STATISTICAL ANALYSIS PLAN

Protocol	RAIN-2020 (NCT05054114) version 2.0 from 17.02.2021
Date	12/10/2021
Version	2
Protocol	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)
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CONTENT

VERSION HISTORY

Version	Reason for amendment	Date
1	Final version	08.09.2021
2	Supplemented version	12.10.2021

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
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SARS-CoV-2 – type 2 coronavirus that causes severe acute respiratory syndrome (SARS)
M – arithmetic mean

1. PURPOSES AND OBJECTIVES

1.1. Purpose of the study

Evaluation of the efficacy and safety 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 the mode 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.

1.2. Research objectives

Evaluation of the effectiveness and safety of the proposed regimen of preventive therapy with Ingaron (INN: human recombinant interferon gamma, lyophilizate for the preparation of a solution for intranasal administration of 100 000 IU) in adult volunteers.

2. CLINICAL TRIAL DESIGN

2.1. Design

Post-marketing non-interventional prospective randomized open-label comparative study.

A total of 4 visits are planned (0–3). Visit 0 and 1 can be combined.

During randomization, participants are randomly distributed in a 1:1 ratio into two groups:

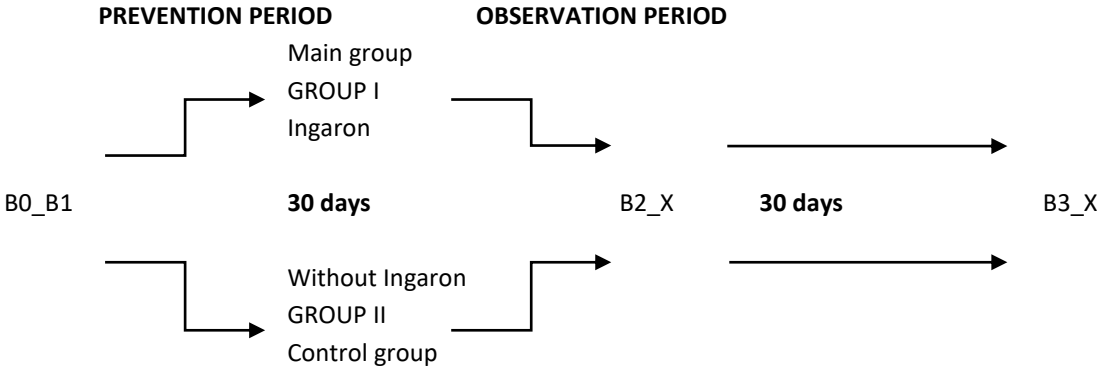
Group I (main) and Group II (control).

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).

The effectiveness of preventive therapy will be recorded. The presence and severity of any adverse events and events will also be evaluated, regardless of the alleged connection with the use of the study drug Ingaron®.

The schedule of visits and procedures is identical for all study participants. A detailed description of the research procedures is provided in the Protocol.

The schedule of research procedures is presented in the section DESIGN of NON-INTERVENTIONAL RESEARCH Protocol. The study periods with the planned time are shown in the diagram below:



X – effectiveness evaluation

Scheme 1. Design

2.2. Randomization

The methodology of the study involved the use of randomization to distribute participants into groups. Randomization was block-based. All blocks were balanced, i.e., each block should have an equal number of participant numbers with 2 types of preventive treatment.

2.3. Blinding procedure

This study is open-label.

3. EVALUATION OF EFFECTIVENESS PARAMETERS

3.1. Endpoints of the study

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).

The scientific hypothesis is that the prophylactic administration of Ingaron will lead to a decrease in the incidence of acute respiratory viral infections, including COVID-19, among adult volunteers.

The preventive efficacy of the study drug will be evaluated by the following primary and secondary endpoints.

Primary endpoint:

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 endpoints:

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).

3.2. Registration, analysis and evaluation of effectiveness parameters

The effectiveness will be evaluated based on the data obtained during the study visits. The effectiveness assessment will include the presence of a case of ARVI, including COVID-19.

