the developer at any point in the study to assess safety and / or immunogenicity.
Upon reaching the primary points involved in immunogenicity assessment described in the Protocol, a report on the results of the safety and immunogenicity assessment will be drawn up on the basis of the results obtained on the 28th day of the study to help make a decision on the registering the drug in accordance with Russian Federation government Resolution No. 441 dated April 3, 2020 “On the Specifics of Handling Human Medicinal Drugs Intended for Use During the Threat of or an Actual Emergency Situation, and Emergency Response, and for Arranging Medical Assistance to Persons Affected by Emergency Situations, Preventing Emergency Situations, Preventing and Treating Diseases That Pose a Serious Hazard to the Public, Diseases and Injuries Resulting from Adverse Chemical, Biological, and Radiation Factors”. This report will include the results of assessing the immunogenicity for not less than 50 participants at the 28-day point.
Along with that, the study will be continued in accordance with the Protocol, accompanied by all the prescribed procedures and visits up to 180 days of observation.
Visit 0: screening (as an outpatient).
Visit No. 1 vaccination (outpatient)
Visits No. 2, 3, 4, 5, and 8: follow-up on days 10, 28, 42, 90, and 180 after vaccination (outpatient).
On days 120 and 150, visits 6 and 7 will be accomplished by telephone contact / telemedicine conference or, if necessary, in the form of an in-person visit.
Any volunteer who received a dose of the study drug will be registered as a trial participant, and his/her data will be used to help assess the drug’s safety and tolerability.

The following biomaterials will be sampled in order to evaluate safety and immunogenicity:
A) Urine sampling:
– for a common urine test with sediment microscopy – during the screening, before the vaccine injection, and on the 28th day of the study, 2 times altogether;
– for a narcotics and psychostimulant substances test, during the screening and prior to the injection of the study drugs, 2 times altogether;

B) Blood sampling:

- for a test for hepatitis B and C, HIV and syphilis, once during the screening visit (tests obtained within 1 month prior to the screening will be regarded valid);
- for a SARS-CoV-2 IgM and IgG antibody test a single time (volunteers with negative or equivocal – close to lower normal limit – IgG test could be included in the study);
- in order to determine the safety parameters (a complete blood count (CBC) with absolute and relative WBC count and differential, erythrocyte sedimentation rate, and biochemical blood assay (BBA) – ALT, AST, total protein, bilirubin, total cholesterol, LHD, ALP, Quick's value (prothrombin ratio), glucose, urea, creatinine): during the screening, prior to the vaccine injection and on the 28th day of the study, 3 times altogether;
- immunological analysis (T and B cell populations (quantity and relative content: CD3, CD4, CD8, CD16, CD19, CD4/8), white cell activity (phagocytic index), definition of main immunoglobulin classes: IgM, IgG, IgA, IgE) - 3 times (Day 1, 28 and 42)
- in order to evaluate immunogenicity:

Titers of specific antibodies were identified using the EIA method – prior to immunization and on 10th, 28th, 42nd, 90th and 180th days after immunization, 6 times in total;
Serum neutralizing activity detection – prior to the vaccination and 28 and 42 days after the vaccination, 3 times in total;
Cell-mediated immunity evaluation — prior to the vaccination and 10 days after the vaccination, 2 times in total.
C) Biological material sampling for SARS-CoV-2 using the PCR method, on screening visit, prior to the drug injection, and on days 10 and 28, 4 times.

Alcohol test, during the screening and prior to the vaccine injection, 2 times.
Narcotics test, during the screening and prior to the vaccine injection, 2 times.
The follow-up and examination of volunteers is to be carried out in accordance with the schedule of procedures during 180 days.
Observation results will be described in the report. The final report will be prepared basing on the results of observation for 180 days.

3.7. Description of measures aimed to minimize/eliminate subjectivity

It was an unblinded non-randomized study. No measures to minimize/exclude subjectivity during this study are not envisaged.

3.8. Description of the study product, dosage and schedule of the study product application

In this study, the drug will be administered at a calculated therapeutic dose of $1x10^{11}$ v.p. intramuscularly into the deltoid muscle of the shoulder:
The investigational drug is injected once.

Detailed information about the study drug is described in its Instruction for Medical Use and the Investigator's brochure.

3.9. Expected duration of subject's participation in the study

Every volunteer will participate in the study during 201 days.

3.10. Description of "study stopping rules" or "withdrawal criteria" for certain subjects, parts of or the entire study

The clinical trial could be early terminated or suspended by the Sponsor.
Separate subjects can be withdrawn from the study for the following reasons:

- at their own request,
- upon decision of the study physician due to insufficient cooperation by the volunteer and gross violations of the protocol,
- due to development of conditions or events that constitute exclusion criteria.

The causes, as well as the date and time of volunteer's withdrawal from the clinical trial shall be documented in CRF. All information on volunteers who decided to withdraw from the study shall be fully recorded in CFR till the moment of withdrawal.

3.11. Procedures for recording the study product and placebo

Placebo intake is not contemplated by this study.
The product can only be stored in the center approved for the conducting this study. The principal investigator shall guarantee product storage in appropriate conditions preventing loss, theft or violation of storage conditions in accordance with the draft instruction on medical use and the requirements of the Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation.
The principal investigator shall appoint a responsible person to control the product storage conditions and consumption recording.
Product consumption recording and control shall be documented.
The study product can be administered to study participants only.

3.12. Treatment randomization code storage and disclosure procedures

The study is non-randomized.

3.13. Documenting for the clinical trial

To collect all the information on the volunteer participating in the study and transfer this information to an authorized employee of the Sponsor, a special Case Report Form (CFR) will be used.
CFR shall be formalized for each volunteer, data on volunteers shall be entered formally, i.e. by selecting an appropriate definition from the list. The investigator also can specify particulars of the volunteer's condition, entering respective comments in the remarks column. Instructions on filling in CFR are submitted to the research center within the study file.
All data on the volunteer, obtained during the study, shall be first entered in the primary documents, and then transferred to the volunteer's Case Report Form. The CFR data shall coincide with the primary document data. This study does not provide for data recorded directly to CFR, considered to be primary data, but not to be entered in the primary documents.
The following original documents, data, and entries should be deemed primary documentation within the study

a. electronic form being filled out directly during the subject visit
b. paper form being filled out directly during the subject visit
c. subjects´diaries, telemedicine conferences protocols,
d. medical records, outpatient treatment records, laboratory records, notes, diaries kept by the subjects of research, questionnaires, medication logbooks, records kept by automated devices, verified and certified copies or excerpts, microfiches, photograph

negatives, microfilm or magnetic media, X-rays, or any records related to the patient, including those stored in the pharmacy, laboratories, and departments with the diagnostics equipment used in the clinical study

e. this clinical trial specific fillable forms: drug dispensing logs, automatic device entries, subject registers, training forms, delegation of authority forms, adverse event forms, serious adverse event forms, pregnancy forms, protocol deviation forms and other protocol specific forms

To ensure data integrity, all of the above listed primary documents are subject to storage and further archiving. All primary documents should be made available for monitoring, auditing, and inspection checks.

If the inspection protocol is maintained in electronic form, a printout signed and dated by the document author (copy) and an electronic file (original) are subject to storage and further archiving.

4. Subjects selection and exclusion

The study subjects are healthy volunteers — men and women. The following two subsections describe inclusion and exclusion criteria for subject enrollment for participation in the study. In case of any questions regarding the inclusion and exclusion criteria described below, before subject inclusion in the study, the investigator shall consult the Sponsor's representative.
The study subjects shall be socially isolated to the greatest possible extent after confirmation of meeting the inclusion and exclusion criteria.

4.1. Inclusion criteria

1. The subject's written informed consent to participate in the trial;
2. Males or females 18 years old or older;
3. No history of COVID-2019: negative SARS CoV2 IgM and IgG EIA test (at most 14 days prior to enrollment);
4. Negative COVID-2019 PCR test result at the screening visit
5. No contact with COVID-2019 persons within at least 14 days before the enrollment (by the subject's account);
6. Negative HIV and hepatitis test results;
7. Consent to use effective contraception methods during the trial;
8. Negative drugs or psychostimulants urine test at the screening visit;
9. Negative alcohol test at the screening visit;
10. Negative pregnancy test (women of reproductive potential)
11. No evident post-vaccinal reactions or complications after receiving immunobiological drugs in the medical history
12. No acute infectious and/ or respiratory diseases within at least 14 days before the enrollment.

4.2. Exclusion criteria

1. Any vaccination / immunization performed within 14 days prior to enrollment in the study, or a planned vaccination within 14 days after being administered the study drug;
2. Steroid therapy (except hormonal contraceptives or drugs used as hormone

replacement therapy for menopause) that has not been completed 30 days before enrollment

3. Therapy with immunoglobulins or other blood products not completed 30 days before enrollment in the trial;
4. Immunosuppressor therapy that was completed within 3 months before being included in the trial;
5. A vaccination against COVID-2019 using any other drugs, including in the course of other clinical trials
6. Female subjects during pregnancy or breastfeeding (*for women of reproductive potential);
7. Acute coronary syndrome or stroke suffered less than one year before enrolling in the trial;
8. Tuberculosis, chronic systemic infections;
9. Medical history with aggravated allergies (severe life-threatening allergic reactions), hypersensitivity or allergic reactions to immunobiological drugs, known allergic reactions to the drug's components, exacerbation of allergic diseases occurs on the day of inclusion in the study;
10. Neoplasms in a person's medical history (ICD codes C00-D09);
11. Donated blood or plasma (450+ ml) within 2 months before enrollment;
12. Splenectomy in the medical history;
13. Neutropenia (absolute neutrophil count <1,000 mm3), agranulocytosis, significant blood loss, severe anemia (hemoglobin <80 g/L), immunodeficiency in the medical history within 6 months before the enrollment;
14. Active form of a disease caused by the human immunodeficiency virus, syphilis, hepatitis B or C;
15. Anorexia, protein deficiency of any origin;
16. Large tattoos at the injection site (deltoid muscle area), which does not allow the localized response to administering the study drug to be assessed;
17. Alcohol and drug addiction in a person's medical background;
18. Registered psychiatric patient;
19. Participation in any other interventional clinical trial within 90 days before the start of this trial;
20. Any other condition that the researching physician considers to be a hindrance to completing the trial as per the protocol;
21. Research facility staff and other employees directly involved in the trial (research team members) and their families.
22. Any related conditions that, in the opinion of the study physician, could be a hindrance to participating in the trial.

4.3. Criteria for subject exclusion

Subjects will be excluded from the study in the following instances:

1. Inclusion of a volunteer not meeting the inclusion criteria and meeting any exclusion criteria, but at 2 visits maximum.
2. Infecting with SARS-CoV-2 determined with the PCR method.
3. Gross violation of the Protocol. The Volunteer did not comply with the Protocol requirements, and during participation in the study, the volunteer developed one of the exclusion criteria, and further participation poses a risk for the volunteer's health.

4. Following up the volunteer is impossible. The volunteer did not appear for the next study visit, and all attempts to reach out to them failed. The attempts to get in contact with the volunteer have to be documented.
5. Voluntary exit from the study. A volunteer has the right to refuse to participate in the study at any moment without giving any reason. The cause of withdrawal, if provided by the volunteer, has to be recorded in CRF.
6. The investigator decided that it was necessary to exclude the volunteer from the study in the best interests of the volunteer.
7. The need for a concomitant therapy involving the drugs not permitted for use in this study.

Other mentioned below violations of the Protocol do not necessarily lead to volunteer exclusion from the study. The Sponsor has to take decisions individually in each case:

1. failure to carry out any planned observation procedure during one or more visits;
2. Increase in the interval between visits in the excess of the visit schedule;
3. development of any concomitant disease or condition leading to difficulties during any obligatory study procedure, which, in the investigator's opinion, could affect objectivity of results, when assessing the condition of a study subject;
4. adverse events developed during participation in the study. The volunteers removed from the study due to AEs development will receive the necessary therapy in accordance with the existing clinical standard, and they have to be observed till recuperation or stabilization, or until acceptable explanation of the reason for development of such an event is found. All the information on AE outcome, related to this issue, shall be documented in CFR.

There is no provision for substitution of the removed subjects.

Reasons leading to exclusion of a subject from the study should be documented.

In accordance with the informed consent and provisions of the Declaration of Helsinki, a volunteer has the right to discontinue their participation in the clinical trial at any time. Each volunteer can discontinue their participation in the clinical trial ahead of schedule without giving any reason for their decision. However, when possible, the volunteer has to discuss their decision with the investigator. The causes, as well as the date and time of volunteer's withdrawal from the clinical trial shall be documented in CRF. All information on volunteers who decided to withdraw from the study shall be fully recorded in CFR till the moment of withdrawal.

4.4. Withdrawal procedures

1. Each subject will be informed of their right to withdraw from the study at any time and for any reason.
2. Positive urine drug test or positive alcohol test before hospitalization will cause removal from the study.
3. investigator may remove a subject from the study at any time, if, in the investigator's opinion, further participation in the study adversely affects the subject's health, or the subject is not cooperative enough.
4. The reasons for removal of a subject from the study will be recorded in the CFR study completion form. The investigator will inform the sponsor in writing of early termination of the subject's participation in the study for any reason.
5. After withdrawal from the study, upon investigator's decision and with the consent of the subject, the subject's blood sample may be taken for clinical blood analysis, biochemical blood assay, urine test may be made, and physical examination may be carried out.
6. If participation in the study is terminated due to an adverse event, which, in the

investigator's opinion, may be related to administration of the study products, LEC (Ethics Committee) will be notified accordingly. Any serious adverse drug reaction has to be reported to the Sponsor within 24 hours and to LEC in accordance with its procedures.

