LLC "NPP "Pharmaclon"

Protocol of post-marketing non-interventional study

"Prospective randomized open-label comparative study of the use of the intranasal form of human recombinant interferon gamma for the prevention of acute respiratory viral infections, including diseases caused by coronavirus infection 2019 (COVID-19)"

RAIN-2020 (NCT05054114)

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SYNOPSIS

Title study	Protocol of post-marketing non-interventional study "Prospective randomized open-label comparative study of the use of the intranasal form of Interferon gamma human recombinant in patients for the prevention of acute respiratory viral infections, including coronavirus infection disease 2019 (COVID-19)" Protocol of post-marketing non-interventional study "Prospective randomized open-label comparative study of the use of intranasal form of interferon gamma human recombinant in patients for the prevention of acute respiratory viral infections, including coronavirus infection disease 2019 (COVID-19)" RAIN-2020
Design study	Post-marketing non-interventional prospective randomized open-label comparative study
Purpose of the study	**Primary objective** Evaluation of the effectiveness of the prophylactic use of Ingaron (INN: human recombinant interferon gamma, lyophilizate for the preparation of a solution for intranasal administration of 100,000 IU) in regimen of 3 drops in each nasal passage intranasally every other day for 10 days with a break of 7 days (two 10-day cycles) in adult volunteers. **Secondary objectives** Safety assessment of the prophylactic use of Ingaron (INN: human recombinant interferon gamma; lyophilizate for the preparation of a solution for intranasal administration of 100,000 IU), applied 3 drops into each nasal passage intranasally every other day for 10 days with a break of 7 days (two 10-day cycles) in adult volunteers.
Study drug	**Trade name:** Ingaron® **International Nonproprietary Name:** interferon gamma human recombinant **Product license number** – 001330 **Pharmaceutical dosage form:** Lyophilizate for preparation of a solution for intranasal administration of 100,000 IU **Composition:** Drug substance: interferon gamma – 100,000 IU. Excipients: mannitol 14.5 mg. **Pharmacotherapeutic group:** immunomodulatory agent **ATX Code:** [L03AB03] Ingaron® is a recombinant human gamma interferon, consists of 144 amino-acid residues, deprived of the first three amino-acid residues Cys-Tyr-Cys, replaced by Met. Molecular weight is 16.9 kDa. Obtained by microbiological synthesis in a recombinant strain of *Escherichia coli* and purified by column chromatography. Interferon gamma (immune interferon) is the most important anti-

	inflammatory cytokine, the producers of which in the human body are natural killer cells, CD4 Th1 cells and CD8 cytotoxic suppressor cells. Macrophages, neutrophils, natural killer cells, cytotoxic T-lymphocytes have receptors for interferon gamma. Activates the effector functions of these cells, their bactericidal activity, cytotoxicity, production of cytokines, superoxide and nitrous oxide radicals (thereby causing the death of intracellular parasites). Cancels the suppressive effect of interleukin-4 on interleukin-2-dependent proliferation and generation of lymphokine-activated killers. Activates the production of proteins of the acute phase of inflammation, enhances the expression of genes C2 and C4 components of the complement system. Unlike other interferons, it increases the expression of major histocompatibility complex (MHC) antigens of both classes I and II on different cells and induces the expression of these molecules even on those cells that do not express them constitutively. This increases the efficiency of antigen presentation and the ability of their recognition by T-lymphocytes. Interferon gamma blocks the synthesis of β-TGF, which is responsible for the development of lung and liver fibrosis. **Release form:** Lyophilizate for the preparation of a solution for intranasal administration in vials of 100,000 IU per 1 vial. 1 vial of drug, 1 vial of water for injection (5 ml) and 1 cap-dropper made of polyethylene in packaging of polyethylene or medical dropper in contour cellular package or in cassette contour package. **Method of administration and dosage:** Intranasally. 2–3 drops in each nasal passage every other day 30 minutes before breakfast for 10 days. After instillation, it is recommended to massage the wings of the nose with your fingers for several minutes to evenly distribute the drug in the nasal cavity. Preparation: The contents of the vial are dissolved in 5 ml of water for injection. **Effects on ability to drive and use machines:** Not studied. **Manufacturing enterprise/organization accepting consumer claims:** LLC "NPP "Pharmaclon", Russia. Legal address: 142279, Moscow region, Serpukhovskii district, Obolensk workers settlement, Obolenskoe highway industrial zone, building 5A, office 312. The address of the place of manufacture: 143422, Moscow region, Krasnogorskii district, Petrovo-Dalnee village, J.S.C. “Biomed”-Mechnikov Tel/fax (4967) - 36-07-71, (495) – 120-12-47 E-mail: info@pharmaclon.ru Internet: www.pharmaclon.ru
Sample Size	630 adult volunteers randomized into 2 parallel groups with a 1:1 distribution, considering a possible 10% premature exclusion and withdrawal of informed consent during the study. The population for analysis will be at least 572 participants: 286 in each group.

Selection criteria	Eligible volunteers can participate in the study. **Inclusion criteria** 1. Volunteers of both genders over 18 years old. 2. Obtaining a written form of informed consent. 3. Ability and consent to participate in this study. 4. No symptoms of respiratory infection. 5. A negative result of a PCR study for the presence of SARS-CoV-2 RNA according to the biomaterial obtained by nasopharyngeal [1]smear. **Non-inclusion criteria** 1. Any other concomitant diseases or conditions that, in the opinion of the research doctor, may distort the results of the study, restrict the rights of the volunteer, or put him at greater risk. 2. Contraindications to the use of the study drug. 3. Individual intolerance of the ingredients included in the composition of the study drug. 4. Pregnancy or breast-feeding. 5. Controversial result of PCR test for the presence of SARS-CoV-2 RNA according to the biomaterial obtained by nasopharyngeal smear. 6. Participation in a clinical trial using the investigated therapy for 30 days prior to inclusion in this study. 7. Disagreement on following reliable contraceptive measures within the study (sexual abstinence; or a combination of 2 different methods: for example, barrier and spermicides, or barrier and intrauterine device, or barrier and hormonal, etc.) – for participants with preserved childbearing potential.
Effectiveness criteria	**Primary effectiveness criteria:** The proportion of patients with acute respiratory viral infections, including COVID-19, at the end of the period of preventive administration of the drug (measurement time: 28 days). **Secondary effectiveness criteria:** 1. The proportion of patients with confirmed COVID-19 at the end of the period of preventive treatment of the drug (measurement period: 28 days). 2. The proportion of patients with acute respiratory viral

[1] It is permissible to accept the results of a nasal or pharyngeal smear, as well as the results of studies performed before inclusion in the study for no more than 72 hours.

	infections, including COVID-19, at the end of the follow-up period (change period: 2 months). 3. The proportion of patients with confirmed COVID-19 at the end of the follow-up period (change period: 2 months). 4. Frequency of development of complicated course of ARVI. 5. The proportion of participants with each of the scores (0–8) on World Health Organization (WHO) Ordinal Scale for Clinical Improvement (change period: 28 days). 6. The proportion of participants with each of the scores (0–8) on World Health Organization (WHO) Ordinal Scale for Clinical Improvement (change period: 2 months). 7. The duration of the symptoms of the disease of the study participants who fell ill with ARVI, including COVID-19 (change period: 2 months). 8. The duration of the symptoms of the disease of the study participants who fell ill with ARVI, including COVID-19 (measurement period: 28 days).
Safety criteria	The assessment of the safety of treatment will be carried out based on the registration of adverse events by analyzing complaints and subjective symptoms, as well as analyzing their severity using the CTCAE scale version 4.03 from 2010.
Financing and insurance	Financial support for this non-interventional post-marketing study will be provided at the expense of the manufacturing company in accordance with contracts with research centers. Additional payments and insurance of participants are not provided.

ABBREVIATIONS

ATC – Anatomical Therapeutic Chemical Classification System
VI – viral infections
CI – confidence interval
IU – international unit
BMI – body mass index
INN – international nonproprietary name
IEC – Independent Ethics Committee
AE – adverse event
ARVI – acute respiratory viral infection
ARD – acute respiratory disease
SAR – serious adverse reaction
SARS – severe acute respiratory syndrome
COVID-19 – coronavirus disease 2019 (coronavirus disease 2019)

CTCAE – Toxicity Scale (Common Terminology Criteria for Adverse Events)
SARS-CoV-2 – type 2 coronavirus that causes severe acute respiratory syndrome (SARS)
M – arithmetic mean
Max – Maximum value
Me – Median
Min – minimum value
N – number of values
SD – standard deviation

ETHICAL AND LEGAL ASPECTS

This study will be conducted in accordance with the Research Program, the Helsinki Declaration (ICH Harmonized Tripartite Guideline for GCP) and current local regulatory requirements (GOST R 52379-2005 "Good Clinical Practice", Order of the Ministry of Health of the Russian Federation No. 200n dated 01.04.2016 "On approval of the rules of good clinical practice"),The Rules of Good Clinical Practice of the Eurasian Economic Union (approved by the Decision of the Council of the Eurasian Economic Commission No. 79 of November 03, 2016), as well as according to the principles of the Independent Ethical Committee (IEC) accompanying this study. The research protocol, informed consent, participant diaries and the list of researchers must be submitted to the IEC before the start of the study and the inclusion of the first participant.

Informed consent

Each potential participant of the study will be informed about the study drug, objectives, and essence of the study, expected benefits, degree of risk and the requirements that he/she must fulfill during the study.
The participant's information sheet with the informed consent form will be signed and dated by both the volunteer and the researcher in two copies. One copy is transferred to the participant, and the other remains in the file of the research center. Each volunteer will receive information about the study in writing on hand. Information about the study is presented in Russian.

Risks and benefits for the study participant

The study drug has a low degree of toxicity and possible efficacy in relation to the prevention of COVID-19. All information that will be provided to the volunteer to decide on participation, including information about potential risks, is indicated in the participant's information sheet with an informed consent form.