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 dynamic. 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	no activit	activity restrict	hospitalized, no	hospitalized, oxygen	non-invasive lung	endotracheal	ventilation + additional	death

	or virological signs of infection	y restri ctions	ions	oxygen therapy	therapy through a mask or nasal cannula	ventilation or high-flow oxygen therapy	intubat ion and mecha nical ventilat ion	organ support – pressor drugs, renal replacement therapy, extracorpore al membrane oxygenation (ECMO)	

4. ASSESSMENT OF SAFETY PARAMETERS

4.1. Safety Endpoints

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

The study will evaluate the following safety variables:

- frequency of AE/SAE registration in treatment groups (in general and by organ systems);
- changes in vital signs (heart rate, blood pressure, body temperature, respiration rate and SpO_2) during the study (by visits and groups).

4.2. Registration, analysis, and evaluation of safety parameters

Adverse events were recorded from the moment of signing the informed consent until the end of the study. The safety analysis of the drug will consider the data of physical examination, diaries of participants, laboratory tests or other assessments. The study will analyze the frequency of occurrence and the nature of AE and SAE. The safety assessment was carried out throughout the study.

Adverse event (AE)

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[1].

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.

Adverse reaction (AR)

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.

Determination of a serious adverse event (SAE)

Serious adverse event (SAE) – AE that leads to death[2], poses a threat to life[3], requires hospitalization of the patient or its prolongation[4], leads to persistent or severe uncapacity or disability, to congenital anomalies or malformations[5], requires medical intervention to prevent the development of these conditions.

[1] 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.

[2] 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.

[3] 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.

Unexpected adverse event (Unexpected AE) – adverse event, the 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 Clinical Investigation Brochure for an 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.

Intensity of adverse event

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 because 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.

Criteria for assessing the association of adverse event with the intake of study drug

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 the AE with specific administration of the drug (for example, the 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;

[4] 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.

[5] Pregnancy cases in the participants of the clinical study are not subject to registration as AE, except in cases when the child has formed a congenital anomaly or malformation (the case is registered with SAE).

- 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 study drug (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 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.

In order to determine the unambiguous connection of AE with the intake of the study drug, an approach will be used in which the presence of at least a possible relationship is assumed.

5. STATISTICAL DATA PROCESSING

5.1. Statistical methods of analysis

To create conditions for an independent evaluation of the results obtained, statistical data processing at the end of the study will be carried out by employees who are not related to the management of the subjects participating in the study. The primary data base was created in Excel when processing registration cards received from the clinical center. Data processing will be performed in the software environment of the R package (R: A language and environment for statistical computing. R Core Team. R Foundation for Statistical Computing, Vienna, Austria)[6] version 4.1.0 using "A Guidance Document for the Use of R in Regulated Clinical Trial Environments"[7].

Descriptive statistics are presented for all baseline indicators collected during the study for all subjects included in the study (safety-population). The distribution of subjects, demographic and initial characteristics are presented using descriptive statistics methods.

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);
- 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 (%).

Verification of the normality of the distribution will be carried out by one of the generally accepted methods (visualization of data in a dot diagram in combination with the calculation of the Kolmogorov-Smirnov test, as well as the test for asymmetry and kurtosis).

In the case of a normal distribution, an intergroup comparison of quantitative characteristics will be carried out using the t-test (or the Mann-Whitney test otherwise). For categorical data, the $\chi 2$-criterion or the exact Fisher test will be applied if the expected frequency in any of the cells is less than 5.

If statistically significant differences between the groups are found, the magnitude of the differences between the study groups will be estimated using confidence intervals. Significance levels and confidence intervals will be calculated as two-sided, and the statistical significance of the differences is by default two-sided and refers to a significance level of 0.05.

Correction for multiple comparisons is not required.

Analysis of the source data

Demographic characteristics, baseline, and follow-up characteristics such as anamnesis, comorbidities and medications used will be described by treatment groups for the ITT population and then safety, if they differ.

[6] URL https://www.R-project.org/
[7] https://www.r-project.org/doc/R-FDA.pdf

Primary Endpoint Analysis

The main parameter of the effectiveness of the preventive use of Ingaron® 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).

In accordance with the purpose and objectives of the study, the null and alternative hypotheses are formulated as follows:

- Null hypothesis (H_0) consists in the assumption that the prophylactic administration of Ingaron will not lead to a change in the incidence of acute respiratory viral infections, including COVID-19, among adult volunteers;
- Alternative hypothesis (H_a) is that in the study group, the proportion of ARVI cases, including COVID-19, will differ from the control group.

$$H_0: \mu_1 = \mu_2$$

$$H_a: \mu_1 \neq \mu_2,$$

where μ is the fraction of the main variable for the corresponding group.