5. Use of the study drug

5.1. Study procedures. Visits description

Total expected study duration for each subject is about 187 days with the following time allocation:

– Screening: day -7 – day -1;
– Drug administration: day 1;
– Observation day 180 Table 5. List of tests

Table 5. List of tests

serologic tests	for HIV, hepatitis B and C, and syphilis
Tests for	alcohol
	pregnancy test (for women with preserved reproductive potential)
	narcotics
COVID-2019 diagnostics	SARS-CoV-2 identification using the PCR method (swab)
	IgM and IgG to SARS-CoV-2
CBC	complete blood count with absolute and relative WBC count and differential, ESR
BBA	ALT, AST, total protein, bilirubin, total cholesterol, LDH, ALP, Quick's value (prothrombin ratio), glucose, urea, creatinine
Immunological status	WBC phagocytic activity, T and B cell populations (count and relative level of CD3, CD4, CD8, CD16, CD19, CD4/8), Ig classes: IgM, IgG, IgA, IgE
Urine test	General urinalysis with sediment microcopy, narcotics urine test, pregnancy test (for women of reproductive potential)
Immunogenicity parameters	Humoral immunity
	Serum neutralizing activity
	Cell immunity

Procedure for signing of the Volunteer's Informed Consent

The Volunteer's Informed Consent has to be obtained before the volunteer joins the study, prior to any scoring procedures under the Protocol for this study. In the primary documentation, the investigator has to specify the time and the date of the Volunteer's Informed Consent signing for participation in the study according to this Protocol.

Informed consent to participate in the study must be signed by the volunteer personally.

The volunteer should be given sufficient time to familiarize themselves with information on the upcoming clinical trial, and the responsible investigator should answer all questions regarding the conduct of the study.

The volunteer confirms their consent to participate in the clinical trial by signing 2 copies of the Volunteer Information Sheet and Volunteer's Informed Consent to Participate in the clinical trial

of Medicinal Products under this Protocol, then this document is signed by the responsible investigator. One copy of the Informed Consent is handed over to the volunteer, and the second copy is saved in the files of the research center. The primary documentation records the date and time of the Informed Consent signing. After the Informed Consent signing, a screening number is assigned to the volunteer.

No procedures are carried out with the volunteer until the signing of the Informed Consent

The information of the fact of the Informed Consent obtaining with indication of the date and time must be specified in the primary medical documentation of the volunteer.

The volunteer must be informed about the study in accordance with his ability to understand this information, for which a separate Informed Consent will be provided to the volunteer for review.

Procedure for assigning a screening number to a volunteer

After receiving the Informed Consent and assigning a screening number to the volunteer, screening examination takes place including collection and analysis of the following data:

- collection of demographic data: (sex, age, ethnic origin);
- registration of the volunteer's complaints;
- health history taking;
- history taking on concomitant diseases or data on other significant conditions, surgeries, allergic reactions;
- interview on prior therapy and concomitant medications taken at the time of screening;
- clinical examination (objective examination) with a clinical diagnosis;
- laboratory and instrumental methods of examination. Identification number will have the following form:

06LIGHT- XXX

Where

06LIGHT – is a brief code of the Study Protocol;

XXX is the sequence number of the volunteer in the clinical center.

The individual identification code assigned to the patient may not be changed. The Investigator keeps a separate log for identification of numbers, last names, addresses, phone numbers, and medical documentation numbers (if any). The Investigator keeps in strict confidentiality the documents not intended to be transferred to the Sponsor, including the signed Forms of Informed Consent and the Identification Sheet of the Study Subjects. The 11-digit number assigned to the volunteer will be used to further identify the volunteer. If a volunteer decides to stop their participation in the study or does not complete the study for any reason, their number will not be used for another volunteer.

The information of assigning of an identification number should be recorded in the primary documentation and the volunteer screening log.

Documenting screening failure

The investigator is responsible for all volunteers who sign an Informed Consent.

Volunteers, who sign Informed Consent but do not meet the inclusion / exclusion criteria as a result of screening, are deemed screening failure. The reason why the volunteer may not be included in the study should be indicated in the primary documentation. Screening numbers assigned to volunteers, who proved to be screening failure, may not be reused.

Additional examination, repeated tests and re-screening

In case of ambiguous or doubtful results of laboratory tests obtaining at screening, re-analysis (re-test) may be carried out based on the decision of the investigator or in agreement with the sponsor or its representative.

Volunteers, who do not meet the inclusion / exclusion criteria due to recoverable conditions, may

be re-screened in agreement with the sponsor or its representative.
If the research physician considers it necessary, the volunteer may undergo additional diagnostic procedures using instrumental and laboratory research methods that are not provided for in this Research Protocol to make a decision on compliance with the inclusion / non-inclusion criteria.
In case of non-compliance with the inclusion criteria or if there are non-inclusion criteria for volunteers who may be included in the study in the investigator's opinion, it is necessary to specify this in the primary documentation, then fill out the Registration of Violations / Deviations from the Protocol Form and send it by fax / email to the clinical trials Department of the N. F. Gamaleya Federal Research Center for Epidemiology & Microbiology of the Ministry of Health of the Russian Federation. Then an authorized employee of the Sponsor must be contacted to obtain approval for inclusion of such volunteer in the study.
If the drug developer decides that the volunteer is not eligible for inclusion in the study, the investigator should record the screening failure in the primary documentation.
The researcher must ensure that the anonymity of the volunteers is respected. In the CRF and other documents, volunteers should not be identified by their first and last names, but only by the assigned identification codes.
The Investigator should keep a separate log/ register for identification codes, last names, addresses, phone numbers, and medical documentation numbers (if any).

At visit B0 (screening and grouping), the investigator is required to provide the volunteer with information about the study (Volunteer Information Sheet). In a conversation with a volunteer at a level comprehensible to the latter, the following points should be discussed:

- the research is experimental in nature
- the research purpose
- features (pharmacological group, mechanism of action, indications and contraindications for use, possible adverse events, route of administration and dose) of the medicinal product to be studied;
- availability of permission to conduct the study;
- research procedures, including the conditions for blood sampling and the time of the volunteer arrival to the clinical site;
- volunteer's responsibilities;
- the conditions, in which the volunteer will be during the study;
- day regimen, timing of food ingestion, restrictions on medications, use of adequate methods of contraception (including those for female partners of research participants);
- the absence from a medical point of view of any other benefit, except for examination and obtaining information (within the scope stipulated by the Protocol) about the state of their health;
- the possibility of adverse reactions and their manifestations;
- the possibility of providing medical assistance during the study;
- conditions of insurance and remuneration;
- the possibility to voluntarily withdraw from the study;
- confidentiality of information about the volunteer: the name and other personal information will be kept confidential and may be disclosed only to the extent permitted by law and will not be indicated in publications;
- by signing the Informed Consent Form for participation in the study, the volunteer gives their permission to the monitor, auditor, representatives of the IEC and regulatory

authorities for direct access to the original medical records to verify the procedures and data of the clinical trial without violating the confidentiality of their data;
- if new information becomes available that may affect the volunteer's desire to continue participating in the study, it will be promptly provided to them together with any additional information about the study and participants' rights, contact information of individuals and organizations that can be contacted for additional information and in case of a change in health;
- possible circumstances and/or reasons why the participation of a volunteer in the study may be terminated;
- the estimated duration of the study and the number of volunteers to be included in the study.

The volunteer should have ample time to reflect on their participation. The volunteer should be given the opportunity to ask additional questions. The volunteer's consent to participate in the study must be confirmed by the signed Informed Consent Form. The informed consent form must be signed and dated in duplicate by both the volunteer and the investigator / co-investigator. One copy of the signed Form must be provided to the volunteer, and the other copy must be kept together with the primary documentation at the research center.

5.1.1. Schedule of visits for Volunteers

Visit B0

A screening period in the study begins from signing of the informed consent and lasts for no more than 7 days until the volunteer is included in the study. No procedures related to the study are allowed with regard to the subject until the informed consent form is signed.
During Visit 0, the volunteers will be assessed for inclusion and exclusion criteria. The potentially eligible volunteers will be offered to participate in the clinical trial.
During the screening visit, the following procedures will be carried out:

- Signing by the study subject of an informed consent form and issuance of an insurance policy;
- Collection of historical, demographic, and anthropometric data:
    - comorbidities and previous diseases, concomitant therapy, collection of information on allergies, contacts with COVID-19 patients, previous vaccinations/ immunizations, blood donation.
    - sex, race, age.
    - the volunteer’s weight and height were measured without shoes, body mass index (BMI) was measured using the formula: BMI=weight/height^2(kg/m^2), where weight is in kg and height in meters;
- Assessing vitals: heart rate, respiratory rate, systolic and diastolic blood pressure, body temperature. Heart rate and blood pressure should be measured after a volunteer has 5 minutes of rest sitting;
- Assessing exposure risk to infection category:
    - A high risk means that the job involves interactions with the patients having the confirmed COVID-19 diagnosis;

- A medium risk means a professional contact with many people (general medical officers, social services employees, shop assistants, etc.);
- A lower risk means that there are no additional risks related to professional activities;

- Physical examination that includes assessing the following body parameters: condition of skin, locomotive system, gastrointestinal tract, respiratory organs, cardiovascular system, urogenital system. Examination of lymph nodes (submandibular, cervical, cubital, inguinal lymph nodes) by touch should include assessment of their size, consistency, tenderness, mobility, matting with each other and with surrounding tissues and skin. Auscultation data should include description of breathing pattern (vesicular breathing, rattling);
- Collection of data on comorbidities and medical conditions. Concomitant diseases include problems found during physical or instrumental examination, which will be described in the study subject's source documents and in an electronic case report form, including the study subjects' medical history data. When describing a concomitant disease or medical condition, the date when such condition started and the therapy (if any) conducted for this reason should be indicated;
- Collection of data on the previous therapy: it should be found out whether a study subject took any drugs, including vitamins and biologically active food supplements, including if drug taking was finished at the screening visit or within 30 days prior to the inclusion in the study. At the same time, the source documents should show drug's international non-proprietary name (INN), indications for use, daily dose, drug taking frequency and period.
- HIV, syphilis, hepatitis B and C tests;
- Biomaterial sampling for clinical urine analysis and complete blood count, as well as for assessment of biochemical parameters.
- COVID-19 PCR testing. A swab will be taken and tested using the method accepted by the investigation site. No food intake, drinking, brushing the teeth, mouth/throat rinsing, gum chewing, or smoking is allowed within 3–4 hours prior to taking oropharyngeal (guttur) swabs. No using nasal drops/sprays or nasal rinsing is allowed within 3–4 hours prior to taking nasal swabs;
- All study subjects will be taken blood samples from a vein for a SARS-CoV-2 IgM and IgG antibody test at the screening stage. Venous blood will be drawn and tested using the method accepted by the investigation site. Blood should be collected in the morning in fasting state (drinking is as usual; overeating should be avoided the day before);
- Pregnancy test (done for women with preserved reproductive potential);
- Narcotics or psychostimulants testing. Urine should be collected in a designated container in the morning after external genital organs have been washed. Urine sample should be handed over to the investigation site's laboratory within 4 hours upon collecting;
- Breath test for alcohol;

Visit B1 Day 1

The study drug will be administered on an outpatient basis.

The subjects will be asked about any changes in their health condition or taking any medicines after the screening day.

A swab will be taken for SARS-CoV-2 test with the PCR method.

Urine sample will be taken for:

– a drug test

– pregnancy test (women with preserved reproductive potential).

– common urine analysis with microscopic sediment examination (specific gravity, pH, transparency, protein, glucose, ketones, microscopy: erythrocytes, leucocytes, epithelium, bacteria, blennuria, salts).

Exhaled air will be tested for alcohol.

Positive result of the urine test for drugs or of the exhaled air test for alcohol will result in removing the subject from further participation in the study.

The subjects that were allowed to take part in the study will undergo physical examination; health workers will record their vital signs (heart rate, blood pressure, breathing rate, and body temperature).

Those that were allowed for drug administration (volunteers without exception criteria detected: no pregnancy, no drug traces in urine, negative test for alcohol, etc.) will give blood samples for tests.

Subjects´ blood samples will be taken for:

– complete blood count (CBC) with absolute and relative WBC count and differential, erythrocyte sedimentation rate, and biochemical blood assay (BBA) – ALT, AST, protein, bilirubin, total cholesterol, LDH, ALP, Quick's value (prothrombin ratio), glucose, urea, creatinine.

– immunological analysis
  - Population of T and B cells (quantity and relative content: CD3, CD4, CD8, CD16, CD19, CD4/8)
  - activity of leucocytes (phagocytic index)
  - definition of main classes of immunoglobulins: IgM, IgG, IgA, IgE

– study of humoral immunity

– study of serum neutralizing activity

– study of cellular immunity

– PCR test swab (before the shot!)

Drug administration: an intramuscular injection will be made to subjects. Immediately after the injection and in 0.5h local and systemic reactions will be evaluated.

The subject will be requested to evaluate the discomfort experienced from the injection using a VAS scale (see Appendix 2).

Diet standardization, constraints

The study drug will be administered under fasting condition — the volunteer does not take food for 10 hours before administration of the study drug.

After injection of the drug the liquid intake regime as well as the motion activity should be unrestricted, except heavy physical loads. Food could be consumed at least 30 minutes after the drug has been administered.

The volunteer must abstain from intensive physical exercises and combat sports for 24 hours until

the start of the study and during the whole period of the study.
The volunteer must not take any medicines without agreement by the study physician (including botanical medicines and nutritional supplements).
The volunteers are to use adequate contraception during the whole period of their participation in the study.
Adverse events (AE) will be recorded. The healthcare workers will record any changes in concomitant therapy and health conditions of the volunteer.

Visit B2. Day 10

A swab will be taken for SARS-CoV-2 test with the PCR method.

The subjects will undergo physical examination, healthcare workers will check their vital signs, the volunteer will be asked to evaluate their health condition regarding constitutional reactions.
Administration site will be checked for any local reaction during physical examination (hyperemia in the drug administration site, edema, evaluation of regional lymph nodes).
Volunteer's diary will be checked.
Blood samples will be taken to

- study humoral immunity
- study cellular immunity

Visit B3. Day 28

The subjects will undergo physical examination, healthcare workers will check their vital signs, the volunteer will be asked to evaluate their health condition regarding constitutional reactions.
The study participants will be subjected to ECG procedure.
Administration site will be checked for any local reaction during physical examination (hyperemia in the drug administration site, edema, evaluation of regional lymph nodes).