Possible risks

The following side effects have been registered for the injectable dosage form of the drug (lyophilizate for the preparation of solution for intramuscular and subcutaneous administration). The appearance of these effects during intranasal administration of the drug Ingaron® is not expected.

It is noted that the use of the drug Ingaron® may be accompanied by the development of side effects, represented mainly by manifestations of flu-like syndrome: fever, chills, headache,

muscle pain, joint pain, weakness, which develop after the first injections of the drug and are amenable to correction with drugs with antipyretic and analgesic effects, without requiring withdrawal of the drug. In most cases, fever did not rise above 37.5 °C and was controlled independently.

Basically, registered side effects were reversible and easily controlled by the appointment of concomitant therapy (antidepressants for depression; antiallergic agents for skin rash): thrombocytopenia[2]*, neutropenia[3]*, anemia[2]*, lymphopenia[4]; autoimmune thyroiditis, allergic reactions[5]; vomiting [2]*, nausea[2]; weight loss, anorexia[3]; depression; general malaise, headaches[3], dizziness; rhinorrhea; allergic rash, alopecia[6]**; myalgia[3]; increased concentration of liver enzymes [3]**, increased concentration of bilirubin [3]*, creatinine[3]*, urea [3]*, glucose [3]**.

Risks from the use of the studied drug Ingaron® for the course of pregnancy, fetal development or for a breastfed child has not been sufficiently studied. In this regard, pregnant and lactating women, as well as women capable of childbearing and unwilling to follow reliable methods of contraception, as indicated in the inclusion/non-inclusion criteria, are not allowed to participate in this study. If a case of a participant's pregnancy is detected during the study, she is excluded from the study ahead of schedule and is subject to medical supervision during the entire period of pregnancy, as well as within 6 months after the birth period to assess the condition of the woman and the born child (observation is carried out if possible and only if she has her desire and consent to such observation).

Risk/benefit ratio

Considering the above, as well as the satisfactory study of the drug Ingaron® for intranasal administration when used in clinical practice, including for preventive purposes, the risk/benefit ratio in this study can be considered acceptable.

Benefit

Participation in the study does not imply receiving monetary, other material compensation, or any other direct benefit for the subject. However, the participant will have the opportunity to receive the study drug Ingaron®, registered for medical use in the Russian Federation for indications of prevention and treatment of acute respiratory viral infections. During the study, study group participants will receive 2 vials of the drug based on 2 cycles of 10-day prevention. Participants of the control group will have the opportunity to receive 1 bottle of the drug upon

[2] It was noted in patients receiving complex therapy for hepatitis B, C, as well as in the treatment of oncological diseases
[3] It was noted in patients who received the drug as part of chemotherapy for oncological diseases
[4] It was noted in patients receiving the drug with disseminated melanoma of the skin
[5] It was noted in patients receiving complex therapy for hepatitis B, C, as well as in the treatment of disseminated melanoma
[6] It was noted in patients receiving complex therapy for hepatitis C, as well as in the treatment of oncological diseases
* It was noted with the same frequency in patients who received the drug as part of chemotherapy or who received only chemotherapy
** It was noted with a lower frequency in patients who received the drug as part of chemotherapy, compared with patients who received only chemotherapy

completion of participation in the study for self-use within the instructions for medical use if they express a desire.

Introduction

The first coronavirus was isolated back in 1965 from a patient with SARS. But it has been of particular interest since the early 2000s, when the first outbreaks of coronavirus infections with fatal outcomes began. To date, science knows 37 types of RNA-containing coronaviruses.

A new coronavirus infection COVID-19 has been observed in the human population since the end of 2019. The characteristic symptoms of the disease are fever, cough, shortness of breath, myalgia. According to computed tomography (CT), in most cases, bilateral lung damage of the "ground-glass opacity" type is registered. Histological examination reports of patients' lungs indicate bilateral diffuse alveolar and bronchial [1] damage, pulmonary edema, hyaline membrane formation, false respiratory distress syndrome, accumulation of neutrophils, macrophages, and lymphocytes [2][3]. A characteristic feature is the presence of synth [4][5]. In addition to acute respiratory symptoms, weight loss may be observed [6][7].

The first stage of the SARS-CoV-2 life cycle is the adsorption of the viral particle by the target cell through ACE2, a receptor different from other types of coronaviruses for introduction into the host cell. After receptor binding, the stages of the SARS-CoV-2 viral cycle are similar for all coronaviruses [8][9][2 6].

The initial outbreak in China was represented in every fifth case by a severe form of the disease. The severe course of COVID-19 is associated with the high tropicity of the SARS-CoV-2 virus to the lung tissue, which determines its similarity to the pathogenesis of severe acute respiratory syndrome (SARS), registered in 2003. Since the beginning of the spread of COVID-19, quite a lot of reports have been received about a mild and even asymptomatic form of the disease without affecting the lower respiratory tract [1].

There is limited information about the systemic and local immune response of the body to the SARS-CoV-2 virus and the localization of virus replication in the tissues of the respiratory tract. Single scientific works on the study of this problem indicate the activity of replication in the tissues of the upper respiratory tract, including the nasal cavity, bronchi, bronchioles and alveoli, and the important role of the respiratory organs as "site of entry" for SARS-CoV-2. An important difference between SARS-CoV-2 and other epidemiologically important coronavirus strains was established, which consisted in the detection of the virus antigen in the ciliated epithelium of the nasal mucosa, which was combined with a high risk of transmission of the viral agent, as in cases of influenza infections [1]. The condition of a patient with active replication of the virus in the upper respiratory tract is of great epidemiological importance, posing a threat of spread [10], but may be reversible in terms of the development of subsequent complications and damage to the underlying respiratory tract [11].

The SARS-CoV-2 virus persists in the pharynx, throat, and lungs during the first week of infection and is well detected in a smear from the throat during this time period. At the same time, with age, there is a longer release of the virus in the upper respiratory tract [1], which was also noted in patients infected with SARS-CoV [12][13]. The detection limit is maximum at the beginning of infection. Unlike MERS-CoV, but just as in cases of SARS-CoV, SARS-CoV-2 infects both type I and type II pneumocytes, which explains the similarity of the histological

picture and explains pulmonary edema and the formation of hyaline membranes. Active replication of the virus in the lower respiratory tract is associated with the development of complications and lung damage [1][2 6]. Viral RNA can be detected in sputum within a month from the moment of manifestation of symptoms of the disease. SARS-CoV-2 is also identified in intestinal tissues [14]. Blood and urine samples do not give a positive result for the presence of viral RNA [11].

By the 14th day of the disease, seroconversion, and an increase in the concentration of IgG and IgM antibodies occur in all patients against the background of the remaining viral load [11].

However, it should be noted that acquired immunity against coronavirus infections is not persistent and does not protect against re-infection. Although the severity of the disease is associated with age and the presence of concomitant pathologies [1][26], susceptibility to SARS-CoV-2 is high in all population groups [8][15][16].

The interferon system is the most important and integral part of the body's immune system, which is responsible for the formation of an immune response, to produce specific antibodies and the activation of individual clones of immune system cells responsible for the detection and destruction of infectious pathogens: viruses and bacteria. It has been proven that it plays a key role in triggering the cellular immune response against any viral expansion, including lethal viruses (Ebola, SARS-CoV, MERS-CoV, hepatitis, etc.), which opens promising opportunities for the safe use of interferon-based drugs to provide preventive and therapeutic care. [18][19][20][21]

Studies on the role of interferons of different classes in the immune response processes have shown that interferons alpha and beta have their own antiviral activity, and interferon gamma is a powerful endogenous regulatory cytokine that activates the antiviral immune response, while it also has its own antiviral activity.

One of the unique manifestations of immune influence is the ability of interferon gamma to stimulate other cells of the immune system using the mechanism of "antigen presentation". This is a process in which phagocytes "place" fragments of pathogen proteins on the surface of their cells, thereby presenting these fragments are used by other cells of the immune system to develop an antigen-specific response. This mechanism significantly increases the ability of the immune system to target respond to a virus or any other intracellular pathogen.

Drug product called Ingaron (human recombinant interferon gamma), presented in two dosage forms: lyophilizate for the preparation of solution for intranasal administration, as well as intramuscular or subcutaneous administration, have many years of clinical experience in the prevention and treatment of viral infections, including coronavirus, influenza, and pneumonia. Efficacy and safety have been demonstrated in randomized controlled and placebo-controlled clinical trials [2 2][2 3][2 4].

A drug for intranasal administration based on recombinant interferon gamma was studied to assess the effectiveness of preventive administration during the epidemic rise in the incidence of influenza and ARVI. According to the results of a placebo-controlled randomized trial, the incidence during the prevention period and within 1 month after two 10-day cycles of using the drug decreased by more than 2 times. Among those who did get sick, a complicated course of infection was observed 2 times less often [2-4].

The nasal form of the drug has additional advantages. Firstly, a more favorable safety profile was noted with intranasal use. Secondly, the form is convenient for use, does not require a violation

of the skin, does not have an irritating effect on the gastrointestinal tract. But one of the main advantages should be noted that the intranasal route of administration contributes to the protection of cells, primarily the epithelium of the nasal mucosa, and performs the function of an additional mechanical barrier, which can contribute to a more rapid elimination of the virus from the upper respiratory tract, prevent its penetration into the lower respiratory tract and provide effective preventive protection.

The drug was included in the training manual "New coronavirus infection COVID-19: etiology, epidemiology, clinic, diagnosis, treatment and prevention" [8] and recommended by the Expert Council on Science by the Department of Health of the City of Moscow as a preventive measure to prevent infection with COVID-19 [15].

It is worth paying attention to the fact that during clinical studies to evaluate the antiviral efficacy of Ingaron 100,000 IU, a lyophilizate for the preparation of a solution for intranasal administration, therapeutic efficacy of the drug was noted in patients with coronavirus infection [2 5].