A swab will be taken for SARS-CoV-2 test with the PCR method

The volunteers will give urine samples for common urine tests with microscopic sediment examination (specific gravity, pH, transparency, protein, glucose, ketones, microscopy: erythrocytes, leucocytes, epithelium, bacteria, blennuria, salts).
Blood samples will be taken for:

- complete blood count (CBC) with absolute and relative WBC count and differential, erythrocyte sedimentation rate, and biochemical blood assay (BBA) – ALT, AST, protein, bilirubin, total cholesterol, LDH, ALP, Quick's value (prothrombin ratio), glucose, urea, creatinine.
- immunological analysis
    - Population of T and B cells (quantity and relative content: CD3, CD4, CD8, CD16, CD19, CD4/8)
    - activity of leucocytes (phagocytic index)
    - definition of main classes of immunoglobulins: IgM, IgG, IgA, IgE
- study humoral immunity
- study of serum neutralizing activity

Adverse events (AE) will be recorded. The healthcare workers will record any changes in concomitant therapy and health conditions of the volunteer since the previous visit.
Volunteer's diary will be checked. Evaluation for any exclusion criteria.

Visit B4. Day 42

The subjects will undergo physical examination, healthcare workers will check their vital signs, the volunteer will be asked to evaluate their health condition regarding constitutional reactions.
Administration site will be checked for any local reaction during physical examination (hyperemia in the drug administration site, edema, evaluation of regional lymph nodes).
Blood samples will be taken for:

– immunological analysis
  - Population of T and B cells (quantity and relative content: CD3, CD4, CD8, CD16, CD19, CD4/8)
  - activity of leucocytes (phagocytic index)
  - definition of main classes of immunoglobulins: IgM, IgG, IgA, IgE
– study humoral immunity.
– study serum neutralizing activity.

Adverse events (AE) will be recorded. The healthcare workers will record any changes in concomitant therapy and health conditions of the volunteer since the previous visit. Evaluation for any exclusion criteria
Volunteer's diary will be checked.

Visit B5. Day 90
Interview with the volunteer on past diseases.
Blood sampling will be done for a humoral immunity test.

Visit B6. Day 120 Telephone contact

Visit B7. Day 150 Telephone contact

Visit B8. Day 180
Interview with the volunteer on past diseases.
Blood sampling for a humoral immunity test will be taken. End of study

5.1.2. Unscheduled visits

By decision of the study physician, the subjects may be invited to an unscheduled visit at any time in the course of the clinical trial for safety reasons, in case of any repeated examination or procedure required. During unscheduled visits, the investigator may perform any required procedures, including laboratory and instrumental examinations, not stipulated by this Study Protocol. Any unscheduled visits must be recorded in the primary documentation and in CRF. Such unscheduled visits should not affect the schedule of scheduled visits stipulated by this clinical trial Protocol.
In case of emergence of respiratory diseases, it is recommended to run a differential diagnosis to exclude COVID-19.

5.2. Parameters to be assessed during the trial

For the entire period of hospital observation, information on safety will be collected using the following parameters:

– Development, intensity of, and relation to the study drugs of all the adverse events (AEs) – for the whole period of the study;

– Frequency and intensity of local signs and symptoms, relation to general signs and symptoms of the study drug, after administration of the study drugs;
– Data obtained from physical, laboratory, and instrumental examinations;
– Dose dependence of adverse events.

The immunogenicity data will be collected using the following parameters:
– Seroconversion rate;
– Specific antibody level;
– T-cell immunity level
– Level of neutralizing activity in the blood serum.

5.3. Drugs / therapy types that are allowed (including emergent therapy) or not allowed before and/or during the study

5.3.1. Permitted medical drugs

During this study, it is allowed to apply fever reducers (NSAIDs) and antihistamines for stopping adverse events occurred in a volunteer.

Drugs for adverse events treatment and emergency therapy (if necessary) shall be prescribed in accordance with the approved Medical Application Guidelines and the pharmacotherapeutic group as per anatomical, therapeutic, and chemical classification recommended by the World Health Organization, subject to the drugs' method of administration and application. The schedule of other drugs application shall be selected according to the recommendations for use and dosages of such drugs. Such drugs shall be approved for use in the Russian Federation.

All the therapy will be recorded in CRF and primary documentation of the volunteer.

During the observation following drug administration, the volunteers are required to inform the investigator about any drug intake during the study. Administering any concomitant drugs should be recorded in the Case Report Form, which specifies the active substance, dosage, timing, and reasons for using the drug.

The medical institution that performs the clinical trial should have all the necessary first-aid equipment. If first aid is required, all the measures taken and the drugs necessary for use must be recorded in the primary documentation and CRF.

5.3.2. Forbidden drugs and procedures

During this study it is prohibited to use any immunotropic drugs (immunity suppressors, immunomodulators) and steroids (except for corticosteroids for emergency treatment and contraceptives or drugs used as hormone replacement therapy for menopause) and/or immunoglobulins or other blood products that have not been completed 30 days before enrollment. No other vaccination is allowed 30 days before and 30 days after inclusion in the study. No transfusion of blood and its components, plasma exchange and donation are allowed throughout the study. No use of immunoglobulins, monoclonal antibodies, interferons, colony-stimulating, and growth factors is allowed. In case of a need for therapy involving the above drugs and procedures, the volunteer should be removed from the study.

If there is a need for administering such drugs to a volunteer for medical reasons, the volunteer will be removed from the study and followed up.

No use of phytopreparations and dietary supplements throughout the study is allowed.

No other vaccination against COVID-19, including as a participant of other clinical trials, is allowed.

5.4. Control measures to observe compliance with procedures by the subjects

During the course of this study, the subject is required to observe the schedule prescribed by the Protocol as well as to observe the rules of preparation for the study including the observation of recommendations for taking meals (it is important to limit consumption of fats 3 days before each visit in order to ensure high quality of biological material for laboratory research), abstaining from alcohol and absence of concomitant therapy. Due to the fact that all the specified procedures should be described in primary documentation and CFR, it is the study physician who controls how volunteers observe the prescribed recommendations.

The Protocol includes the following allowed deviations from terms of procedures that do not require documenting as deviations from the Protocol:

Table 6. Terms of procedures that do not require documenting as deviations from the Protocol

visit/inspection, biological sampling	admissible deviation
day 1 observation in 30 min after drug administration	10 min
day 10	day 1
day 28	day 1
day 42	2 days
day 90, 120	7 days
day 150, 180	14 days

6. Safety assessment

Safety assessment will be based on recording adverse events in the course of the study as compared to the background values (before drug administration) for each volunteer and at the second stage as compared to the background values.

Safety assessment will be performed by the study physician.

Safety and reactogenicity assessment will be based on recording adverse events in the course of the study. Changes in the instrumental (ECG) and laboratory parameters (complete blood count and biochemical blood assay, common urine test), dynamics of vitals (blood pressure, heart rate, body temperature) will be assessed as well.

Safety of the study drug will be assessed throughout the study by occurrence and development of the adverse events (AE) to be recorded ultimately based on complaints of the volunteers as well as by the physical examination data and the laboratory and instrumental examination results. All the facts of applications for medical assistance will be recorded in the observation cards during the whole period of observation of the vaccinated volunteers indicating the diagnosis. All the volunteers participating in this study will be included in the safety data list. All adverse events will be recorded and shown as tables, based on their severity and treatment given. In case the volunteers are early removed from the study, the sponsor will be informed of the reason for and date of such removal from the study.

If applicable, a share of the volunteers that are early removed from the study, reason for early removal and time until such removal as well as a share of the volunteers that are early removed from the study due to the occurrence of AE and the time of their removal will be also assessed.

Selection of parameters and safety assessment timelines for the laboratory test data was conditional upon the results of the in-house pre-clinical trials and clinical trials for the study drug and vaccines

on the similar process platforms (for prevention of Ebola fever, influenza, MERS).
Reactogenicity for the vaccine is assessed based on local (drug administration site) and general (bodily reactions to product administration) reactions. Local reactions will be assessed throughout the follow-up period, on vaccination day local reaction shall be registered 2-3 min and 30 min after injection, then local reactions registration will be done at clinical exams during the follow-up period in accordance with the visit schedule and that of study procedures.
In case an adverse event is not completed by the time of the visit, it is incomplete and at the next visit the investigator should inquire the volunteer of that adverse event (it has resolved, the volunteer's condition has improved/deteriorated).
When recording the adverse event outcome, the investigator will specify whether the event has resolved, the volunteer's condition has improved/deteriorated, any complications, other diseases, or events have appeared resulting from the initial adverse event.

6.1. Definitions

Adverse event (AE) is the onset of (or worsening of any already existing) adverse sign(s), symptom(s), or medical condition(s) after administration of the study drug.
AE, which occur, or get worse, should be registered in separate electronic case report form (e-CRF). AE, already existing at the time of the informed consent, should be specified in the Concomitant Diseases section of the e-CRF. AE should be observed within at least 30 days after the subject takes the last dose of any study drug.

AE should be described with specification of the diagnosis in all instances and mention of separate signs and symptoms should be avoided. If it is impossible to establish a diagnosis, every sign and symptom should be specified as separate AE.

Adverse events will be assessed and classified in accordance with the common terminology criteria used for adverse events in MedDRA classification.

If it is impossible to assess AE according to the MedDRA classification, then five-level AE severity score should be used, which provides for moderate, medium, significant degree, life-threatening condition and death related to AE corresponding to grades 1 to 5, accordingly. Information about death of subjects (both related and not related to AE) will be collected in the death reporting form. The possibility of AE development should be taken into account during the interview with the subject, screening procedures after signing the informed consent and at every visit during the study. AE can also be detected during analysis of complaints of the subject during screening or other doctor's visits as well as during physical examination, laboratory or instrumental observations.
Each AE should be assessed as much as possible to determine:

- AE severity;
- Its duration (start and end date);
- Assessment of the possible AE connection with the study treatment: No/Yes;
- Measures taken in relation to the treatment under the protocol (no changes, dose modification, treatment suspended, stopped, unknown, not applicable);
- Whether drug treatment or other treatment of AE was assigned (absence of the associated drug/drug-free treatment or presence of the associated drug/drug-free treatment);

- Whether AE is serious and based on which criteria taking into account the SAE criteria specified in section 8.2.1

If AE course is worsening, information about such AE should be repeatedly entered in the e-CRF with specification of the date of worsening, if such worsening is associated with the toxicity. The e-CRF should also include information about improvement in severity of AE (grade 3–4), if intensity of such AE decreased. If drug or other treatment was used when AE was detected, information about such treatment should be specified in the e-CRF.
The study physician should observe the subject from the moment of AE detection to its elimination or stabilization. The condition of the subject should be assessed at each visit or more frequently, if necessary. In this case, any changes in the AE severity, possible AE connection with taking the study drug, interferences which may be necessary for treatment of the subject as well as AE outcome should be assessed.

6.2. Adverse events of special interest

Investigators are particularly interested in whether ADE effect is likely to develop or not. Antibody-dependent enhancement is indicated in case of vaccination with split product vaccines. Currently, there are no reports on development of ADE effect in case of immunization with vector vaccines. There are no premonitory markers indicating development of such complications in a human. However, during this study, the disease incidence in the study participants should be monitored and the disease severity in the immunized volunteers should be analyzed.

6.3. Serious adverse events

6.3.1. Definitions

A serious adverse event is any AE matching any criterion listed below:

- It caused death or is life-threatening;
- It resulted in permanent disability / work incapacity;
- Birth of a child with congenital abnormalities;
- It is medically significant, i.e. it is an event threatening the subject or requiring surgical or therapeutic intervention in order to prevent one of the events specified above;
- It resulted in hospital admission of the subject or in prolongation of the current hospital admission;

It should be noted that hospital admission of the subject due to the reasons listed below **should not** be considered as SAE:

- Hospital admission for the subject that is not related with the worsening of his/her condition;
- Planned inpatient treatment because of concomitant diseases existing before enrollment into the study;

SAEs are recorded upon signing the IC form by the subject.

6.3.2. Procedure for reporting of occurrence of serious adverse events

In order to ensure safety of the subject, each SAE, irrespective of a supposed causal relationship with the treatment with the study drugs, which occurred after signing by the subject of the informed consent form and within 30 days after treatment end, should be reported to the study organizer

within 24 hours from the moment when such event became known.

Any additional information about SAE related to its complication, course, occurrence of repeated symptoms, relapses should be additionally reported to the study organizer within 24 hours from the moment when the study physician learned such information. If the SAE occurred during the other time interval or is considered as non-related to the previous SAE, occurrence of such SAE should be reported separately. Any SAE occurred more than 30 days after the treatment end should be reported to the study organizer only if a causal relationship with the treatment with the study drugs is suspected.

The information about occurrence of all SAEs should recorded to a special form of SAEs occurrence. All sections of this form should be completed to ensure the report completeness. The study physician has to assess a possibility of a relation between the SAE and treatment with each study drug, to complete the form of report on SAE occurrence and send this form to the study organizer within 24 hours. A detailed instruction on the procedure to report on SAE occurrence will be located in the relevant section of the investigator file. Any additional information about SAE should be reported to the study organizer in the format equal to the format of primary information about SAE occurrence.

If the SAE is not described in the study brochure or in the instruction for medical application of MP and there is a possibility that occurrence of SAE is related to the treatment with the study drugs, the study organizer may request any additional information from the study physician to report the SAE to the regulatory authorities.

Assessment of the laboratory parameters will depend on the normal reference values provided by the research center laboratory for each parameter. Laboratory deviations should be classified by severity level, depending on presence and intensity of clinical signs or symptoms related to these laboratory deviations. All the laboratory parameters received in the course of the study required by this Protocol and any other clinical circumstances should be checked. All the abnormal changes resulting in the volunteer pathway, e.g. need for prescription of additional drugs or consultations of a medical specialist, or clinically relevant, in the investigator's opinion, should be recorded as an adverse event/serious adverse event. Clinical relevance of changes in the laboratory parameters should be assessed by decision of the study physician.