In this regard, the following tasks were set in this study:

- to evaluate the effectiveness of the proposed scheme of preventive therapy with Ingaron (INN: human recombinant interferon gamma, lyophilizate for the preparation of solution for intranasal administration of 100,000 IU) in adult volunteers. Effectiveness includes evaluation according to primary and secondary effectiveness criteria.
- to evaluate the safety of the proposed regimen of preventive therapy with Ingaron (INN: human recombinant interferon gamma, lyophilizate for the preparation of solution for intranasal administration of 100,000 IU) in adult volunteers. Safety is assessed based on adverse events, clinically significant changes in laboratory parameters during the study, taking into account the assessment of severity according to the STCAE 4.03 scale.

OBJECTIVES OF NON-INTERVENTIONAL RESEARCH

Primary objective

To evaluate the effectiveness of the prophylactic use of Ingaron (INN: human recombinant interferon gamma, lyophilizate for the preparation of solution for intranasal administration of 100,000 IU) in the mode of 3 drops in each nasal passage intranasally every other day for 10 days with break of 7 days (2 10-day cycles) in adult volunteers.

Secondary objectives

Safety assessment of the prophylactic use of Ingaron (INN: human recombinant interferon gamma; lyophilizate for the preparation of a solution for intranasal administration of 100,000 IU), applied 3 drops into each nasal passage intranasally every other day for 10 days with break of 7 days (two 10-day cycles) in adult volunteers.

Efficacy and safety include evaluation based on epidemiological, anamnestic, and clinical data, as well as laboratory studies and specialized scales.

DESIGN OF A NON-INTERVENTIONAL STUDY

Post-marketing prospective randomized open-label comparative non-interventional study in parallel groups.
A total of 4 visits are planned (0–3). Visit 0 and 1 can be combined.

Main stages of the study

1. Visit 0. Conducted in person[7]. Screening: informed consent, inclusion of volunteers and distribution into groups (Day -3-1)
2. Visit 1. Conducted in person. Randomization. Delivery of the investigated drug and the diary of the researcher participant (Day 0)
3. Visit 2. It is carried out remotely (by phone). Completion of a preventive course, evaluation of preventive efficacy and safety during the period of drug administration. The beginning of the observation period. (Day 28–30)
4. Visit 3. Conducted in person. Completion of the observation and research period. (Day 56–62)

The main procedures and stages of the study are reflected in the Schedule of research procedures.
The total duration of participation is about 2 months (56–62 days).
For participants who have a case of ARVI (COVID-19), visit 3 can be carried out earlier or later, but the total duration of the study should not be more than 90 days. Up to this point, medical researcher should try to collect the most complete information about the patient's condition. If it is not possible to conduct a face-to-face visit, final visit is conducted remotely.

Schedule of research procedures

Visit number	**0**	**1**	**2**	**3**
Setting	In person	In person	Phone call	In person
Visit name	**Screening**	**Randomization**	The end of the course of prevention **Beginning of the observation period**	End of the observation period **Completion of the study**
Study days	-3-1(0)	0	27 (+/-3)	56-62*
Informed consent [1]	+			
Anamnesis [2]	+			
Complaints	+	+	+	+
Physical examination [3]	+	+		+
Pregnancy test	+			
Safety assessment	+	+	+	+
Analysis for RNA to SARS-CoV-2 [4]	+			+[6]
Checking the inclusion/non-inclusion criteria	+	+		
Checking exclusion criteria			+	

[7] A full-time visit can be carried out both at the research center and at home

Randomization		+		
Delivery of the study drug [5]		+		+
Compliance assessment			+	+
Issue of the participant's diary		+		
Effectiveness evaluation			+	+
Assessment of the participant's condition according to the WHO scale	+	+	+	+[7]
Return of study drug and diary				+

* For patients with a registered case of ARVI, duration of participation in the study may be longer, but not exceed 90 days

1 All research procedures, except routine laboratory and instrumental studies, the data of which are used to assess the condition of the study participant, are performed after the procedure of signing the informed consent of the patient

2 The study should indicate the epidemiological history of respiratory viral diseases, status of vaccination (influenza, pneumonia, COVID-19), use of means of nonspecific protection and prevention of acute respiratory viral infections, including COVID-19

3 It includes a standard examination by a doctor, including: thermometry, assessment of visible mucous membranes of the upper respiratory tract, auscultation and percussion of the lungs, palpation of lymph nodes, examination of abdominal organs with determination of the size of the liver and spleen, assessment of the level of consciousness; clinical history; measurement of height, weight, respiratory rate, heart rate, blood pressure, pulse oximetry with measurement SpO_2

4 Within the framework of this study, results of tests performed no later than 72 hours before screening can be accepted at the screening visit; if the PCR test is received as "controversial", patient excluded of the study according to non-inclusion criterion No. 5 and cannot be re-screened further.

5 At the randomization visit, drug is given to participants assigned to the study group immediately for 2 courses (2 vials) with instructions for use and preparation. Upon completion of the study, participants of the control group can also optionally receive 1 vial of the study drug as a means of preventing acute respiratory viral infections for use as part of the instructions for medical use.

6 If performed as part of a routine practice

7 In case of registration of ARVI at the final visit 3, in parallel with the current assessment of the participant's condition, an additional assessment of the case is carried out according to the WHO scale, reflecting the maximum clinical manifestation of the disease.

Rules for stopping research

The sponsor has the right to stop the research at any time. Also, the study may be stopped prematurely by the decision of the IEC or regulatory authorities.

In case of early closure of the research center, all research documentation (except for the one that should remain in storage at the center) must be returned to the sponsor. Research documents, including primary medical records, must be kept at the center for at least 15 years after the completion of the study.

METHODOLOGY OF NON-INTERVENTIONAL RESEARCH

Randomization of study participants

During randomization, patients are randomly distributed in a 1:1 ratio into two groups:
Group I (main) and Group II (control).

According to the methodology approved by this protocol, the participant must use (Group I) or not use (Group II) study drug (depending on the distributed randomization number at Visit 1) for 27 days of the preventive course (10 days + 7 days + 10 days).
Randomization of the study participants is carried out on the same day or the next day after signing the informed consent, but no later than 3 days from the date of material sampling to the PCR test.
Randomization is carried out according to the Randomization List version 1.00 from 16.11.2020.
To randomize a participant into a study, a research physician must contact the employee responsible for randomization (instructions for randomization are provided by the sponsor to the center before the start of the study) by phone and provide the study code and the researcher's full name for identification, as well as the data of the randomized participant: screening number, initials, date of birth. The researcher is informed of the assigned randomization number of the participant and the number of the prevention group (I or II). After the call, a Randomization Form is sent to the researcher's email as confirmation. The form must be printed out, signed by the researcher, and attached to the primary documentation of the participant.
The intake of the study drug is carried out independently by the participant at home, with the Diary of the participant of the study.

Other preventive measures

Any non-specific measures for the prevention of a new coronavirus infection COVID-19 are allowed, including personal protective equipment (respirators, glasses, gloves, protective suits).

Previous therapy

As a previous therapy, it is prohibited to take any drug with test status 1 month before participating in this study.

Concomitant therapy

According to the design of the non-interventional study, participants can receive any concomitant therapy for concomitant chronic diseases, except medications prescribed off-label or for research purposes.

Prohibited therapy

For the study group: use of any medications that may or may have preventive effects against ARVI, including COVID-19, is ***prohibited***; use of non-specific methods of preventive protection is ***not prohibited***.
For the control group: use of interferon gamma is ***prohibited***; use of any medications that may or may have preventive effects against ARVI, including COVID-19, as well as the use of non-specific methods of preventive protection is ***not prohibited***.
All preventive measures, including pharmacotherapeutic ones, should be indicated in the diary filled in by the participant.

Exclusion criteria

A participant should be excluded from the study if at least one of the following criteria is met:

1. The use of the prohibited therapy indicated above, specific to each of the groups.
2. Withdrawal of informed consent.
3. Compliance to the study therapy is 50% or less.
4. Systematic non-compliance with protocol procedures by the participant.
5. Development of individual intolerance to the study drug (for the study group).
6. The development of concomitant diseases or conditions that, according to the researcher, may distort the results of the study, restrict the rights of the volunteer or put him at greater risk.
7. The appearance of contraindications to the use of the study drug in the period before the last intake of the second 10-day cycle (for the study group).
8. Participation in a clinical trial using a different therapy.
9. Disagreement on following reliable contraceptive measures (sexual abstinence; or a combination of 2 different methods: for example, barrier and spermicides, or barrier and intrauterine device, or barrier and hormonal, etc.) – for participants with preserved childbearing potential in the period before the last intake of the second 10-day cycle (for the study group).
10. Pregnancy.

A woman who excluded from the study due to the onset of pregnancy during the clinical trial is subject to medical supervision during the entire period of pregnancy, as well as for 6 months postpartum period to assess the condition of the woman and the born child (observation is carried out if possible and only if her desire and consent to such observation is mandatory). Information about the course of pregnancy and its outcome is entered in the primary documentation (with the consent of the woman). During the entire period of pregnancy, together with an obstetrician-gynecologist (with the consent of the pregnant woman and, if possible, contact with a doctor), observing a woman, her general condition, data reflecting the nature of the course of pregnancy, results of laboratory and instrumental examination methods, including ultrasound, are analyzed. Monitoring of the born child is carried out with the consent of the woman together with the district pediatrician (if possible, contact with him) until the child is 6 months old to analyze the clinical status of the child, data from laboratory and instrumental research methods.

There are no procedures for replacing excluded participants.

Diaries of participants

The diaries of the participants (study groups and control groups) are presented in Appendices 1 and 2. The diaries include 2 blocks to be filled in by the research participant: 1) initial information about the participant: initials, gender, date of birth, presence of smoking experience; 2) information about compliance with the accepted therapy, about the tolerability of preventive therapy, cases of ARVI incidence, severity and duration of symptoms, treatment methods.
To reduce the risk of violation of the dosage regimen, participant diary in the study group provides detailed instructions on the preparation, administration and features of the use of the drug under study, as well as the diary will contain a calendar for registering the days of

instillations. In addition, when issuing a diary to a participant, it indicates the contact details of the doctor for direct communication with the researcher in case of symptoms of acute respiratory viral infections during the study period.

Nasopharyngeal smear

Prior to the start of preventive observation, the participant must take a smear from the mucous membranes of the upper respiratory tract (nasopharyngeal[8]). It is allowed to use the results of a PCR test before inclusion in the study, but no later than 3 days. If the study is completed with the registration of a confirmed case of COVID-19, PCR test is not performed at visit 3, the results of the tests performed to confirm the patient's recovery are accepted.

The procedure for working with biological material:

1. The biomaterial is taken on an empty stomach or not earlier than 2 hours after eating and drinking; before rinsing, irrigation with medicines.
2. The study is conducted before the start of treatment with antibiotics, antiseptics, antifungal and antiviral drugs.
3. Caution should be exercised in the presence of pronounced inflammatory processes in the pharynx. In case of severe edema, the material is not taken.
4. The material is taken before carrying out hygienic procedures.

Taking a nasopharyngeal smear for the presence of SARS-CoV-2 RNA is carried out as follows:

1. Scraping of epithelial cells from the oropharynx is carried out with a dry probe, rotational movements from the surface of the tonsils, palatine arches and posterior wall of the oropharynx.
2. Scraping of epithelial cells from the nasopharynx, a smear is taken with a dry sterile probe. The probe is inserted with a gentle motion along external wall of the nasal cavity to a depth of 2–3 cm to the inferior nasal concha. Then the probe is slightly lowered to the bottom, inserted into the inferior nasal meatus under the inferior nasal concha and removed along external wall of the nasal cavity, producing rotational movements (3–4 cm in children and 5–6 cm in adults).
3. After taking the material, the tampon should be placed in a sterile disposable tube of the type "Eppendorf" with 500 ml of transport medium, mix with a few neat movements, squeeze the tampon on the inside "Eppendorf", remove the probe and the working part of the tampon – do not leave it in Eppendorf. Next, close the cap of the test tube tightly, sterilize with a disposable alcohol wipe, wait for drying and label.
4. The probe and its working part must be disposed of immediately after inoculation in Eppendorf according to the rules for the disposal of potentially infected material (Class B waste).

Scraping from the oropharynx is performed with the maximum possible pressure. At the same time, the participant should not experience pain or discomfort, but it is necessary to press cotton swab as tightly as possible.

[8] It is permissible to accept the results of a nasal or pharyngeal smear, as well as the results of studies performed before inclusion in the study for no more than 72 hours.

Both smears are placed in the same test tube to create the highest possible concentration of the virus (if present).

Labeling and packaging:

1. A test tube of the type "Eppendorf" should be treated with an alcohol wipe (after taking the biomaterial and closing cap Eppendorf, let it dry (2-3 seconds) and stick-on 1st barcode;
2. Eppendorf with the taken material should be placed in a packaging bag with zip lock. It is allowed to place material from only one patient in one packaging bag.
3. Place the sealed bag inside a plastic sterile sputum container (with a red cap). Paste the 2nd barcode on the sputum container. It is allowed to place material from only one patient in one container.
4. Put the prepared containers in a large zip package (up to 5 containers are included).
5. To transport the biomaterial, use a separate shipping container. It is necessary to attach the "Transfer Acceptance Certificate" (Number of samples. Inscription: to the PCR department URGENTLY!).

Transportation:

1. Transportation of samples is carried out in compliance with the requirements of SP 1.2.036-95 "Procedure for accounting, storage, transfer and transportation of microorganisms of pathogenicity groups I - IV" by employees trained in the practice of safe handling of biomaterials, in compliance with precautionary measures and the use of personal protective equipment (PPE).
2. The biomaterial is transported to the laboratory at a temperature of +2 ... +8 °C, and if it is impossible to deliver the biomaterial to the laboratory within 48 hours, biomaterial should be frozen at -20 °C.

It is allowed to use eppendorfs only with locking systems. Eppendorfs without locking system cannot be used since they can open spontaneously. When taking the biomaterial and closing the Eppendorf, precautions must be taken especially carefully to prevent the biomaterial from entering the environment, because after placing the probe in the Eppendorf and at the time of its closure, a slight shaking of the eppendorf and spilling from the test tube is possible.

The study of the nasopharyngeal smear for the presence of SARS-CoV-2 RNA during screening is carried out with the support of DiaLab LLC Plus."

Used process aids and personal protective equipment (PPE):

1. Urogenital disposable sterile probe type A "Universal" (provided by DiaLab LLC Plus").
2. Eppendorf with transport environment (provided by DiaLab LLC Plus").
3. Package with zip lock (provided by DiaLab LLC Plus").
4. Personal protection kit.

The collection of clinical material is carried out with the mandatory use of personal protective equipment.

Medical waste management:

1. Medical waste generated when working with biological material belongs to class "B" – epidemiologically hazardous waste.
2. Personal protective equipment is required for medical workers engaged in the collection and disposal of Class B medical waste.
3. Work on the treatment of medical waste of class "B" is organized in accordance with the requirements of Sanitary Regulations and Norms - SanPiN 2.1.7.2790-10 "Sanitary and epidemiological requirements for the treatment of medical waste" and SanPiN 2.1.3.2630-10 "Sanitary and epidemiological requirements for organizations engaged in medical activities".

In case of a positive PCR test before the start of the drug, volunteer is not included in the study, is isolated and falls under the supervision of a district doctor. In case of a positive PCR test during or after the preventive course, volunteer continues to participate in the study, is isolated under observation and, if possible, comes to visit 3 after the quarantine is lifted (at least 14 days from the date of signing Consent for the treatment of a new coronavirus infection COVID-19 in outpatient conditions (at home) and observing the isolation regime or discharge from the hospital in case of laboratory confirmation of COVID-19) with the provision of data on their condition to the researcher coordinator.

STUDY POPULATION

Adult volunteers who do not have clinical symptoms of ARVI.

Inclusion criteria

1. Volunteers of both genders over 18 years old.
2. Obtaining a written form of informed consent.
3. Ability and consent to participate in this study.
4. No symptoms of respiratory infection.
5. A negative result of a PCR study for the presence of SARS-CoV-2 RNA according to the biomaterial obtained by nasopharyngeal [9]smear.

Non-inclusion criteria

1. Any other concomitant diseases or conditions that, in the opinion of the research doctor, may distort the results of the study, restrict the rights of the volunteer, or put him at greater risk.
2. Contraindications to the use of the study drug.
3. Individual intolerance of the ingredients included in the composition of the study drug.
4. Pregnancy or breast-feeding.
5. Controversial result of PCR test for the presence of SARS-CoV-2 RNA according to the biomaterial obtained by nasopharyngeal smear.
6. Participation in a clinical trial using the investigated therapy for 30 days prior to inclusion in this study.
7. Disagreement on following reliable contraceptive measures in the framework of the study

[9] It is permissible to accept the results of a nasal or pharyngeal smear, as well as the results of studies performed before inclusion in the study for no more than 72 hours.

(sexual abstinence; or a combination of 2 different methods: for example, barrier and spermicides, or barrier and intrauterine device, or barrier and hormonal, etc.) – for participants with preserved childbearing potential.

Number of participants

In this study, the main parameter of effectiveness is the proportion of patients with acute respiratory viral infections, including COVID-19, at the end of the period of preventive administration of the drug. The study is planned to show that in the study group, the number of patients with acute respiratory viral infections, including COVID-19, will be significantly less compared to the control group.

The efficiency parameter was selected based on international recommendations for manufacturers of medicines and biological products [28].

The null hypothesis will be tested by comparing the number of cases in the two groups at the end of the period of preventive administration of the drug. It is expected that at least 90% of randomized patients will be suitable for inclusion in the population of the primary analysis (PP).

The statistical purpose of the study is a comparative study of the effectiveness of the preventive regimen of the drug. In the main group of study I, study drug Ingaron 100,000 IU, lyophilizate, will be used to prepare a solution for intranasal administration, 1 time a day every other day for 10 days with a repeat of the 10-day course of preventive administration after 7 days of interruption.

To estimate the sample size in this study, an 80% power level was taken (P – probability of not missing the present effect is 0.8) and a one-sided level of statistical significance of 5% (α – the probability of making an erroneous decision about the presence of an effect is less than 0.05). The statistical criteria used are one-sided due to the availability of information about the superiority of the effect of the study drug over the lack of preventive measures against the nosology being studied [28].

Thus, the sample size was calculated based on the following parameters:

- at the required significance level $\alpha = 0.05$, the value of $Z = 1.96$;
- level of statistical power is assumed to be 80%, the value of $Z = 0.84$;
- method of sample formation – randomization using random elements.

The primary criterion of effectiveness is the proportion of patients with acute respiratory viral infections, including COVID-19, at the end of the period of preventive administration of the drug (measurement time: 28 days). Secondary efficacy criteria: proportion of patients with confirmed COVID-19 at the end of the period of preventive administration of the drug (measurement period: 28 days); proportion of patients with acute respiratory viral infections, including COVID-19, at the end of the follow-up period (change period: 2 months); proportion of patients with confirmed COVID-19 at the end of the follow-up period (period of change: 2 months); and the frequency of development of complicated course of ARVI.

The literature analysis conducted on similar studies of the effectiveness and safety of the use of interferon-gamma shows that the incidence of ARVI can be observed in 2% of cases in the main group of patients taking interferon gamma, as well as in 14% of the control group taking alternative methods of protection and representing medical workers working in the "red zone" and those at high risk through frequent and prolonged contact with infected patients ($p<0.05$).

Provided incidence in the control group is from 1 to 5% (taking into account the assumption that the incidence in the control group will be approximately equal to the average incidence of the general population) [29], and incidence in the study group will be at least 3% lower (which can already be considered a minimally clinically significant decrease in incidence in the absence of preventive measures with proven effectiveness, which could be taken as a standard), minimum sample size should be 630 patients (taking into account 10% of early retirement). Such a sample size will also make it possible to establish a decrease in incidence by 4% or more when incidence is set at up to 8% in the control group and a decrease in incidence by 6% or more when the incidence is set at up to 18% in the control group (Table 1 – Dependence of the sample size on various parameters).