Safety parameters will be recorded by the study physician in the course of the study, starting from the time of intake of the first dose of the study drug by the volunteer.

The investigator will assess presence of adverse events in the volunteer at each visit based on the results of the examination and the volunteer's complaints.
By frequency, taking into account the classification[4] accepted by WHO, adverse reactions are classified as:

- Very common — 1/10 prescriptions (≥10%);
- Common — 1/100 prescriptions (≥1%, but <10%);
- Uncommon — 1/1,000 prescriptions (≥0.1%, but <1%);
- Rare — 1/10,000 prescriptions (≥0.01%, but <0.1%);

[4]Guidelines for Preparing Core Clinical Safety Information on Drugs – Report of CIOMS Working Group III. Geneva, WHO, 1995, Chapter 5, GoodSafetyInformationPractices

– Very rare — less than 1/10,000 prescriptions (<0.01%);

Table 7. Relevance degrees of cause-and-effect relation (Guideline for Expert Examination of Drugs. Volume III. – M.: Polygraph Plus, 2014. – 343 p.).

Reliability	**Reliability determining**
1. Definite (Associated – for clinical trial)	Clinical signs of AE associated with vaccine administration by time, cannot be explained by a disease, application of other MDs or chemicals, reappear with repeated vaccine administration (revaccination)
2. Probable (Probably related — for clinical trial)	Clinical AE signs associated with vaccine administration by time, unlikely related to a disease or application of other MDs
3. Possible (Possibly associated – for clinical trial)	AE signs associated with vaccine administration in terms of time, can be explained by a disease or application of other MDs
4. Unlikely	AE signs not matching the time of drug administration; cause-and-effect relation is unlikely, can be explained by the underlying disease or application of other MDs or chemicals
5. Conditional	Signs classified as AEs not matching by time, can be explained by the underlying disease or application of other MDs
6. Unclassified (Unknown – for clinical trial)	Report on a suspected AE cannot be assessed, as the information is insufficient or inconsistent

To evaluate the association with the study drug an investigator may use the Naranjo algorithm.

The following factors should be taken into consideration:

– association with study drug/reference drug use by time. The event should occur after administration of the study drug. The time from exposure to the study drug till the event shall be assessed in the clinical context of the event.
– underlying, coexisting, intercurrent diseases. Each adverse event report should be assessed in the context of the history, course, and treatment of the underlying and any other disease the volunteer may have.
– concomitant drug. Any other drugs or treatment received by the volunteer should be studied in order to understand whether they might be the cause of the adverse event.
– known nature of the reaction for the study drug class. Clinical and/or preclinical data can show that the certain reaction is probably caused by that drug class.
– exposure to physical and/or psychological stress. Stress exposure may result in the adverse changes in the recipient and provide a logical and more suitable explanation for the event.
– pharmacological and pharmacokinetic properties of the study drug. Known pharmacological properties (absorption, distribution, metabolism, and excretion) of the study drug shall be taken into consideration.

6.4. Methods and timelines of assessment, recording and analysis of safety parameters

All information on adverse events should be recorded in primary documentation and then in CRF.

Data to be recorded includes: event description, starting and ending dates, outcome, intensity degree, severity category, measures taken on the study drug, required treatment, and relation to the study drug.

Safety of the study drug will be assessed throughout the study by occurrence and development of the adverse events (AE) to be recorded ultimately based on complaints of the volunteers as well as by the physical examination data and the laboratory and instrumental examination results. Population for safety assessment will include all volunteers that took the drug.

Painfulness at the administration site will be assessed using the VAS (Appendix 2).

All the facts of applications for medical assistance will be recorded in the observation cards during the whole period of observation of the vaccinated persons indicating the diagnosis. All the volunteers participating in this study will be included in the safety data list. All adverse events will be recorded and shown as tables, based on their severity and treatment given. In case the volunteers are early removed from the study, the sponsor will be informed of the reason for and date of such removal from the study.

If applicable, a share of the volunteers that are early removed from the study, reason for early removal and time until such removal as well as a share of the volunteers that are early removed from the study due to the occurrence of AE and the time of their removal will be also assessed.

Responsibility for medical assistance to the study subjects in case of an AE/SAE will be borne by the investigator.

Responsibility for SAE reporting will be borne by the center investigators assigned with filling in the SAE reports for the sponsor during the study. The investigators will be responsible for filling in the initial and subsequent SAE reports and sending them to the study sponsor.

When providing an initial urgent report on the detected serious unexpected adverse reaction within the prescribed period, the minimum information includes:

- indication to a suspected study drug, identification code of the study subject with the adverse reaction developed;
- description of the adverse reaction or its outcome, which are determined as serious and unexpected and for which a cause-and-effect relation with taking the study drug is supposed;
- cause-and-effect relation assessment result;
- source of information on the adverse reaction, identification number of the adverse reaction report assigned by the sponsor;
- study Protocol number.

In case the investigator is aware of a serious adverse event in the volunteer at a visit or by telephone call from the volunteer or their relatives, this event should be recorded in the primary documentation and reported within 24 hours from the time[5] the investigator is notified of this event to the pharmacovigilance officer in the development company.

Upon submitting the urgent report on the serious adverse event, the investigator should provide the sponsor with a detailed report with detailed information on the serious adverse event allowing the sponsor to evaluate whether it is necessary to review the benefit-risk profile of the clinical trial.

In case a SAE is detected, the investigator should report the SAE, regardless of whether they consider this SAE related to drug intake or not. Information on SAE detection should be submitted to the pharmacovigilance officer of Federal State Budgetary Institute N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation and to the clinical trial department of Federal State Budgetary Institute N. F. Gamaleya Research

[5]from the date of detection (or receipt of the information on detection) of serious adverse events

Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation by sending a filled-in form of notice of a side effect, adverse reaction, or no expected therapeutic effect of a medicine (Appendix No. 3) by fax/via e-mail within 24 hours after SAE detection.
Marina Yuryevna Chernukha, Head of Biological and Technical Control Department, Pharmacovigilance Officer. Tel.: +7 (499) 190-44-78, E-mail: chernukha@gamaleya.org.
The primary investigator of the center is responsible for notifying the Ethics Committee of the SAE occurred in accordance with the local committee's SOPs.
The investigator should inform the Ethics Committee of:
a) deviations from the Protocol or changes in the Protocol to remove a threat to the life and/or health of the clinical trial participant;
b) changes directly affecting the clinical trial and/or increasing the risk of participation in the clinical trial;
c) all adverse reactions that are both serious and unexpected;
d) new data that may indicate an increased risk for clinical trial participants or may affect the course of the clinical trial.

6.5. Requirements for reports, procedures for recording and reporting adverse events and intercurrent diseases

Information on all adverse events should be recorded in the volunteer's primary documentation and in the appropriate section of CRF.
SAE should be recorded from the time of inclusion in the study.
AE should be recorded after administration of the study drugs. AE severity and AE cause-and-effect relation to the vaccination should be assessed by the study physician.
All the above safety parameters will be recorded and reported by the investigators as adverse events after intake of the first dose of the study drug by the volunteer and until completion of the study or the volunteer's removal from it.
The adverse event confirmed during the volunteer's visit should be recorded by the investigator in the volunteer's initial documentation and entered into the volunteer's CRF, including the following information:

- AE description;
- starting date of AE recording;
- ending date of AE recording;
- maximum degree, AE intensity;
- AE outcomes;
- AE relation to the study drug: whether the AE is caused by the study drug;
- actions with respect to the study drug;
- required AE correction with drugs.

In case an adverse event is not completed by the time of the visit, it is incomplete and at the next visit the investigator should inquire the volunteer of that adverse event (whether it has resolved, whether the volunteer's condition has improved/deteriorated).
In case of AE development, the actions taken with regard to application of the study drug should be documented using the following categories:

- drug administration terminated;
- drug administration continued in accordance with the scheme provided for by the protocol;
- unknown;
- not applicable (in case of the volunteer's death or if the therapy was completed before the event development).

When recording the adverse event outcome, the investigator will specify whether the event has resolved, the volunteer's condition has improved/deteriorated, any complications, other diseases, or events have appeared resulting from the initial adverse event. The medical outcome of the AE should be commented as follows:

– completed recovery/resolution;
– recovery/resolution in progress;
– no recovery/resolution;
– recovery/resolution with consequences;
– death (only if this outcome is probably related to the event);
– unknown.

If the AE outcomes are different from resolution or retention of the same condition, a new AE should be recorded in the CRF.

For adverse event description, uniform terminology is recommended to be used. For this purpose, the terms of the directories of the Automated Information System of Roszdravnadzor (Federal Service for Surveillance in Healthcare) (hereinafter the AIS of Roszdravnadzor) being the pharmacovigilance information resource, which are the Russian equivalents of the World Health Organization Adverse Reaction Terminology (WHO-ART), may be used. When describing adverse reactions, the specialists may also use the terms of the ICH medical terminology for regulatory purposes (MedDRA) translated by themselves.

The indications for application of the drug are recommended to be specified in accordance with the WHO International Classification of Diseases, 10th revision, introduced in the healthcare institutions of the Russian Federation by Order on Switching of Healthcare Bodies and Institutions of the Russian Federation to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision No. 170 of the Ministry of Health of Russia dated May 27, 1997.

In the Drug Therapy of AEs, only the drugs used to reverse the AE are to be specified. In addition, the starting and ending dates of the therapy must be specified. If the drugs are prescribed to be administered by intermittent doses, in the Daily Dose subsection
the drug administration scheme should be specified based on the daily dose, e.g. "50 mg every other day". If the medicinal drug is used as a single dose, the starting and ending dates of the therapy will be the same.

In the Non-drug Therapy section, the method (operation), the number of courses (if applicable) and the starting and ending dates of the therapy should be specified. In case any method is used on a single time basis, the recorded starting and ending dates of the therapy will be the same.

The investigator should provide the Ethics Committee of the Research Center (or any other Independent Ethics Committee controlling this study) with brief written reports on the course of the study on an annual basis or more frequently upon its request.

The investigator should immediately submit written reports to the development organization, the Ethics Committee, and, if required, to the healthcare institution on all the changes with a significant impact on the study and/or increasing the risk for the participants.

The investigator should notify the development organization of all the SAEs. The investigator should observe the applicable regulatory requirements to submission of reports on serious unexpected side effects to the regulatory bodies and the Ethics Committee.

In accordance with the requirements for the reporting and within the timelines determined by the Protocol, the investigator should notify the development organization of any negative events and/or abnormal changes in the laboratory parameters stipulated by the Protocol for assessment of safety and efficiency.

All the SAEs should be observed by the investigator until their resolution or stabilization. If, during the SAE observation, any additional information is obtained, it should be sent to Federal State Budgetary Institute N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation as an additional report.

In case a SAE is detected, the investigator should report the SAE, regardless of whether they consider this SAE related to drug intake or not. Information on SAE detection should be submitted to the pharmacovigilance officer of Federal State Budgetary Institute N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation and to the clinical study department of Federal State Budgetary Institute N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation by sending a filled-in form of notice of a side effect, adverse reaction, or no expected therapeutic effect of a medicine (Appendix No. 7) by fax/via e-mail within 24 hours after SAE detection.

Detection of a serious adverse event in the volunteer should be reported as soon as possible within 24 hours after the study physician is aware of it. The information on the SAE should be entered in SAE record form available in the corresponding section of the Investigator's File. The filled-in form should be sent by fax or its scanned copy should be sent to the following address: to the person responsible for clinical trial safety in the company, which will be specified in the Contact Information of the Study Sponsor section: Marina Yuryevna Chernukha, pharmacovigilance officer. Tel.: +7 (499) 190-44-78, E-mail: chernukha@gamaleya.org.

At the same time, the clinical center monitor should be notified of the SAE orally and the Local Ethics Committee of the clinical center should be notified of the same in writing. SAEs should be monitored for their subsequent development. Each improvement or deterioration of the volunteer's condition requires repeated reporting according to the same algorithm as described above bearing "Repeated" mark on the SAE report form. The SAE course should be monitored up to any SAE outcome (completion).

The contact telephones of the clinical trial department and e-mail of the pharmacovigilance officer of Federal State Budgetary Institute N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation will be available in the research center.

Urgent and subsequent reports should identify the volunteers only by their unique identification codes assigned to the volunteers of the clinical trial, but not by their last names, first names, and patronymics.

In case of hazard for life or health of a participant of the clinical trial, the investigator must inform thereof the head of the medical facility and the medicinal drug clinical trial organizer within 24 hours. A decision to temporarily stop the clinical trial should be taken by the head of the medical facility and/or the clinical trial organizer; a decision to terminate such study should be taken by the relevant federal executive authority.

6.6. Method and duration of follow-up of the participants after adverse event onset

In case of development of adverse events (any deviations considered by the study physician as clinically relevant) or serious adverse events, the subjects' condition will be observed along with the appropriate treatment until resolution of the situation or stabilization of the condition according to the clinical judgement of the primary investigator. All the information obtained in the course of observation will be recorded in the subject's CRF until full recovery of the subject or until the primary investigator's statement that the subject's condition is stable, there is no threat to his or her life and health or the subject does not need medical assistance any longer. Follow up data will be documented in CRF.

6.7. Safety data analysis

The safety data analysis will include all the subjects received the drug. The evaluated safety criteria include:

- AE development data,
- results of evaluating the indicators for vital functions,
- results of instrumental examinations,
- results of physical examination,
- clinical blood test, biochemical blood assay, and urine test results.

7. Efficacy assessment

7.1. Immunological efficacy (Immunogenicity) Assessment

Immunity strength after the study drug administration will be assessed by determining the antibodies titer and evaluating the antigen-specific cell-mediated immune response. Immunological efficacy assessment method was based on comparison with the values before the study drug administration.

7.2. List of efficiency parameters

Selecting these parameters was based on the results of in-house preclinical trials and available literature.