The calculation of the required sample size was performed using a formula for calculating the sample size for a qualitative sign [30]:

$$n = \frac{P_1 * Q_1 * t^2 + P_2 * Q_2 * t^2}{(P_1 - P_2)^2}$$

Note to the formula:
P – proportion of cases in which the study sign occurs,
Q – proportion of cases in which the study sign does not occur,
t – critical value of the Student's t-test at the appropriate level of significance.

Considering the ratio of the distribution of patients into groups 1:1 with the above parameters, the study should complete at least 572 patients: 286 in each group. Considering the possible 10% premature exclusion and withdrawal of informed consent, it is necessary to randomize 630 patients (315 in each group).

Below is the dependence of the sample size on the parameters of the magnitude of the expected effect and the minimum difference that needs to be detected (Table 1 – Dependence of the sample size on various parameters).

Thus, the sample size in each group with a random distribution method will be[10]:

Table 1 – Dependence of the sample size on various parameters

The proportion of sick patients in the control group, %	Decreased proportion of cases compared to the control group, %							
	2	3	4	6	8	10	12	14
2	207	-	-	-	-	-	-	-
3	411	136	-	-	-	-	-	-
4	613	227	101	-	-	-	-	-
5	809	315	151	-	-	-	-	-
6	1001	400	200	66	-	-	-	-
8	1373	526	295	109	48	-	-	-
10	1728	686	386	151	72	37	-	-
12	2066	840	473	189	95	53	31	-
14	2387	988	556	228	117	67	41	25

[10] The calculation is given for a power of 80%, a one-sided significance level of 0.05 and taking into account 10% of the early exclusion of patients from the study

16	2692	1126	634	263	136	80	51	33
18	2979	1257	707	297	156	92	59	40
20	3249	1382	777	329	175	106	68	46
22	3502	1498	843	359	193	117	76	53
24	3739	1607	904	387	209	128	84	58

Thus, in the present study, taking into account the possible 2% exclusion of patients at the screening stage due to non-compliance with the inclusion/non-inclusion criteria, it is planned to include up to 642 volunteers with a 1:1 distribution in each of the 2 parallel groups (study and control), of which up to 321 people will use study drug Ingaron with preventive objective, up to 321 people, will not use the study drug and will form a control comparison group.

The screening number of the participant is assigned in the order of inclusion of participants in the study and consists of numerical character corresponding to the number of the research center and three numerical characters of the serial number of the participant in this center. That is, the screening number of the first participant in the first center should look like this: 1-001, following: 1-002, etc. The screening number of the three hundred and twenty-fourth participant of the third center will look like this: 3-324. It is prohibited to re-assign a screening number to a participant. The number is unique.

Research hypothesis
Preventive administration of Ingaron will not lead to a decrease in the incidence of acute respiratory viral infections, including COVID-19, among adult volunteers.

STUDY THERAPY

Trade Name: INGARON®

International nonproprietary or generic name: Interferon gamma human recombinant

Registration number: LS – 001330

Dosage form: Lyophilizate for the preparation of solution for intranasal administration.

Drug form: Lyophilizate for the preparation of solution for intranasal administration in vials of 100,000 IU per 1 vial. 1 vial of drug, 1 vial of water for injection (5 ml) and 1 cap-dropper made of polyethylene in packaging of polyethylene or medical dropper in contour cellular package or in cassette contour package.

Shelf life: 2 years. After the preparation of the solution for 10 days.

Method of administration and dosage:
Intranasally. 2–3 drops in each nasal passage every other day 30 minutes before breakfast for 10 days. After instillation, it is recommended to massage the wings of the nose with your fingers for

several minutes to evenly distribute the drug in the nasal cavity. Preparation: The contents of the vial are dissolved in 5 ml of water for injection.

Overdose: Overdose cases are not known.

Effects on ability to drive and use machines: Not studied.

Storage conditions: The drug should be stored in a dry place, protected from light, at temperature not higher than + 25 ° C. The solution of the drug should be stored for no more than 10 days in the refrigerator (do not freeze). Keep out of reach of children.

Manufacturing enterprise/organization accepting consumer claims:
LLC "NPP "Pharmaclon", Russia.
Legal address: 142279, Moscow region, Serpukhovskii district, Obolensk workers settlement, Obolenskoe highway industrial zone, building 5A, office 312.
Address of the place of manufacture: 143422, Moscow region, Krasnogorskii district, Petrovo-Dalnee village, J.S.C. “Biomed”-Mechnikov Tel/fax (4967) - 36-07-71, (495) – 120-12-47
E-mail: info@pharmaclon.ru Internet: www.pharmaclon.ru

Labelling: The inscription "For post-marketing research RAIN-2020" is applied to the primary packaging and secondary (consumer) packaging of the study drug product, the inscription "Not for sale" is additionally applied to the secondary (consumer) packaging in accordance with the requirements of the Federal Law "On Circulation of Medicines" dated 12.04.2010 N 61-FZ as amended Federal Law No. 429-FZ from 22.12.2014.

Compliance assessment
Assessment of compliance with study preventive therapy is evaluated on the basis of data recorded in the participant's diary, on visit 3, as well as in advance as part of an oral survey of the participant on a phone call visit after the end of preventive use of the drug. Compliance is assessed on a 100% scale, where:
100% – participant completed 2 cycles of 10-day courses without violating the dosage regimen and the frequency of admission
90% – participant completed 2 cycles of 10-day courses with a single violation of dosage regimen or dosage frequency
80% – participant completed 1 cycle of the 10-day course without violating dosage regimen or dosage frequency
70% – participant completed 2 cycles of 10-day courses with a double violation of dosage regimen or dosage frequency (single violation of each course)
60% – participant completed 1 cycle of 10-day course with a single violation of dosage regimen or dosage frequency
50% or less – participant completed 1 or 2 cycles of 10-day courses with a systematic (twofold or more) violation of the dosage regimen or dosage frequency in each of the courses (non-compliance with a single dose, frequency of use and/or its duration).
Compliance of 50% or less is the criterion for excluding a participant from the study.

STUDY PARAMETERS OF EFFICIENCY AND SAFETY

Effectiveness criteria

Effectiveness criteria will be evaluated according to the data recorded in the participants' diaries, in primary medical documentation.

Primary effectiveness criterion:

The proportion of patients with acute respiratory viral infections, including COVID-19, at the end of the period of preventive administration of the drug (measurement time: 28 days).

Secondary effectiveness criterion:

1. The proportion of patients with confirmed COVID-19 at the end of the period of preventive treatment of the drug (measurement period: 28 days).

2. The proportion of patients with acute respiratory viral infections, including COVID-19, at the end of the follow-up period (change period: 2 months).

3. The proportion of patients with confirmed COVID-19 at the end of the follow-up period (change period: 2 months).

4. Frequency of development of complicated course of ARVI.

5. The proportion of participants with each of the scores (0-8) according to the WHO Clinical Improvement Scale (change period: 28 days).

6. The proportion of participants with each of the scores (0-8) according to the WHO Clinical Improvement Scale (change period: 2 months).

7. Duration of symptoms of the disease of study participants who had acute respiratory viral infections, including COVID-19 (change period: 2 months).

8. The duration of the symptoms of the disease of the study participants who were infected with ARVI, including COVID-19 (measurement period: 28 days).

Confirmation of clinical cases of ARVI, including COVID-19:

In the following cases:

1) a positive result of PCR on SARS-CoV-2 RNA, regardless of the presence of clinical symptoms;
2) appearance of clinical symptoms of ARVI in the absence of a PCR result on SARS-CoV-2 RNA or in the case of a negative result on SARS-CoV-2 RNA, -

at any stage during participation in the study, a completion visit (Visit 3) is conducted at the end of the quarantine period (at least 14 days from the date of signing Consent for the treatment of a new COVID-19 coronavirus infection in outpatient settings (at home) and compliance with the isolation regime or discharge from the hospital in case of laboratory confirmation of COVID-19), at which the patient returns the participant's diary and reports his condition to the doctor-researcher, transmits information about hospitalization, duration of symptoms, results of tests and performed studies.

Definition of the COVID-19 case:

Suspicious case of COVID-19

Body temperature above 37.5° in addition to one or more of the following signs (in the absence of other known causes that explain the clinical picture, regardless of the epidemiological history):

- Cough (dry or with scant sputum)
- Shortness of breath
- Feeling of congestion in the chest
- SpO_2 no more than 95%
- Sore throat
- Nasal stuffiness or moderate rhinorrhea
- Smell disorders or anosmia
- Ageusia
- Conjunctivitis
- Fatigue
- Myalgia
- Headache
- Vomiting
- Diarrhea
- Skin rash

Probable case of COVID-19

Body temperature above 37.5° in addition to one or more of the following signs:

- Cough (dry or with scant sputum)
- Shortness of breath
- Feeling of congestion in the chest
- SpO_2 no more than 95%
- Sore throat
- Nasal stuffiness or moderate rhinorrhea
- Smell disorders or anosmia
- Ageusia
- Conjunctivitis
- Fatigue
- Myalgia
- Headache
- Vomiting
- Diarrhea
- Skin rash

In the presence of at least one of the epidemiological signs:

- Return from cross-border travel 14 days before the onset of symptoms
- The presence of close contacts over the past 14 days with a person under surveillance for COVID-19, who subsequently became ill
- The presence of close contacts over the past 14 days with a person who has laboratory confirmed diagnosis of COVID-19

- The presence of professional contacts with persons who have a suspected or confirmed case of COVID-19

Or in combination with characteristic changes in the lungs according to computed tomography (CT), regardless of the results of a single laboratory test for the presence of SARS-CoV-2 RNA and an epidemiological history.
Also, a possible case of COVID-19 should include a clinical case in the presence of the clinical manifestations described above (fever in combination with one or more signs) with characteristic changes in the lungs according to imaging studies if it is impossible to conduct a laboratory study for the presence of SARS-CoV-2 RNA.