The following efficiency indicators will be assessed in groups:

a) Humoral immune response stress indicators:

- Seroconversion rate
- Geometric mean SARS-CoV-2 glycoprotein-specific antibody titers
- Neutralizing antibodies titers

b) Indicators of cell-mediated immune response stress:

- Percentage of proliferating T-cells after restimulation with the SARS-CoV-2 S glycoprotein
- Determination of the expression of interferon gamma during antigenic restimulation (at least 30 subjects)
- Determining lymphoproliferative response during antigen restimulation (at least 30 subjects)

According to the WHO recommendations, an anti-SARS-CoV-2 vaccine shall protect at least 70% of vaccinated volunteers from SARS-CoV-2 infection. If a vaccine's clinical efficacy cannot be demonstrated, clinical immunogenicity may be compared to preclinical immunological and protective efficacy study results.

Thus, when studying immunological efficiency, the following possible marker indicators will be identified:

- in human vaccination significantly increased glycoprotein-specific antibody titers with at least 70% seroconversion level shall be detected to be used as a primary endpoint;
- T-cell immunity level (particularly, IFNɣ production or lymphoproliferation) and blood serum neutralizing activity can be used as additional efficacy criteria (secondary endpoints).

Studies of the volunteers included glycoprotein-specific antibody titer, serum neutralizing activity, antigen-restimulated IFN-gamma expression level (at least 30 subjects), antigen restimulation lymphoproliferative response (at least 30 subjects).

Antibody titers in the vaccinated volunteers will be compared with those of patients with COVID-19 and convalescents to analyze the clinical efficiency provided the absence of morbidity history

in the vaccinated volunteers. A patient data selection comparable to that of the volunteers was used for comparative analysis.

7.3 Methods and timelines of assessment, recording and analysis of the efficiency parameters

Immunity strength after the study drug administration will be assessed by determining the specific antibodies titer, virus-neutralizing activity, and evaluating the antigen-specific cell-mediated immune response. Immunological efficacy assessment method was based on comparison with the values before the study drug administration.
Selection of immunogenicity parameters was determined by the results of in-house preclinical and clinical trials and the literature. Protectiveness of the vaccine is determined not only by the antibody titer assessment parameters (including the virus neutralizing reaction), but also the level of cytotoxic T-lymphocytes (T-cell immunity).
Titer evaluation is meaningful for assessment of convalescent plasma (not containing T-lymphocytes) for disease treatment. Currently, for COVID-19 treatment plasma with the titer of 1:80 is used (according to the recommendations of the FDA and own data obtained by FSBI N. F. Gamaleya National Research Center of Epidemiology and Microbiology, Ministry of Health of the Russian Federation, as a part of the work related to assessment of convalescent plasma used for COVID-19 treatment) to be diluted to the titer of 1:2 to 1:8 in the course of transfusion.

In addition, taking into consideration that the current COVID-19 epidemiological situation lasting for 5–6 months does not make it now possible to determine clear criteria of protectiveness (due to the short time and lack of a complete epidemiological data base, including data regarding the herd immunity). It is important to mention that in order to obtain maximum information on the vaccine immunogenicity, all the possible methodological approaches will be used in this protocol: identification of the specific antibody titer in the blood serum using the ELISA method, assessment of virus neutralizing activity, assessment of antigen-specific cell immune response (specific T-cell response).

The following parameters were selected as immunogenicity criteria:

- level of glycoprotein-specific antibodies,
- level of virus-neutralizing antibodies,
- humoral response,
- seroconversion rate,
- level of CD4+ and CD8+ cell proliferative activity,
- level of IFNγ expression with peripheral blood mononuclear cells.

Data classified as positive/negative will be analyzed as a response frequency for each analysis in the immunization group at each time when the assessment takes place. The continuous variables will be analyzed using the statistic study methods to determine efficiency of the vaccine and average values (geometric means for the titer of glycoprotein-specific antibodies and neutralizing antibodies and medians for the proliferating cell percentage and IFNγ concentration growth) setting 95% of the confidence intervals according to the Guidelines on Nonclinical Evaluation of Medicinal Products (Immunobiological Medicinal Products). Part two. – M.: Grif and K., 2012, 212 p. (Chapter 5, 5.2. General Regulations on clinical trials of Vaccines).
The key parameter is the titer of glycoprotein-specific antibodies. The levels of antibodies in the subjects before vaccination and on Days 21, 28, and 42 will be compared.
Presence of glycoprotein-specific antibodies in the immunized volunteers' serum samples will be

assessed using the enzyme-linked immunosorbent essay (ELISA) method. For this purpose, recombinant S glycoprotein of the SARS-CoV-2 virus sorbed to wells of 96-well plates for ELISA will be used. Based on the results of the analysis conducted the samples will be assessed as positive if the average optical density exceeds the average optical density before immunization by more than 2 times at the same dilution. The results will be presented in the form of a titer, i.e. the last dilution where the optical density of the sample meets the above-mentioned criteria.

Additional parameters are the titer of neutralizing antibodies, the percentage of proliferating T-lymphocytes after restimulation with SARS-CoV-2 glycoprotein, and IFNɣ concentration growth in the T-cell culture after restimulation with SARS-CoV-2 glycoprotein.

Presence of neutralizing antibodies will be studied with the use of cytopathic effect (50% tissue cytopathic dose) in the Vero cell culture *in vitro*. Serums of the immunized volunteers will be mixed with 100 infectious particles of SARS-CoV-2 and added to the Vero cells. Based on the results of the analysis conducted, the samples will be assessed as positive if the serum shows virus neutralizing activity (VNA). The highest serum dilution, which inhibits cytopathic effect in 2 wells out of 3, is taken as a VNA titer of the study serum.

Proliferating activity of T-lymphocytes will be assessed using the flow cytofluorometry method. For this purpose, mononuclear cells (PMBC) will be separated from the volunteers' peripheral blood, dyed with CFSE vital stain, and disseminated to 96-well plates. Then SARS-CoV-2 S glycoprotein will be added to PMBCs. Mitogen will be added to the cells as a positive control. Proliferating activity will be counted in 72 hours. For this purpose, the cells will be dyed with antibodies to CD3, CD4, and CD8 molecules and then analyzed using a flow cytofluorometer. The proliferating activity of the CD3+CD4+ and CD3+CD8+ cells will be counted based on changing intensity of CFSE stain fluorescence. The final percentage of the proliferating cells will be calculated using the formula: X = %st-%, where % st is the percentage of proliferating cells after restimulation of splenocytes with recombinant S glycoprotein of SARS-CoV-2 virus, and % is the percentage of proliferating cells without restimulation (intact cells). Based on the results of the analysis conducted, the samples will be assessed as positive if the percentage of proliferating cells in the immunized volunteer at the studied point is higher than at the point before the vaccination.

Interferon gamma (IFNɣ) concentration growth in the culture of T-lymphocytes will be assessed using the ELISA method. For this purpose, mononuclear cells (PMBC) will be separated from the volunteers' peripheral blood and disseminated to 96-well plates. Then SARS-CoV-2 S glycoprotein will be added to PMBCs. FHA mitogen will be added to the cells as a positive control. The IFNɣ concentration growth will be counted in 72 hours. For this purpose, cell media will be collected and IFNɣ concentrations in the medium will be analyzed. The IFNɣ concentration growth will be determined using the formula X = Cst/Cint, where X is the IFNɣ concentration growth (times), Cst is the IFNɣ concentration in the medium from stimulated cells (pg/ml), Cint is the IFNɣ concentration in the medium from unstimulated (intact) cells (pg/ml). Based on the results of the analysis conducted, the samples will be assessed as positive if the IFNɣ concentration growth in the immunized volunteer at the studied point is higher than at the point before the vaccination.

All the data provided will be analyzed and the following parameters will be calculated:

Key parameters:

- - Titer of glycoprotein-specific antibodies in the blood serum for all the subjects 28 and 42 days from the start of vaccination.
- Geometrical mean values and 95% confidence intervals of the glycoprotein-specific antibody titer in the blood serum of the volunteers 28 and 42 days from the start of vaccination.

- Seroconversion rate (for seroconversion rate calculation valid increase in the antibody titer by 4 times and more will be taken into consideration).
- Titer of neutralizing antibodies for all the subjects and visits before administration and on days 28 and 42.
- Geometric mean values of the titer of neutralizing antibodies before administration and for visits on days 28 and 42.

Additional parameters:

- - Percentage of proliferating T-lymphocytes after restimulation with SARS-CoV-2 glycoprotein for the subjects of stage 1 of the study and visits on days 0, 10.
- Medians and 95% confidence intervals of the percentage of proliferating T-lymphocytes after restimulation with the SARS-CoV-2 glycoprotein for visits on days 0, 10.
- IFNγ concentration growth in the T-lymphocyte culture after restimulation with the SARS-CoV-2 glycoprotein for all the participants and visits on days 0 and 10.
- Medians and 95% confidence intervals of the IFNγ concentration growth in the T-lymphocyte culture after restimulation with the SARS-CoV-2 glycoprotein for visits on days 0 and 10.

These calculations will make it possible to assess the key and additional efficiency criteria.
The duration of immune response is evaluated on the follow-up stage (days 90 and 180).

7.4. Efficiency data analysis

Vaccine immunogenicity will be assessed using several parameters.
The key parameter is the titer of glycoprotein-specific antibodies. The levels of antibodies in the subjects before vaccination and on days 21, 28, and 42 from the start of vaccination will be compared.
The efficiency criterion will be a valid growth ($p<0.05$) of the titer of glycoprotein-specific antibodies in the blood serum of a group of volunteers compared to the data obtained prior to the vaccination (Wilcoxon rank sum test).
For this parameter, kinetics of changes in the titers of glycoprotein-specific antibodies up to day 42 of the study and the seroconversion rate will be also analyzed in all the subjects.
Additional parameters are the titer of neutralizing antibodies, the percentage of proliferating T-lymphocytes after restimulation with SARS-CoV-2 glycoprotein, and IFNγ concentration growth in the T-cell culture after restimulation with SARS-CoV-2 glycoprotein. Comparison of all the three parameters will be conducted, based on the Wilcoxon rank sum test to compare the data collected during the corresponding visits with the data obtained prior to the vaccination. The additional efficiency criteria will be considered as follows:

- Valid growth ($p<0.05$) of the titer of neutralizing antibodies in the blood serum of a group of vaccinated volunteers compared to the data obtained prior to the vaccination (Wilcoxon rank sum test).
- Valid growth ($p<0.05$) of the percentage of proliferating cells in a group of vaccinated volunteers compared to the data obtained prior to vaccination (Wilcoxon rank sum test).
- Valid growth ($p<0.05$) of IFNγ concentration growth in the cell medium in a group of vaccinated volunteers compared to the data obtained prior to vaccination (Wilcoxon rank sum test).

8. Statistical aspects of the clinical trial

Statistical data processing will be based on the STATISTICA application package or equivalent.
Statistical data resulting from the study, including safety data, will be subject to analysis.
The study sponsor will analyze the data upon completion of the study, when the database is ready for disclosure of codes. For purposes of statistical programming analysis, STATISTICA and/or

other statistical software will be used, if required.
The conclusion on immunogenicity, presence or absence of adverse events of the study should be given based on all the objective and subjective data and laboratory examination results obtained in the course of the study arranged in compliance with the Protocol. Data on all the volunteers initially included in the study is subject to statistical processing, i. e. the volunteers excluded from the study for medical reasons will be taken into account for the safety analysis purposes.
The statistical analysis of the key parameters of immunological efficiency will include all the volunteers who have completed the study as per the Protocol.
The descriptive statistics will include the average value, the standard deviation, the median, the maximum and minimum values, the scope, the number of valid cases for quantitative variables; the number, the share, and the distribution for qualitative variables or, in case of abnormal distribution, the median, minimum, and maximum values and the quartiles should be specified.
If comparison of several study groups is required, Student's t-test or another method making it possible to assess dynamics of any parameter and its validity (Kruskal-Wallis test, Mann-Whitney test, Wilcoxon test) is to be used for normally distributed parameters.
Data on changes in the objective parameters of the volunteers' health condition or on occurrence of any adverse events will also be covered by statistical processing.

8.1. Description of statistical methods

8.1.1. Study hypothesis

Administration of the developed vaccine induces development of strong immune response to the SARS-CoV-2 virus.

8.1.2. Planned number of subjects

The design of a planned clinical study is based on general methodological principles set out in IMP Study Guidelines, including the fact that drug registration is planned to be in accordance with Government Resolution No. 441 [6].
Upon reaching the primary points involved in immunogenicity assessment described in the Protocol, a report on the results of the safety and immunogenicity assessment will be drawn up on the basis of the results obtained on the 28th day of the study to help make a decision on the registering the drug in accordance with Russian Federation government Resolution No. 441 dated April 3, 2020 "On the Specifics of Handling Human Medicinal Drugs Intended for Use During the Threat of or an Actual Emergency Situation, and Emergency Response, and for Arranging Medical Assistance to Persons Affected by Emergency Situations, Preventing Emergency Situations, Preventing and Treating Diseases That Pose a Serious Hazard to the Public, Diseases and Injuries Resulting from Adverse Chemical, Biological, and Radiation Factors". This report will include the results of assessing the immunogenicity for not less than 50 participants at the 28-day point.
Along with that, the study will be continued in accordance with the Protocol, accompanied by all the prescribed procedures and visits up to 180 days of observation.

8.1.3. Significance level applied

The significance level was determined as 0.05 (5%), the test strength is 0.8 (80%). Study termination criteria
Study termination is provided for in the following cases:

1. Due to unfavorable safety profile, the study can be terminated by the chief investigator after a consultation with the Sponsor.

[6]Guidelines on preclinical evaluation of drugs (Immunobiological medicinal drugs). Part Two / Under the editorship of A. N. Mironov. -M.: Grid and K., 2012.

2. The clinical trial can be early terminated or suspended by the Sponsor after repeated assessment of risks of the clinical trial.

8.2. Procedure for recording missing, unanalyzable or falsified data

The employee responsible for keeping the electronic database checks the base for inconsistencies, erroneously made records, or missing data after entering all the data. In case of any questions to the investigators, the Questions to Investigators form will be sent to the primary investigator in the clinical center. After receiving replies to the asked questions from the investigators, the employee responsible for keeping the study database checks the base for inconsistencies, erroneously made records, or missing data. After final completion of data collection and entry from all centers, the database is closed and statistical processing may start.

No replacement of missing, unanalyzable or uncertain data is envisaged in this study.

Uncertain and unanalyzable data will be additionally identified in the course of analysis for outliers by review of dispersion diagrams and box-whisker diagram. If there are any outliers, analysis for differentiating extremum parameters and errors of entry into the base will be conducted.

A decision that exclusion of outliers from the statistical analysis and analysis of sampling clear of outliers are required will be taken by the biostatistician jointly with the specialist responsible for drawing up the Final Report.

8.3. Procedures for reporting any deviations from the initial statistical plan

If it is impossible to use the initially determined statistical methods, then the final statistical and general reports should provide a ground for changes with references to the calculations made, statistical indicators, and general analysis of the existing situation that result in these changes. A grounded decision on extraordinary changes (assumptions modifying the data) should be taken by the Study Sponsor; the ground should be included in the clinical trial report.

8.4. Selection of subjects for analysis

For statistical analysis, the data of the volunteers having completed the study according to the Protocol (intake of the study drug dose provided for by the Protocol and going through all the procedures provided for by the Protocol in strict compliance with the study plan) will be processed separately.

Regardless of the reason for study completion, data of all the volunteers having received a dose of the study drug will be taken into consideration during safety analysis.

The cases of the volunteers early removed from the study as well as deviations from and violations of the Protocol will be analyzed separately.

8.5. Mid-term and final analysis, NCMC

In the course of the study, an analysis (with preparation of a corresponding report) on the end points of immunogenicity and safety is planned after determining SARS-CoV-2 glycoprotein-specific antibodies titer in 28±2 days after vaccinating.

This report will be submitted to the Ministry of Health of the Russian Federation to make a decision on a drug registration in accordance with Regulation No. 03.04.2020 of the Government of the Russian Federation dated April 3, 2020 “On Specifics of Handling Human Medicinal Products Intended for Application in Case of a Threatened or Actual Emergency Situation and Emergency Response and for Arrangement of Medical Assistance to Persons Affected by Emergency Situations, Prevention of Emergency Situations, Prevention and Treatment of Diseases Being of Serious Hazard for the Public, Diseases and Injuries Resulting from Adverse Chemical, Biological, and Radiation Factors”. This report will include the results of assessing the immunogenicity for

not less than 50 participants at the 28-day point. By doing so, a summary report will include observation findings of all the volunteers up to day 180 as per the Protocol.
The current CT Protocol stipulates NCMC creation after CT authorization obtainment and not later than a week before the first safety report application.

The person responsible for this research will write a report about the course of the trial for NCMC with information about results of interim safety data analysis and, if available efficiency report by the date, of each trial stage and also information about protocol deviations and violations, etc.

9. Direct access to primary data/documentation

In accordance with the legal requirements, the sponsor organization, the sponsor's authorized representative, and the competent healthcare authorities are entitled to conduct a check (audit) of the study procurement and documentation. For this purpose, the Investigator should provide direct access to the documentation and all required information as well as provide required explanations to the persons authorized to carry out monitoring, audit, ethical review, or inspection of the competent authorities without delay and to the extent provided by the requirements of Federal Law No. 61-FZ and Russian state standard GOST R 52379.
At the same time, all the information on the study and the collected data are strictly confidential. The investigator is not allowed to provide information on the study to persons who do not immediately participate in the study and not being persons authorized to carry our monitoring, audits, ethical expert examination or inspection without the sponsor's written consent.

10. Quality control and quality assurance

Prior to the start of the study for the whole team of the investigators a study instruction will be developed to describe the study procedures, the rules for obtaining the participants' ICs, keeping the project-specific investigator file (IF) forms, and work with the e-CRF.
The investigating physician is obligated to store all the primary documentation in the way to ensure access to it to the sponsor representatives and the auditors from the regulatory authorities and not to prevent from direct access to the primary data / documentation for monitoring, audit, ethical expert examination and inspection by the authorized agencies.
All the information included in the e-CRF will be recorded in the primary documentation of the participant.

10.1. Documentation

For clinical trials, a quality management system is implemented in Federal State Budgetary Institute N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Health Ministry of the Russian Federation to include written SOPs to ensure conducting clinical trials and obtaining, documenting, and reporting data in accordance with the protocol, the Good Clinical Practice principles, and the applicable regulatory requirements.
The investigator should keep primary documentation on each subject participating in a study, containing their personal data (including hospitalization and medical history) and records made during visits, including demographics and medical data, laboratory test data, and data of all the other tests and procedures. Any information entered into the CRF should be sourced from the primary documentation. The investigator should also keep the original Informed Consent signed by the subject.
The investigator should provide for the monitor's access to all the primary documentation related to the subject to confirm accuracy of the data entered into the CRF. The Sponsor's corporate monitoring standards provide for total check of the informed consents, inclusion/exclusion criteria, AE/SAE documentation, and drug safety and tolerability data in the primary documentation.

Additional checks for CRF records compliance with the primary documentation are carried out in accordance with the monitoring plan for this study. No primary documentation ascertaining identity of the subjects will be disclosed.

Regular visits of the study monitor under the sponsor's assignment prior to the start of the study, in the course of the study, and upon completion of the study contribute to successful arrangement of the study and ensure collection of accurate data and timely identification of any possible errors, protection of the volunteers' rights and compliance of the study process with the requirements of the law of the Russian Federation and the good clinical practice.

In the course of regular monitoring visits, total verification of CRF data and control over compliance with the study procedures, the rules for storage of study drugs, reagents, and expendables as well as due and timely keeping of the main documents of the clinical trial, including reporting provided for by the good clinical practice, the law of the Russian Federation, and the protocol-specific SOPs and the clinical center's SOPs, subject to acceptance of this documentation as standard by the sponsor confirmed by documents, are provided for. In addition, the sponsor, the Sponsor's authorized representative, and the healthcare authorities are entitled to conduct an unscheduled check (audit) of the study procurement and documentation.

The Sponsor's representatives may visit the research center at any time during the study or after its completion to conduct a study audit in accordance with the regulatory requirements and the company's policy. For such audits, access to all the documents related to the study, including the primary documents, for inspection and comparison with the CRFs will be required. However, confidentiality of the subjects' data should be observed. The investigator and the personnel should be present in the course of regular planned visits to the research center for the purpose of an audit by the Sponsor or persons appointed by the Sponsor to provide a consultation, if required.

An audit may also be conducted by representatives of any competent authority. The investigator should immediately notify the Sponsor in case of an application by the competent authority with regard to any further inspection.

For clinical studies, a quality management system is implemented in Federal State Budgetary Institution of N. F. Gamaleya Research Institute of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation.

Quality management in the clinical trials involves managing the corresponding processes:

- all stages and operations of a clinical trial;
- preparation of main clinical trial documents (Protocol, Brochure, data record forms (Case Report Form));
- protection of volunteers' rights, safety, and wellbeing (preparation of an Informed Consent Form and information sheet);
- safety monitoring during the study;
- procedures for recording the study drug;
- subjectivity minimization methods during the study;
- inspection and self-inspection;
- study documentation storage.

10.2. Standards of laboratory tests and their quality assurance

Prior to the start of the study, the investigator will provide a list of reference intervals for all the laboratory tests to be done and the data on the quality control method. These documents will be kept in the investigator's file and a copy of the same will be sent to the Sponsor. Upon request, a description of the methods used for each test should be provided. The Sponsor should be promptly notified of any changes in the laboratory, its procedures, reference intervals, parameters, etc. in the course of the study.

11. Ethics aspects

11.1. Regulatory and legal framework

This study will be conducted in accordance with the Declaration of Helsinki of the World Medical Association "Ethical Guidelines for Biomedical Research on Human Participants" of 1964, as amended in 2013 (Fortaleza, Brazil); National Russian Federation Standard "Best Clinical Practices" (GOST R52379-2005) dated September 25, 2005; Russian Federation Ministry of Health Decree No. 266 dated June 19, 2003 "On Ratifying the Rules for Clinical Practice in the Russian Federation",
Federal Law 61-FZ "On Circulation of Medicines" as well as ICH GCP guidelines.
Before being included in the study, the volunteer is given written information and oral explanation about the objectives and methods of the study as well as about the expected benefits and possible risks associated with participation in the study, about the voluntary nature of participation in the study, and that the volunteer has the right to refuse to participate in the study at any time. The consent of the volunteer should be obtained before the study procedures, with the exception of procedures with anamnestic data (e.g., data from previous studies).
The processing of the data collected during the study will be carried out in compliance with the confidentiality of the volunteers' data. The volunteers should be informed about the purposes of the planned computer processing of data and about conditions for publishing such data (e.g., for presentation at medical conferences, in magazine articles and other open sources) presented only in a coded format that does not allow for identification.
The volunteers should be also informed that the authorized health officials and the sponsoring company will have access to their confidential health information for monitoring, inspection, and auditing purposes. At the same time, however, strict confidentiality of all information allowing for identification of the subject and non-disclosure of such information should be guaranteed.

11.2. Endorsement by regulatory boards and an ethics committee

The clinical trial of the medicinal drug will be carried out on the basis of a permit to conduct a clinical trial issued by the Ministry of Health of the Russian Federation based on the results of examination of documents for obtaining permit to conduct a clinical trial and ethical review provided for in Article 39 of Federal Law No. 61-FZ dated April 12, 2010 "On Circulation of Medicines".
The examination of documents for obtaining permit to conduct a clinical trial of a medicinal drug is carried out by the federal state budgetary institution for examination of medicines, the ethical review is carried out by the Ethics Council.
If there is an independent/local ethics committee in the medical organization where the clinical trial is planned to be conducted, the clinical trial organizer should obtain a confirmation that this independent ethics committee is organized and operates in accordance with these Rules.
If any member of the Ethics Committee directly participates in the study, a written notice that he or she abstains from voting should be received. The medicine developer or its representative will ensure that the corresponding documents are collected for submission to the Ethics Committee in order to consider a possibility to conduct a study under the Protocol: approved protocol, investigator's brochure, a copy of the Informed Consent Form, and other documents that are required in accordance with the requirements.
A written approval of the Protocol and the volunteer's Informed Consent by the Ethics Committee should be obtained and submitted to the medicine developer or its representative before the study starts.

11.3. Ethics Committee

This study protocol, the informed consent form, the Investigator's brochure, and volunteer's information sheet should be submitted to the Institutional Review Board (Ethics Committee/Institutional Review Board/Local Ethics Committee (LEC)) of the research center for review and approval. Any amendments to the protocol or subsequent changes in the informed consent form as a result of changes in the protocol and/or the investigator's brochure approved by the Sponsor should be also approved by the LEC, and the documentation for such approval should be provided to the Sponsor. Records of review and approval of all documents relating to this study by the LEC should be kept by the investigator and are subject to inspection by the competent authorities and/or the Sponsor during the study or after its completion.

The investigator should consent to submit to the LEC any necessary study progress reports, reports on SAEs, life-threatening conditions, or deaths. If the subject stops their participation in the study due to an adverse event that, in the investigator's opinion, may be related to the study drug, information will be sent to the LEC of the research center within 48 hours, unless otherwise is provided for by the LEC's SOP.

Prior to the start of the study, the investigator (or the sponsor, if applicable) will submit to the Ethics Committee current and complete copies of the following documents:

- Approved Protocol and, if applicable, amendments thereto
- Investigator's Brochure and, if applicable, amendments thereto
- Investigator's profile or equivalent information,
- Information relating to funding, the Sponsor's name, affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the Ethics Committee requests to perform its obligations.

This study will be initiated only after the LEC approves the final protocol, amendments thereto (if any), the informed consent form, corresponding study inclusion materials, and subject compensation programs, and the sponsor receives a copy of such approval.

During the study, the investigator (or the sponsor, if required) will submit the following documents and amendments, as applicable, to the LEC for review and approval:

- Amendments to the Protocol
- Revised informed consent form and any other written materials to be provided to the subjects
- New edition(s) of the Investigator's Brochure and amendments/supplements thereto
- Deviations from or changes in the protocol
- Any other documents requested by the LEC

In case of all amendments to the Protocol (excluding the amendments that are absolutely administrative, having no consequences for the subjects, data, or the study), an amendment to and related revisions of the informed consent form should be immediately submitted to the LEC for review and approval before the change(s) is (are) implemented.

All approvals of the Ethics Committee and corresponding documentation on these items should be handed over to the medicine developer or its representative.

At the end of the study, the investigator (or the sponsor, if required) will notify the LEC of the study completion.

11.4. Confidentiality

The medicine developer and its representatives confirm and adhere to the principle guaranteeing the volunteer's privacy right. During the study, the volunteer's data will be linked to the medicine developer's database or documentation by a unique identification number. As permitted by all applicable laws and regulations, a number of volunteer's characteristics such as sex, date of birth, and initials of the volunteer may be used to verify the volunteer and ensure accuracy of the volunteer's unique identification number.

All results handed over by the investigator to the developer will contain only anonymized personal data of the study participants, and the anonymization will be performed by the investigator personally; no information that makes it possible to determine the ownership of personal data by a specific subject will be handed over to the developer.
The volunteer's data will be stored and processed anonymously, only using the volunteer's unique identification number. The volunteer's data may only be used for the purposes of this study. It should be ensured that no unauthorized persons have access to the data of the volunteer.
The sponsor will use a unique identification code assigned to the volunteer to ensure that all data collected from each volunteer is identified. This unique identification number assigned by the investigator to each volunteer of the clinical trial ensures the volunteer's identification and is used in place of his/her last name, first name and patronymic.
In order to comply with the instructions and verify compliance with this Protocol, the medicine developer requires that the investigator allow the monitor of the medicine developer or of its representative, representatives of any regulatory authority, auditors authorized by the medicine development company, and the corresponding ethics committees to review the original medical records of the volunteer (source or documents), including (but not limited to) reports on laboratory test results, summaries of admissions and discharges upon admission to the hospital if it occurs during the volunteer's participation in the study, and autopsy reports.
Direct access to the volunteer's original medical records for monitoring, auditing, IRB/IEC review, and inspection by the competent authorities requires a special permission from the volunteer, which is indicated in the Informed Consent.