Confirmed case of COVID-19
A positive result of laboratory test for the presence of SARS-CoV-2 RNA using nucleic acid amplification methods or SARS-CoV-2 antigen using immunochromatographic assay regardless of clinical manifestations, or a positive result for IgA, IgM and/or IgG antibodies in patients with clinically confirmed COVID-19 infection.

In the case of ARVI symptoms characteristic of a suspicious case of COVID-19, accompanied by a negative result of PCR test, registered during or after a preventive course (during the period of participation in the study after randomization until the end of the observation period), the patient may additionally undergo a quantitative test for the presence of IgM and IgG antibodies to SARS-CoV-2 by the ELISA method for the purpose of additional verification and detection of COVID-19 cases. An additional quantitative test for antibodies to SARS-CoV-2 can be performed from the 10th to the 21st day after the appearance of the first symptom of ARVI to register the immune response of the acute phase of infection at the beginning of its development (increased IgM levels) or during high-grade response (increased IgM and IgG), considering the seronegative the period of the disease (5-7 days). The analysis is taken only in the absence of fever and a satisfactory general condition of the patient, accompanied by a favorable recovery dynamics. When interpreting the results, it is necessary to consider the probability of obtaining false positive results (for example, the presence of "cross-reacting" antibodies). If the interpretation of the results is difficult, it is allowed to conduct a repeated ELISA study using the same test systems after 5-7 days to assess the dynamics of indicators. Quantitative determination of IgM and IgG antibodies in the blood by the ELISA method will be carried out with the support of DiaLab LLC Plus."

The condition of the study participant is assessed according to the WHO standard scale of clinical improvement from 0 to 8 points at each visit, including a phone call visit. In case of registration of ARVI at the final visit 3, in parallel with the current assessment of the participant's condition, an additional assessment of the case is carried out according to the WHO scale, reflecting the maximum clinical manifestation of the disease.

WHO Clinical Improvement Scale

Assessment on the WHO scale	0	1	2	3	4	5	6	7	8
Select the appropriate score from 0 to 8	Not infected	Outpatient		Hospitalized with mild form		Hospitalized with severe form			Died
	there are no clinical or virological signs of infection	no activity restrictions	activity restrictions	hospitalized, no oxygen therapy	hospitalized, oxygen therapy through a mask or nasal cannula	non-invasive lung ventilation or high-flow oxygen therapy	endotracheal intubation and mechanical ventilation	ventilation + additional organ support – pressor drugs, renal replacement therapy, extracorporeal membrane oxygenation (ECMO)	death

Safety criteria

The assessment of the safety of treatment will be carried out based on registration of adverse events by analyzing complaints and subjective symptoms, comparative analysis of clinically significant changes in laboratory parameters, as well as the severity of these changes, using the CTCAE scale version 4.03 from 2010.

Each participant should be monitored by a researcher for the occurrence of adverse events, which should be classified according to the severity and connection with the drug under study during the entire period of participation in the study.

Adverse events:

Adverse reaction (AR) – an unintentional adverse reaction of the body associated with the use of a drug and suggesting the presence, at least, of a possible relationship with the use of a suspected medicinal product.

Adverse event (AE) – any adverse change in the state of health of the patient or the subject of a clinical trial to whom the drug (study) product was prescribed, regardless of the causal relationship with its use. AE may represent any adverse and unintended change (including deviation of the laboratory indicator from the norm), symptom or disease, the time of occurrence

of which does not exclude a causal relationship with the use of drug product, regardless of the presence or absence of a relationship with the use of drug product[11].
Symptoms of acute respiratory infection: fever, manifestations of general infectious intoxication, signs of respiratory damage are not considered as adverse event, however, they are recorded during the study and analyzed as data for evaluating effectiveness.

Assessment of the causal relationship:
Methods for assessing the degree of causal relationship are based on the following criteria:

- the presence of a reliable temporary association of the AE with the use of the study drug (AE are registered after the start of the use of the study drug before the completion of participation in the study);
- presence of a direct temporary connection of AE with specific administration of the drug (for example, development of AE during instillation);
- possibility of explaining the development of AE by the pharmacological effect of the drug;
- availability of information about such AE as a possible side effect in Clinical Investigation Brochure/guidelines for medical use;
- description of similar cases in the literature;
- presence of additional specific data indicating the association of AE with the drug (for example, the presence of specific antibodies, positive result of allergological tests);
- positive test with the withdrawal of the study drug (AE was resolved or its severity decreased after the drug was discontinued);
- positive test with repeated administration of the drug under study (AE reappeared or its severity worsened with repeated administration of the drug after withdrawal);
- presence of other reasons for the development of this AE (manifestations of the underlying disease, concomitant diseases and conditions, concomitant therapy, food, lifestyle, etc.).

The association of adverse events with the study drug will be evaluated based on the following principles in accordance with the WHO classification:

- **reliable** – clinical manifestations, including violations of laboratory parameters that occur during the period of taking drug s and which cannot be explained by the presence of existing diseases and the influence of other factors and chemical compounds. Manifestations of an adverse reaction regress after the drug is discontinued and occur when it is re-prescribed;
- **probable** – clinical manifestations, including changes in laboratory parameters associated with the instillation of the drug, which are unlikely to be related to concomitant diseases or other factors and which regress with the withdrawal of the drug. The response to the rechallenge is unknown;
- **possible** – clinical manifestations, including changes in laboratory parameters associated with the use of the drug, but which can be explained by the presence of

[11] Due to statistical necessity, adverse events are recorded both in the study group and in the control group. Evaluation and registration of adverse events begins from the moment of signing the informed consent form.

concomitant diseases or taking other drugs and chemical compounds. Information about the reaction to drug withdrawal is unclear;

- **questionable** – clinical manifestations, including changes in laboratory parameters, which occur in the absence of a clear temporal connection with taking medication; there are other factors (drugs, diseases, chemicals) that may be the cause of their occurrence;
- **conditional** – clinical manifestations, including violations of laboratory parameters attributed to "adverse reactions" that need additional data (for an accurate assessment) or these obtained data are currently being analyzed;
- **unclassifiable** – reports of a suspected adverse reaction cannot be evaluated because there is not enough information or it is contradictory.
- **unrelated** – clinical manifestations are not associated with the use of the drug.

Serious adverse reaction (SAE) – AE, which leads to death[12], poses life threatening[13], requires hospitalization of the patient or its extension[14], leads to persistent or severe disability, to congenital anomalies or malformations[15], requires medical intervention to prevent the development of these conditions.

Unlabeled adverse reaction (unlabeled AE) – an undesirable reaction, nature, severity or outcome of which does not correspond to the information in the current instructions for the medical use of the drug or in investigator's brochure for unapproved drug.
All **unexpected serious adverse events (unexpected SAE)** those recognized by the researcher as related to the drug are classified as **unexpected serious adverse drug reactions (unexpected SAE)**. Serious adverse drug reaction report form is presented in Appendix 3.

Persistent AE – AE, lasting for a long time, including between cycles of therapy. Persistent AE is registered once. If there were no AE symptoms at the visit before the first use of the study drug, time of AE completion is the moment when AE is completely stopped. If AE symptoms were registered at the visit before the first use of the study drug, time of AE completion is the moment when the values of the deviated indicators/severity of AE symptoms (degree according to CTCAE) return to the basic (initial) values, i.e., before the use of the product under study. If AE symptoms continue at the time of completion of the study, AE registration form is marked "ongoing". If AE changes the degree to a higher one (for example, from 1 to 3 degrees), a note about the change in AE degree with the date is made in the same AE registration form. At the

[12] Death is an outcome, not the SAE itself, so such a name should not appear as a name. If a case of death for an unknown reason is identified, researcher should make every effort to identify its suspected causes. SAE in such cases can be referred to as "Death by unexplained cause" only in cases where the causes of death are not known and cannot be clarified. In case of a fatal outcome due to COVID-19, the information is recorded in the primary medical documentation of the study participant without registration of the SAE.
[13] The term "Life threatening" in this context means that the volunteer participating in the study was at immediate risk of death during the occurrence of adverse event. This term does not apply to cases where adverse event could hypothetically cause the death of a participant if it were more intense in severity or longer in duration.
[14] Hospitalization for optional or pre-planned treatment of concomitant diseases that the participant had prior to inclusion in the study, the course of which did not worsen during participation in the study, is not considered to SAE, as well as being in a hospital for less than 24 hours or hospitalization for social reasons.
[15] Pregnancy cases in the participants of the clinical study are not subject to registration as AE, except in cases when the child has congenital anomaly or malformation (case is registered as AE).

same time, when closing AE registration form, maximum severity of AE is indicated, which was observed for the entire period of AE persistence as part of the subject's participation in the study.

Recurrent AE – AE, which was completely resolved, for example, during one cycle of therapy, and then reappeared, for example, on the next cycle of therapy, while the participant is in the study. Each recurrent AE is registered separately.

All AE are registered in the primary medical documentation of the participant based on physical examination, survey, and diary records. The following information must be recorded in the primary medical documentation (outpatient card) for each AE:

- severity (mild, moderate, severe);
- nature of adverse event;
- relationship with study drug;
- duration (date of occurrence and end date), preferably with an indication of the time interval (hours) from the moment of administration of the study drug;
- whether adverse event is serious.

The severity is assessed using the CTCAE scale version 4.03 from 2010. The CCAE scale contains a list of the most frequent AE recorded in clinical study, in tabular format, indicating criteria of various degrees of severity (from 1 to 5, where 5 is death as a result of AE). For AE that are not in the tabulated list, the severity is determined in accordance with the textual description of the degrees of severity.

The terms "serious" and "severe" are not synonymous. The term "severe" is often used to describe the intensity (severity) of a particular event (for example, anemia of severe, moderate or mild severity); however, the event itself may be clinically insignificant (for example, severe headache).

The concept of "severe" is not equivalent to the concept of "serious". The criteria of the latter are the outcome of the event or the measures, which are usually associated with the elimination of life threatening or severe disorders of vital activity. The criterion of seriousness, and not the severity of adverse event, should be guided when determining the need for expedited safety report of LLC "NPP "Pharmaclon" and authorized agencies.