11.5. Information for the Volunteer and Volunteer's Informed Consent to Participate in the clinical trial

Upon obtaining and documenting the Informed Consent, the investigator should comply with regulatory requirements, good clinical practice and ethical principles set out in the WHO Declaration of Helsinki.
Prior to the start of the study, the investigator should obtain a written authorization/approval from the IRB/IEC and the local Ethics Committee, a written Informed Consent Form, and any other written materials to be provided to the subjects.
The information for the volunteer and the volunteer's Informed Consent Form should be written in a language fully understandable to the prospective volunteer. The wordings used in oral and written study information, including the written Informed Consent Form, should contain no specific professional terms not understandable to the volunteer.
Applicants desiring to voluntarily participate in the study will be informed:

1. That the clinical trial is investigational in nature, participation of a person in the clinical trial is voluntary, and such person may refuse to participate in the clinical trial at any time;
2. objective of the clinical trial, its duration, and the approximate number of participants;
3. treatment options during the clinical trial and the likelihood of random distribution by one of the treatment groups;
4. clinical trial procedures, including all invasive procedures;
5. responsibilities of a clinical trial participant;
6. expected risk and/or benefit for the clinical trial participant and, as appropriate, for the embryo, fetus, or infant;
7. of the treatment procedures or methods provided for by the Protocol that may be available to a clinical trial participant as well as of their potential gain, benefit, or risk;
8. of the insurance and compensation in case of any harm caused to their health as a result of participation in the clinical trial;
9. of the planned payments, if any, to a clinical trial participant for their participation in the

clinical trial;

10. that a clinical trial participant, by signing the Volunteer Information Sheet, gives their permission for the person appointed to conduct monitoring, auditors, independent ethical committees, competent authorities to access the clinical trial participant's medical records;
11. on the fact that the records identifying a clinical trial participant will be kept confidential, and disclosing them is allowed only in accordance with Russian Federation legislation, and that when the clinical trial results are published the data on the clinical trial participant will be kept confidential;
12. that a clinical trial participant will be immediately communicated any new information that may have an effect on their desire to continue participating in the clinical trial;
13. of the persons who may be contacted for additional information on the clinical trial and of the rights of the clinical trial participants;
14. of any possible circumstances and (or) reasons why a person's participation in the clinical trial may be terminated.

A written consent to hospitalization will be obtained from the volunteer. The study physician and designated personnel (nurses involved in inclusion in the study) will give explanations about the study to all potential subjects. Such explanations will also include a description of the drug to be assessed, potential risks associated with allergies, and possible adverse reactions.

Each subject will have an opportunity to ask questions and each subject will be informed of their right to withdraw from the study at any time for any reason.

Each participant will acknowledge receipt of this information and their independent offer to volunteer in this study by reading and signing the informed consent form (an information sheet containing the consent form) specifying the date. The investigator should document the date and time when the volunteer signs the Informed Consent Form in the volunteer's primary documentation prior to the study screening procedures. One copy of the subject information sheet with the informed consent form signed by the subject will be handed over to them, another copy will be kept on file at the research center. A copy of the informed consent form (Russian version) should be submitted along with this protocol and should be approved by the Ethics Committee prior to the start of the study. The original informed consent form dated and signed by volunteers will be kept in the archives of the research center for 15 years.

The volunteers should be informed that the data storing and scientific processing will be carried out anonymously.

All revised Informed Consent Forms/Supplements to the Informed Consent Form should be reviewed and signed as the original Informed Consent. The date when the revised Consent/Supplement to the Consent is obtained should be recorded in the primary documentation and the volunteer should receive a copy of the revised Informed Consent Form/Supplement to the Informed Consent Form.

11.6. Involvement of subjects from vulnerable and special groups

The inclusion/exclusion criteria do not provide for participation of subjects from vulnerable groups in the trial.

The special condition group in this trial includes women with retained child-bearing potential who, in accordance with the inclusion and exclusion criteria, can participate in the trial only if they consent to the usage of adequate contraception methods for the period from the beginning of the screening till the end of the trial.

12. Data processing and logging

In this study the electronic data capture system (EDC) will be used, using which the study physician will record all the study data.

The Investigators will introduce all the required medical data of the participants into the e-CRF, and the investigator will guarantee their authenticity and compliance with the primary documentation.
If required, after completion of the clinical part of the study, the medical investigator will be proposed to give explanation of any record in the e-CRF by sending a special data refinement form (DRF).

12.1. Primary documentation. Direct access to primary data/documentation

Trial subjects must be indentifiable from the primary documentation data. On the day when the informed consent form is signed it must be noted in the primary documentation that the volunteer is included in the trial.
The author of the entries in the primary documentation must be identifiable. All entries in the primary documentation must be dated.
The principal investigator and the persons authorized by the principal investigator must not prevent direct access to the primary data/documentation for trial-related monitoring, audit, ethics review and inspection by regulatory bodies.

12.2. Filling in the volunteer's diary

For safety assessment in the period between the visits, the volunteers will be asked to keep a self-observation diary to record any symptoms the physician could qualify as an adverse event. The diary will be provided at the observation stage after the injection of the vaccine. The volunteer's diary is a fillable form with symptoms and the time of their occurrence (Appendix No.7). The purpose of the volunteer's diary is to log the information on the volunteer's general condition and to make this information available to the study physician.
The study physician must instruct the volunteer about keeping the diary and point out the fact that it is required to log the information on the volunteer's general condition after vaccination for the physicians to be able to assess the safety of the product and, if required, to provide timely aid for the volunteer. The volunteer fills in the form in case of any adverse events occurred which he or she reports to the physician during a visit or a phone contact. It is allowed to leave the fields unfilled if the volunteer experiences no changes in their health condition. Changes in the body temperature are recorded in the diary only if the temperature is above normal (higher than 37C).
In case of development of the symptoms listed in the form, the volunteer makes a note in the corresponding column of the diary. Any symptom not included in the list can be entered into the "other" column and specified in the comments. In case of a disease development after the vaccination the diagnosis must be entered into the "comments" column and the period of the disease must be specified.
Local reactions are assessed by the study physician with the VAS during visits, therefore no such column is included in the diary.
The volunteer assesses the intensity of the adverse event as follows:

–	No
+	mild (does not interfere with activity, slight discomfort)
++	medium (interferes with activity, major discomfort)
+++	severe (prevents from daily activity)

The data from the volunteer's diary (Appendix 6) constitute material for analysis and adverse event detection by the study physician.

12.3. Registration of adverse events

In case of any adverse events the study physician must enter the necessary data in the primary documentation and then fill out the corresponding pages in the volunteer's CRF and decide whether it is appropriate for the volunteer to continue their participation in the trial (decide whether

to exclude the volunteer from the study or to continue the trial treatment). Adverse events will be registered from the day the volunteer is included in the trial (after the administration of the investigational product) till the end of the volunteer's participation in the trial.
A CRF fill-out guideline will be provided before the beginning of the trial and will be reviewed by the staff taking part in the trial. The sponsor will check the accuracy and completeness of the CRF during the monitors' visits to the research center and upon receival by the sponsor; any discrepancies must be resolved together with the investigator or an appointed employee as applicable. After the data is loaded into the clinical trial database its accuracy and consistency will be checked through comparison with the primary data.

12.4. Monitoring

clinical trial monitoring is defined as activities providing control over the clinical trial process as well as ensuring that its arrangement, data collection and representation of results is done in accordance with the Protocol, standard operating procedures, good clinical practice (GCP), and regulatory requirements.
Monitoring visits by the development company or persons authorized by it will take place before the inclusion of the first volunteer in order to check the pre-start conditions of the trial, on a regular basis in the course of the trial, and upon completion of the trial by the last volunteer.
The center opening visit is arranged after the approval of the study by the ethics committee and upon making an agreement with the research center and solving all the organizational issues, including issues related to the logistics and storage of the investigational product. The first routine monitoring visit to the center must be arranged after the first volunteer enrollment at the research center, but not later than 10 business days after the day of the first volunteer enrollment at the research center. Further routine monitoring visits to the research center will be arranged as further volunteers are involved in the trial in accordance with the monitoring plan.
The research center closure visit will take place after the official notification of the research center by the Trial Sponsor about the completion of volunteer enrollment for the trial, when the last volunteer involved in the research center completes all the visits and procedures provided for in the Trial Protocol. As a part of the monitoring visits for the trial, 100% verification of the signed Informed Consent Forms for all the volunteers included in the study is required.
The monitoring will be performed directly at the Research Center facilities. These visits are arranged in order to check the observance of the rights and health protection of the volunteers participating in the clinical trial, to check the accuracy and completeness of clinical study data recording and compliance of the records with the primary documents as well as observance of the applicable approved Protocol/adjustments and provisions of the applicable regulatory requirements in the course of the clinical trial.
Primary documentation will be submitted for checking the data recorded in the CRFs.
Primary documentation includes the ambulatory records and the supporting documents controlling the selection of volunteers for the study, their treatment and withdrawal, the center file, etc. The investigator and the institution must ensure access to the volunteer's primary documentation and CRF for the representative of the medicinal product development company and the Ethics Committee.
The representative of the medicinal product development company will review all the aspects of the trial and its documentation, including, but not limited to, the Investigator File, the investigational product, volunteers' medical records, Informed Consent Forms and CRF. It is important that the investigator and other employees conducting the trial are present during the monitoring visits and that sufficient time is planned for the monitoring.

12.5. Data storage

To ensure safe-keeping of the data for further audits by the regulatory authorities, the medical

investigator undertakes to store all the documentation related to the study for the period determined by the law of the Russian Federation of the clinical trial agreement.
The investigating physician is obligated to store all the primary documentation in the way to ensure access to it to the CRO representatives, the sponsor and the auditors from the regulatory authorities and not to prevent from direct access to the primary data / documentation for monitoring, audit, ethical expert review, and inspection by authorized agencies.

13. Financing and insurance

The clinical trial was financed by the organization the developed the medicinal product: Federal State Budgetary Institution Russian Federation Ministry of Healthcare N.F. Gamaleya Scientific Research Center of Epidemiology and Microbiology.
The financial aspects of the trial will be documented under a contract between the organization that developed the medicinal product (the Sponsor) and the research organization.
Neither the Sponsor nor the investigator bear any financial liability for the study / treatment of any medical conditions that may be found during the screening process.
The trial's Sponsor will provide the drug being researched in the amount necessary for the trial, and cover all the expenses to manufacture the product. The clinical center where the trial takes place is responsible for safekeeping the drug being researched from the moment the product is given to the clinical center by the Sponsor.
The volunteers will receive remuneration for their participation in the trial, payment conditions will be described in the volunteer contract.
The subjects involved in the trial are guaranteed life and health risk insurance in accordance with the legal requirements of the Russian Federation. The researcher will inform the subject about this insurance, and the volunteer will receive an insurance policy after signing the Informed Consent Form.
In accordance with current legislation, the scopes of insurance coverage are:
a) if the insured person dies: 2,000,000 (two million) rubles. The insurance compensation payout specified is equally divided among the beneficiaries in proportion to the number of beneficiaries;
b) in case the health of the insured person worsens, resulting in:
disability, group I – 1,500,000 (one million five hundred thousand) roubles; disability, group II - 1,000,000 (one million) roubles; disability, group III – 500,000 (five hundred thousand) roubles;
c) in case of health impairment of the insured person that did not cause disability - max. 300 000 (three hundred thousand) rubles.
The life and health risk insurance for the volunteers participating in the trial will be provided by an insurance company in accordance with established procedures.

14. Publication of clinical trial findings

The Trial Sponsor has all the rights for the clinical trial findings. The investigator is obligated not to make any publications or statements about the trial process or trial findings without prior written consent from the Sponsor. The investigator is obligated to ask the Sponsor's consent for the publication of the findings and, upon receival of written consent, to send a copy of the paper to the Sponsor for review and possible comments at least thirty days before the paper is submitted to the publisher. In order to ensure the accuracy and integrity of the information, only processed, checked and confirmed data is allowed for usage. The publication and/or statement can be postponed for a period necessary for the Sponsor to register the intellectual property.
The sponsor and the investigator must not use each other's names in advertisement materials or publications without prior written consent from the other party.
The sponsor has a right to publish the trial findings at any time without prior approval from the research institutions.

Appendix 1

Assessment scale of clinical relevance of deviations from the reference intervals of laboratory test parameters[7]

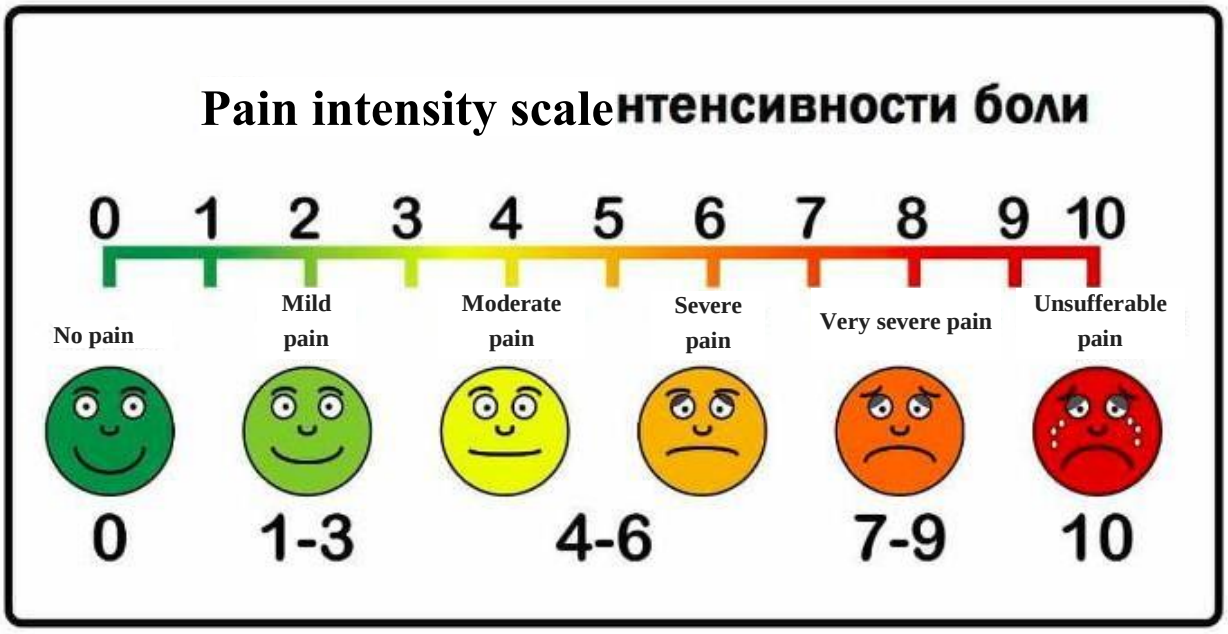
Indicator	Admissible deviation
Complete blood count	
Hemoglobin	< 0.9 RILL
Hematocrit	< 0.9 RILL
Erythrocytes	< 0.9 RILL
Platelets	< 0.8 RILL or > 1.2 RIUL
WBC	< 0.8 RILL or > 1.2 RIUL
Total neutrophils (abs.)	< 0.8 RILL or > 1.2 RIUL
Eosinophils (abs.)	> 1.2 RIUL
Basophils (abs.)	> 1.2 RIUL
Lymphocytes (abs.)	< 0.8 RILL or > 1.2 RIUL
Monocytes (abs.)	> 1.2 RIUL
Erythrocyte sedimentation rate	> 1.1 RIUL
Biochemical blood analysis	
Total protein	< 0.8 RILL or > 1.2 RIUL
Total bilirubin	> 1.3 x RIUL
Creatinine	< 1.1 RILL or > 1.2 RIUL
Aspartate aminotransferase	> 2.0 RIUL
Alanine aminotransferase	> 2.0 RIUL
Alkaline phosphatase	> 2.0 RIUL
Glucose	< 0.6 RILL or > 1.2 RIUL
Total cholesterol	< 0.9 RILL or > 1.1 RIUL
Urine test	
pH	< 0.9 RILL or > 1.1 RIUL
Relative density	< 0.95 RILL or > 1.05 RIUL

Notes: RILL means reference interval lower limit;
RIUL means reference interval upper limit.

[7] Value of reference intervals of laboratory parameters for early-phase clinical trials in healthy volunteers. S.B. Fitilev, A.V. Vozzhayev, I.I. Shkrebneva, D.A. Klyuyev, A.A. Vdovina, L.A. Myasnikova GOOD CLINICAL PRACTICE No. 2 2018 DOI: 10.24411/2588- 0519-2018-10046

Appendix 2

Visual analog scale (VAS) for pain assessment



Comment: pain assessment VAS is used to assess the volunteer's subjective perception. The physician shows the volunteer the scale in the course of complaint enquiry and fixes the VAS score in the primary documentation and the case report form. Assessment of pain severity as an adverse event is performed in accordance with Appendix 6 "Vaccination adverse events assessment scale".

Appendix 3

Frequency and severity of adverse events due to vaccines[8]

Frequency	Number of found adverse reactions in vaccinated people, per cent	Severity of reactions
Very often	≥ 10%	General and usually insignificant reactions: 1. part of immune response to vaccine, 2. reactions are resolved on their own, for instance: — fever, — malaise.
Often	≥ 1% and <10%	
Rarely	≥ 0.1% and <1%	Rare, usually more severe reactions: 1. Usually clinical treatment is necessary, 2. Examples include: — Severe allergic reaction (for instance, anaphylaxis) including exaggerated response to the vaccine antigen or component, — Vaccine-specific reactions.
Rarely	≥ 0.01% and <0.1%	
Very rarely	<0.01%	

[8] VACCINE SAFETY BASICS learning manual. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland

Appendix 4

procedures	**V0**	**V1**	**V2 (outpatient)**	**V3 (outpatient)**	**V4 (outpatient)**	**V5 (outpatient)**	**V6**	**V7**	**V8 (outpatient)**
	-7 – 0	1	10	28	42	90	120	150	180
Informed consent	✓						Telephone contact or TMC	Telephone contact or TMC	
Inclusion/exclusion criteria assessment	✓								
Historical records collection	✓								
Demographics	✓								
HIV, syphilis, hepatitis	✓*								
SARS-CoV-2 with the PCR method	✓	✓	✓	✓					
IgM and IgG to SARS-CoV-2	✓								
Drug test	✓	✓							
Pregnancy test (women with preserved reproductive potential)	✓	✓							
Alcohol test	✓	✓							
Administration of the IMP		✓							
Outpatient visit	✓	✓	✓	✓	✓	✓			✓

Physical examination, VS	✓	✓	✓	✓	✓	✓			✓
AE registration		✓	✓	✓	✓	✓			✓
CBC	✓	✓		✓					
BBA	✓	✓		✓					
Urine test	✓	✓		✓					
Immunogram		✓		✓	✓				
Self-observation diary		✓	✓	✓	✓				
Evaluation for any exclusion criteria		✓	✓	✓	✓				
Humoral immunity		✓	✓	✓	✓	✓			✓
Serum neutralizing activity		✓		✓	✓				
Cell immunity		✓	✓						

* valid 1 month

Appendix 5

Vaccination adverse events assessment scale[9]

Local reaction to the administered drug	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Pain	Does not impair activity	Repeated use of non-narcotic painkiller > 24 hours or impairs activity	Any use of a opioid painkiller or painkiller that prevents from activities of daily living	Emergency aid or hospitalization
Sensations	Mild discomfort by touch	Discomfort on movement	Significant discomfort at rest	Emergency aid or hospitalization
Erythema/Reddening	2.5–5 cm	5.1–10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Edema	2.5 – 5 cm and does not impair activity	5.1 – 10 cm and impairs activity	> 10 cm or impairs everyday activity	Necrosis

Vital indicators	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Fever (°C)	38.0–38.4	38.5–38.9	39.0–40	> 40
Tachycardia, HR	101–115	116–130	> 130	Emergency aid or hospitalization

[9] Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research September 2007

Bradycardia, HR*	50–54	45–49	< 45	Emergency aid or hospitalization
Systolic hypertension, mm Hg	141–150	151–155	> 155	Emergency aid or hospitalization
Diastolic hypertension, mm Hg	91–95	96–100	> 100	Emergency aid or hospitalization
Systolic hypotension, mm Hg	85–89	80–84	< 80	Emergency aid or hospitalization
RR	17–20	21–25	> 25	Intubation

* bradycardia is usually characteristic for sportsmen and people engaged in hard labor

General system indicators	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Nausea/vomit	No impact on activity or 1 to 2 case per 24 hours	Some impact on activity or > 2 cases per 24 hours	Prevents everyday activity, requires outpatient care, intravenous hydration	Emergency aid or hospitalization
Diarrhea	2 to 3 liquid stools or < 400 g per 24 hours	4 to 5 stools or 400 to 800 g per 24 hours	6 or more runny stools or > 800 g per day or requires outpatient care, intravenous hydration	Emergency aid or hospitalization
Headache	No impact on activity	Repeated use of non-narcotic painkillers > 24 hours or some impact on activity	Any use of a opioid painkiller or preventing everyday activity	Emergency aid or hospitalization
Asthenia	No impact on activity	Some impact on activity	Significant; prevents everyday activity	Emergency aid or hospitalization

Myalgia	No impact on activity	Some impact on activity	Significant; prevents everyday activity	Emergency aid or hospitalization

General diseases	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Illness or clinical adverse event (as defined in accordance with applicable rules).	No No impact on activity	Some impact on activity, does not require medical interference	Significant, prevents everyday activity and requires medical interference.	Emergency aid or hospitalization

Biochemical indicators	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Glucose – hypoglycemia, mg/dl	65 – 69	55–64	45–54	< 45
Glucose – hyperglycemia on an empty stomach, mg/dl Random time, mg / dl	100 - 110 110 - 125	111–125 126–200	>125 >200	Need for insulin injection or hyperosmolar coma
Urea, nitrogen, mg/dL	23 – 26	27–31	> 31	Need for dialysis
Creatinine, mg/dL	1.5 – 1.7	1.8–2.0	2.1–2.5	> 2.5 or Need for dialysis
Total protein, hypoproteinemia, g/dL	5.5 – 6.0	5.0–5.4	< 5.0	--
Alkaline phosphatase - increase as isolated factor	1.1–2.0 x RIUL	2.1–3.0 x RIUL	3.1–10 x RIUL	> 10 x RIUL
Liver function tests – increase of ALT, AST	1.1–2.5 x RIUL	2.6–5.0 x RIUL	5.1–10 x RIUL	> 10 x RIUL

Bilirubin, accompanied by any increase in liver function tests	1.1–1.25 x RIUL	1.26–1.5 x RIUL	1.51–1.75 x RIUL	> 1.75 x RIUL
Bilirubin with normal indicators of liver function tests, as an isolated factor	1.1–1.5 x RIUL	1.6–2.0 x RIUL	2.0–3.0 x RIUL	> 3.0 x RIUL

Urine test	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Protein	Traces	1+	2+	Hospitalization or dialysis
Glucose	Traces	1+	2+	Hospitalization in case of hyperglycemia
Blood (microscopy), blood erythrocytes in view field (cells in view field)	1–10	11–50	> 50 or incalculable number	Hospitalization or transfusion of erythrocytes

	Mild grade (class 1)	Moderate grade (class 2)	Severe grade (class 3)	Potential life threat (Class 4)
Lymphadenopathy after vaccination	Local enlargement of lymphatic nodes	Local ulceration; generalized enlargement of lymphatic nodes	-	-

Classification of the severity of the nodal involvement after vaccination (CTCAE v5.0 – November 27, 2017, page 43)

Appendix 6

VOLUNTEER'S DIARY. Template

Date							
observation days	1	2	3	4	5	6	….
temperature							
chills							
headache							
dizziness							
decreased appetite							
nausea							
vomit							
abnormal bowel pattern							
stomachache							
asthenia/malaise							
sweatiness							
joint/muscle pain							
rash							
allergic reactions							
infection diseases							
other							
comment							

Comment: the diary is used to assess the volunteer's subjective perception. Filling in the volunteer's diary is described in section 13.4. The doctor asks the volunteer about complaints recorded in the diary and fixes data in primary documentation and CRF. Assessment of severity of adverse events is performed in accordance with Appendix 6 "Vaccination adverse events assessment scale".

Appendix 7

Recommended form of informing about the severe unpredicted adverse event to the medical drug under clinical trial

Clinical trial protocol No.	
Medicinal product name	
Protocol name	
No. of permit to perform CS in Russia	
Name of medical institution where the adverse event was detected (if the reaction took place in Russia)	

I. Information on unwanted reaction

1. The volunteer's initials	1a. Country	2. Date of birth	2a. Age	3. Gender	4 - 6. Unwanted reaction beginning date (day/month/year)	8 - 12. Mark all that match ☐ Death ☐ Hospitalization or its prolongation ☐ Persistent or permanent disability ☐ Life threat
7 - 13. Description of adverse event (including data of laboratory and instrument research)						

II. Information on suspected medical drug(s)

14. Suspected medical drug (including international non-patented name or group name)	20. Did the reaction disappear after the drug was cancelled? ☐ Yes ☐ No Not applicable

15. Daily dose(s)	16. Administration method(s)	21. Is there a reaction return after secondary administration of the drug?
17. Indications:		☐ Yes ☐ No ☐ Not applicable
18. Treatment dates from to	19. Treatment duration	

III. Concomitant treatment and medical history

22. Concomitant medication(s) and administration dates (except for those that were used to treat unwanted reaction)
23. Other relevant data of medical history (for example, diagnoses, allergies, pregnancy with indication of last menstruation time, etc.)

IV. Other information

24. Name and address of the manufacturer	
24a. Case identification number	24b. Date when information about unwanted reaction was received by the manufacturer
24c. Source of information on adverse reaction ☐ Study ☐ References ☐ Health care professional ☐ Regulatory authorities ☐ Other	
25. Date of this message	
26. Type of message ☐ Primary ☐ Repeat	

Appendix 8

Reference data for detecting persons that consumed alcohol in quantities beyond safe levels[10].

Low risk consumption of alcohol: not more than 20 grams of pure alcohol per day, not more than 5 days per week.

Example (approximate values):

- 1 can of beer (330 ml), 5% alc. x 0.79 (conversion coefficient) = 13 grams of pure alcohol
- 1 glass of wine (140 ml), 12% alc. x 0.79 = 13.3 grams of pure alcohol
- 1 shot of strong liquor (40 ml), 40% alc. x 0.79 = 12.6 grams of pure alcohol

Test for detecting problems due to alcohol consumption: version for interview

1. How often do you have a portion of an alcoholic drink?

0 points - never
1 point - once a month or less frequently
2 points - 2-4 times per MONTH
3 points - 2-3 times per WEEK
4 points - 4 and more times per week

2. How many standard portions of alcoholic drinks do you take on a typical day when you drink alcohol?

0 points - 1 or 2 portions
1 point - 3-4 portions
2 points - 5 or 6 portions
3 points - 7, 8 or 9 portions
4 points - 10 or more portions

3. How often do you take 6 portions and more at a time?

0 points - never
1 point - less than once a month
2 points - each month
3 points - each week
4 points - every day or almost every day

Up to 7 points for males and 6 points for females stands for low risk of alcohol consumption.

[10] Thomas F. Babor John C. Higgins-Biddle John B. Saunders Maristela G. Monteiro World Health Organization AUDIT The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care Second Edition 2001 /WHO/MSD/MSB/01.6a Original: English Distribution: General Department of Mental Health and Substance Dependence