The AE notification form is presented in Appendix 4.

Urgent event:

Urgent events include all serious adverse events.

All SAE detected during the period from the moment of signing the informed consent, even before the application of the first dose of the product under study until the end of the study, are subject to registration. The researcher has the right to provide reports on the development of a disease that has developed at any time after the established mandatory observation period, but it is necessary to provide an appropriate justification for the presence of a causal relationship.

In the event of a serious adverse event, researcher is obliged to:

- provide (if necessary) the study participant with appropriate qualified medical care, including laboratory tests and/or instrumental examinations;

- within 24 hours from the moment when the researcher became aware of the occurrence of adverse event, send the data to LLC NPP Pharmaclon (contact information: tel.: 8 800 777 86 04; e-mail: adversereaction@drugsafety.ru);
- provide a detailed written report as soon as possible;
- continue monitoring the participant until the full resolution of the SAE.

Any additional information and supporting documentation (blinded copies of the results of laboratory tests, procedures, pathologist's report or postmortem epicrisis in case of death, etc.) will be provided by the Researcher in additional written messages of LLC NPP Pharmaclon. In case of death of a participant, the Researcher is obliged to provide any additional information at the request of LLC NPP Pharmaclon.

The initial report (completed form of notification of AR) and subsequent detailed and additional reports should identify the subjects of the study by the unique numbers assigned to them, not by the names of the subjects or their addresses and other personal data.

In connection with the occurrence of serious adverse events, the researcher is obliged to notify the ethics committee. The Ethics Committee may, if necessary, discontinue or cancel the study.

The minimum information that should be included in the initial notification of the occurrence of an urgently reported event should contain the identification data of the participant under which he passes in the study, identification data of the person reporting the occurrence of this phenomenon (full name of the chief researcher or authorized employee), characteristics of the event that occurred and its causal relationship with the use of the investigated drug.

Except those cases when the urgently reported event was sufficiently documented in the initial message about its occurrence, the researcher must provide all additional information available to him in subsequent messages about the urgently reported event using the same form, the same ways of its transmission and the time frame as established for the initial message about the urgently reported event. These procedures should continue until AE has been fully documented and reported.

After sending by e-mail the completed SAE notification, researcher must place the originals of the initial and subsequent messages about urgently reported events in investigator file.

Events deemed NOT to require urgent notification include:

- hospitalization for optional or pre-planned treatment of concomitant diseases that the participant had prior to inclusion in the study, the course of which did not worsen during participation in the study;
- hospitalization, death, or life threatening due to the development of complications of ARVI (COVID-19) – however, this information is necessarily recorded and analyzed to assess effectiveness.

Features of AE registration in some cases:

Lack of preventive effect

Absence of preventive effect of therapy should not be registered as AE.

Pregnancy

All cases of pregnancy that developed in the participants of the clinical trial against the background of the study therapy during the period of participation in the study are subject to mandatory registration in the Pregnancy Registration Form and are not accompanied by the registration of AE/SAE. The signed and dated pregnancy form is sent to LLC "NPP "Pharmaclon" by e-mail: medical@pharmaclon.ru , - within 5 working days from the date of notification of the research doctor.

AE in the period before taking study drug

In the presence of deviations of laboratory, physiological and/or instrumental indicators at the screening or randomization visit before the first use of the drug, in the future, the following are subject to registration as AE:

- all deviations accompanied by an increase in severity according to the version used;
- deviations that are not associated with a change in severity, but have, from the researcher's point of view, clinical significance.

If the participant had deviations of laboratory, physiological and/or instrumental indicators at the visit before the first use of the study drug, after which the indicators during the study normalized or the severity of the deviation changed for the better, and then changed again for the worse, but the values of the indicators remained within the same severity according to If the patient was on a visit before the first use of the study drug, the phenomenon should not be registered as AE, except in cases where it is clinically significant from the point of view of the research physician.

Registration of a disease/syndrome characterized by several symptoms

In case of registration of a disease accompanied by various symptoms, registration of individual symptoms as AE is not required, however, it is recommended to list all the symptoms of the disease in the note to the description of the AE.

For more detailed information on the procedures for registration and evaluation of adverse events under this Protocol, see the Guide on Adverse Events Version 2 of 17/02/2021.

QUALITY CONTROL

Direct access to primary data/documentation

The researcher/research center is obliged to provide direct access to primary data/documentation for examination by the Ethics Council under the Ministry of Health of the Russian Federation, an Independent Ethics Committee, as well as inspections by authorized bodies. Ethics Council/The Independent Ethics Committee, the authorized bodies, and the sponsor of this study, to the extent permitted by law, will have direct access to the original medical records of the participant to verify the procedures and/or research data, without violating the confidentiality of the participant's data. By signing the Information Sheet with the informed consent form, the Participant gives permission for such access.

Inspection

National regulatory authorities may conduct inspections during and after the study.

Accounting of drugs

The researcher or other responsible persons will keep records of the study drug.

The researcher is responsible for the fact that the study drugs:

- stored in proper conditions in a lockable and safe place;
- scheduled, and the registration of drugs is documented with the indication of the number of the participant to whom the drug was issued.

The control of the study drugs should be documented throughout the study.

Storage of drugs

The Ingaron® preparation should be stored in a dry place protected from light, at temperature no higher than +25 ° C. Ingaron® solution should be stored for no more than 10 days in the refrigerator (do not freeze).

All participants will be instructed by the researcher about the required storage conditions when receiving study drug at visit 1.

RESEARCH DOCUMENTATION

Storage of documentation

The researcher undertakes to keep all documentation on the study, including the original medical documentation of the participants (outpatient records, diaries) for 15 years after the completion of the study. This documentation regarding the ongoing research should be available for audits and inspections by regulatory authorities.

STATISTICAL METHODS

Populations for analysis

During the statistical analysis, the following populations of participants will be studied:

- ❖ All participants included in the study (FAS, Full Analysis Set). This population will be used to describe basic characteristics, including demographic and anthropometric indicators, data on concomitant diseases, and will also be used as the main population to assess performance parameters. In this case, the participant's group will be determined by the "intention to treat" (ITT Analysis).
- ❖ Auxiliary analysis of effectiveness parameters is planned for all subjects who completed the study without significant deviations from the study protocol (PP, Per Protocol).

Methods of descriptive statistics

For numerical indicators, such as demographic and anthropometric data (body weight, age, height, BMI), as well as numerical performance parameters will be calculated:

- Number of missing values (N);
- Minimum value (Min);
- Maximum value (Max);
- Arithmetic Mean (M);
- Standard Deviation (SD);
- 95 % confidence interval (CI) for the mean;

- Median (Me).

For qualitative variables (frequency of AE/SAE development, for example), absolute number in the n/N format will be given, as well as the percentage (%).

Analysis of basic characteristics

The distribution of subjects, demographic and baseline characteristics will be presented using descriptive statistics methods for all subjects included in the study (FAS-population). An intergroup comparison of the basic quantitative characteristics will be carried out using the t-test (or the Mann-Whitney test), depending on the type of data distribution. For categorical data, the ^{2}-criterion or Fisher's exact test will be applied if the expected frequency in any of the cells is less than 5.

Standard methods available in the XLSTAT 2020.3 program will be used for data analysis.

When analyzing numerical data, preliminary testing of variables for the normality of the distribution will be carried out using Shapiro-Wilk's test, as well as a test for asymmetry and kurtosis with an indication of the p value when testing the null hypothesis of the normal distribution of the variable. In the case of a normal distribution, an intra-group comparison of parameter changes is carried out using a paired t-test. For a comparative evaluation, the $\chi 2$-criterion or the exact Fisher test will be used if the expected frequency in any of the cells is less than 5.

Significance level

A significance level of 0.05 will be used in all tests. Correction for the multiplicity of comparison is not introduced.

Handling missing data and significance level

There are no plans to use data reconstruction methods in this study. The probability of a type I error (two-way significance level) will be set at 5% for all comparisons. Correction for the multiplicity of comparison is not carried out.

Research Report

The report will be prepared based on the results obtained at the research center.

The submitted report should have the character of a full-fledged reasoned scientific research with a clear description of the amount of work carried out, research methods, principles of the detectable preventive effect of the study drug.

The final report should reflect the number of participants, their characteristics, method, dose and duration of use of the study drugs, tolerability and preventive effect when using them.

The report should reflect the condition of the participants before the appointment of the study drug and the dynamics of their condition under the influence of preventive administration, occurrence of adverse events, etc.

Conclusions should be clear and specific, followed by reasonable practical recommendations reflecting the expediency of the use of the study drug.

The report must be approved by the sponsor of the study and certified with the seal of the organization.

FINANCING AND INSURANCE

Financing

Financial support for this non-interventional post-marketing study will be provided at the expense of the manufacturing company in accordance with contracts with research centers.

Insurance

Additional payments and insurance of participants are not provided.

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Appendixes

Appendix 1

Participant's diary (study group)

LLC "NPP "Pharmaclon"

Medical Researcher:_____
Contact details:_____
Research Center:
_____
_____
_____
_____

Research participant's diary
Protocol of post-marketing non-interventional study
"A prospective randomized open-label comparative study of the use of the intranasal form of human recombinant interferon gamma for the prevention of acute respiratory viral infections, including diseases caused by coronavirus infection 2019 (COVID-19)"
RAIN-2020

Study Group

Participant screening number: |__|-|__|__|__|
Randomization number of the participant: |_____
Date of signing informed consent: |__|__| |__|__| |__|__|__|__|
day month year

The start date for the diary: |__|__| |__|__| |__|__|__|__|
day month year

The end date for the diary: |__|__| |__|__| |__|__|__|__|
day month year

Participant's signature_____
Signature of the medical researcher_____

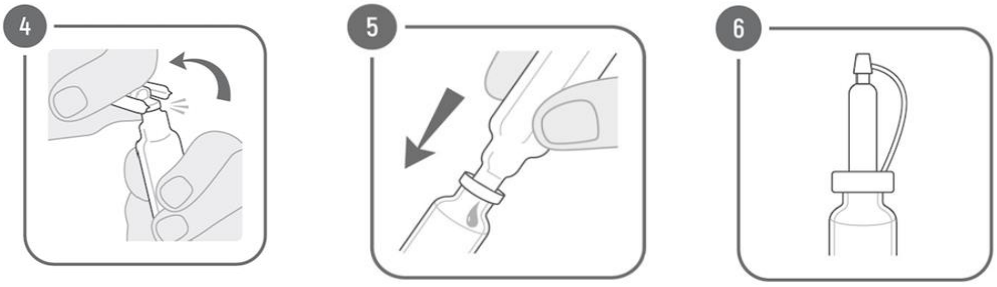
Participant |_____ **(randomization number)**	**Initial data**	**Date** |__|__| |__|__| |__|__|__|__| **day month year**

1.	Initials	
2.	Date of birth	
3.	Gender	male / female
4.	Smoking, history	yes (___ pack/day for ___ years) no

Instructions for the preparation of the drug INGARON

1. Gently pull the plastic nozzle on the glass vial, following the direction of the arrows on the aluminum guard.
2. The plastic cap along with part of the aluminum guard will be removed.
3. In a circular motion, remove the remaining part of the aluminum guard.
   Remove the rubber stopper from the glass vial.

4. Open the vial of water for injection by breaking off its upper part.
5. Pour 5 ml of water for injection into glass vial with a dry substance.
6. Remove the dropper cap from the package and fix it on the neck of the bottle.



Due to the need to store the active substance in a full vacuum, the aluminum cap must be hermetic and durable. Slowly remove the aluminum guard of the bottle, avoid cuts. If the cap breaks off during removal, you can remove the rest of the metal cap with scissors.
Take vial with Ingaron with liquid inside with both hands and turn it over 10–15 times.
Put the vial with Ingaron with the liquid inside in the refrigerator and store there for 10 days. For the second course of prevention (after 1 week), use the second vial.
Return the empty ampoules of water for injection together with the used glass vials to the researcher at the next visit.
Administration
Course 1. The drug is applied 3 drops in each nasal passage every other day 30 minutes before breakfast for 10 days (total of 5 instillations). The use of the drug is carried out according to the following regimen:

- Course 1. Day 1 – mark administration time in your diary
- Course 1. Day 3 – mark administration time in your diary
- Course 1. Day 5 – mark administration time in your diary
- Course 1. Day 7 – mark administration time in your diary
- Course 1. Day 9 – mark administration time in your diary

This is 1 preventive cycle. Then a break of 7 days.
Course 2. Drug administration is carried out similarly to Course 1. Preparation of the drug is carried out similarly to the algorithm described earlier. Dosage regimen is the same:

- Course 2. Day 1 – mark administration time in your diary
- Course 2. Day 3 – mark administration time in your diary
- Course 2. Day 5 – mark administration time in your diary
- Course 2. Day 7 – mark administration time in your diary
- Course 2. Day 9 – mark administration time in your diary

If you missed drug administration, mark the day in your diary with a "check mark" and take the next dose the next morning 30 minutes before breakfast and then continue using it every other day. Remember that the finished solution of the drug is stored for no more than 10 days in the refrigerator. Do not use it after the expiration date. For Course 2, use the second bottle, do not use the first bottle, even if the drug is not fully used.

Course 1 **Day 1**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Administration of study drug

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 2**	**Date** |__|__||__|__||__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 3**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 4**	**Date** |__|__||__|__||__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 5**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1	**Date** |__|__||__|__||__|__|__|__|

Day 6	**day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 7**	**Date** |__|__| |__|__| |__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 8**	**Date** |__|__| |__|__| |__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 1 **Day 9**	**Date** |__|__| |__|__| |__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Participant |_____ **(randomization number)**	**Break between preventive courses**

The break between preventive courses is 7 days

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 1**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Administration of study drug

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 2**	**Date** |__|__||__|__||__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 3**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 4**	**Date** |__|__||__|__||__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 5**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 6**	**Date** |__|__||__|__||__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 7**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 8**	**Date** |__|__||__|__||__|__|__|__| **day month year**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Course 2 **Day 9**	**Date** |__|__||__|__||__|__|__|__| **day month year**

Time of administration: |_____:|__|__|

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Participant |_____ **(randomization number)**	**Observation period**

Follow-up period 1 month

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

Participant |_____ (randomization number)	**Observation period**

Start date	End date	Complaints	Therapy (if taken)

Appendix 2

Participant's diary (control group)

LLC "NPP "Pharmaclon"

Medical
Researcher:_____
Contact details:_____
Research Center:
_____
_____
_____
_____

Research participant's diary
Protocol of post-marketing non-interventional study
"A prospective randomized open-label comparative study of the use of the intranasal form of human recombinant interferon gamma for the prevention of acute respiratory viral infections, including diseases caused by coronavirus infection 2019 (COVID-19)"
RAIN-2020

Control Group

Participant screening number: |__|-|__|__|__|
Randomization number of the participant: |_____
Date of signing informed consent: |__|__| |__|__| |__|__|__|__|
day month year

The start date for the diary: |__|__| |__|__| |__|__|__|__|
day month year

The end date for the diary: |__|__| |__|__| |__|__|__|__|
day month year

Participant's signature_____
Signature of the medical researcher_____

Participant |_____ **(randomization number)**	**Initial data**	**Date** |__|__| |__|__| |__|__|__|__| **day month year**

1.	Initials	
2.	Date of birth	
3.	Gender	male / female
4.	Smoking, history	yes (___ pack/day for ___ years) no

The observation period is 2 months

If you are taking medications to prevent ARVI, please fill out the table below:

Drugs taken for prevention[16]	Drug name	Dosage regimen[17]	On-treatment period

Participant |_____ **(randomization number)**	**Observation period**
Participant |_____ **(randomization number)**	**Observation period**

In case of complaints, symptoms of ARVI, please fill out the table below:

Start date	End date	Complaints	Therapy (if taken)

[16] Before using the drug, it is necessary to familiarize yourself with the current instructions for medical use to exclude contraindications

[17] A single dose and the frequency of dosing are indicated

Appendix 3

Form for reporting unlabeled serious adverse reaction

Reporting of unlabeled serious reaction to a drug being studied in a clinical trial

Research protocol No.	
Name of the research protocol	
Name of study drug	
Study phase	
The name of the medical institution in which the SAE was detected	

Information about the SAE

1. Initials of the patient	**2. Date of birth**	**3. Age**	**4. Gender**	**5. Start date of the SAE**	**6.Mark everything that corresponds to the SAE**
					• Death • Hospitalization or its prolongation • Involved persistence of significant disability or incapacity • Life threatening
7. Description of the SAE, including data from laboratory and instrumental studies					

Information about suspected medicinal product

8. Suspected medicinal product, including international non-proprietory name or generic name		**9. Has SAE resolved after drug withdrawal**
		• Yes • No • Not applicable
10. Daily dose	**11. Administration route**	**12. Did the reaction occur again after repeated use of the drug**
		• Yes • No • Not applicable
13. Indications	**14. Dates of treatment**	**15. Duration of therapy**
	from **to**	

Concomitant drug therapy and anamnesis

16. Concomitant medications and dates of administration (except those used for the treatment of SAE
17. Other relevant anamnesis data (for example, diagnoses, allergies, pregnancy with indication of the time of the last menstruation, etc.)

Other information

18. Name and address of the manufacturer	
19. Case identification number	**20. Date of receipt of the SAE**

	information by the manufacturer
21. Source of information about the SAE	
• Research • Literature • Healthcare Specialist • Regulatory authorities. • Other _____	
22. Date of this report	
23. Type of report	
• Initial report • Follow-up report	

Appendix 4

ADVERSE DRUG REACTION REPORT FORM
MEDICINAL PRODUCT

Primary

Additional information to the message No._____ from_____

Patient data							
Patient initials (patient code)*_____ Gender □ M □ F Weight_____ kg							
Age Pregnancy □, gestational age weeks							
Allergy □ No □ Yes _____							
Treatment □ outpatient □ inpatient □ self-treatment							
Medications suspected of causing AR							
	Name of the drug (trade name)*	Manufacturer	Batch number	Dose, route of administration	Therapy starting date	Therapy end date	Indication
1							
2							
3							

Adverse reaction	**AR initial date_____**
Description of the reaction* (specify all details, including laboratory data)	**Criteria for AR severity:**
	□ Death
	□ Life threatening
	- Hospitalization or its extension
	□ Disability
	□ Congenital anomalies
	□ Clinically significant event
	□ Not applicable
Date of AR resolving_____	

Interventions
□ Without treatment □ Withdrawal of suspected medicinal product □ Drug dose tapering
□ Non-drug therapy (including surgical intervention)
□ Drug therapy_____
Outcome
□ Recovery without complications □ Recovering or resolving □ Condition without changes
□ Recovery with complications (specify)_____
□ Death □ Unknown □ Not applicable

Was drug withdrawal accompanied by AR resolving? □ No □ Yes □ No drug withdrawal □ Not applicable							
Has medicinal product been prescribed repeatedly? □ No □ Yes Result_____ □ Not applicable							
Other medications taken during the last 3 months, including drugs taken by the patient independently (at his own request)							
	Name of the drug (trade name)	Manufacturer	Batch number	Dose, route of administration	Therapy starting date	Therapy end date	Indication
1							
2							
3							
4							

5							

Data of the reporting person
□ Physician □ Other healthcare system specialist □ Patient □ Other
Contact phone/e-mail:* _____
Full name _____
Position and place of work _____
Report Date _____

* Required fields

The message can be sent:

NPP Pharmaclon LLC

e-mail: adversereaction@drugsafety.ru
tel. 24 hours: 8-800-777-8-604,
you can download the form on the website www.pharmaclon.ru
postal address: Moscow, Presnenskii val str., 17c.1