To test these hypotheses, the method of a two-way variant of the Fisher's exact test (with expected frequencies less than 5) or the Pearson's chi-squared test (χ^2) (with the Yates correction for expected frequencies more than 5, but less than 10) will be used.

In all cases, the significance level (α is the probability of an error of the first kind) 0.05 will be used.

The analysis of the primary efficiency parameter will be carried out on the ITT population (main analysis), as well as – additionally – on the PP population (additional analysis).

Data on the case of ARVI (COVID-19) is collected during the entire study by filling out a form on the registration of a case of ARVI.

Secondary Endpoint analysis

The following secondary efficacy parameters in this study are quantitative indicators that will be compared between treatment groups:

- 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 observation period (change period: 2 months);
- percentage of patients with confirmed COVID-19 at the end of the follow-up period (change period: 2 months);
- Frequency of development of complicated course of ARVI.

The proportion of patients will be presented as a frequency, a percentage in % indicating a bilateral 95% CI, measured according to the data recorded at the time of the corresponding measurement period. For a comparative analysis of the proportions between the groups, method of a two-sided version of the Fisher's exact test (with expected frequencies less than 5) or the Pearson chi-squared test ($2\chi^{)}$ (with the Yates correction for expected frequencies more than 5, but less than 10) will be used.

The analysis of secondary performance parameters will be carried out both on the ITT population (main analysis) and on the PP population (additional analysis).

Analysis of safety parameters

The study plans to analyze the following security variables:

- frequency of AE/SAE registration in treatment groups (in general and by organ systems);
- changes in vital signs (heart rate, blood pressure, body temperature, respiration rate and SpO_2) during the study (by visits and groups).

For categorical safety indicators in each group and for each visit, according to the survey scheme of participants, frequency, percentage in% and bilateral 95% CI will be calculated. Comparing groups by categorical indicators with the number of categories less than 5, Fisher's exact test will be used, otherwise Pearson chi-squared test (χ^2) will be used (with Yates correction for expected frequencies of more than 5, but less than 10).

The results of measuring vital signs (assessment of heart rate, respiration rate, blood pressure, body temperature and SpO_2) will be presented by treatment groups using descriptive statistics.

The analysis of safety parameters will be carried out on the safety population.

5.2. The size of the sample under study

The estimation of the sample size of subjects was based on the following parameters:

- bilateral significance level α=0.05 Z value = 1.96;
- statistical power level is 80%, Z-value = 0.84;
- method of sample formation — randomization using elements of randomness;
- statistical criteria used are two-sided due to the lack of aposteriori information about the superiority of the effect of the study drug over the placebo effect.

Calculation results:

- number of volunteers who must complete participation in the study in accordance with the protocol is 286 in the group or a total of 572 participants.
- number of randomized participants is 315 in a group or total 630 people
- number of screened volunteers – up to 642.

5.3. Missing / incorrect data

For all parameters, the analysis will be carried out only on the available information, without filling in the data. There are no plans to use data reconstruction methods in this study.

5.4. Deviations from the protocol and the original statistical plan

An additional analysis is planned for the sensitivity of the results of the evaluation of the primary endpoint, depending on the vaccination status.

To maintain the balance and comparability of the groups, as well as to exclude the influence of the period of active antibody formation caused by the vaccine [8]on the results, as part of an additional analysis, a subpopulation of participants vaccinated with at least one dose of the drug during participation in the study will be excluded from both groups.

[8]Due to the small proportion of vaccinated participants, the number of doses of the vaccine received by the participant and its type (trade name) will not be taken into account

Participants vaccinated prior to inclusion in the study will be included in a modified sample with the formation of a separate population "not vaccinated during the study" to achieve the necessary statistical power.

The conditions for the uniform distribution of patients by vaccination status between groups will be checked beforehand.

All changes in the initial statistical plan with their justification will be reflected in the final report on the clinical trial.

5.5. Populations of participants for analysis

The following populations will be formed for analysis: ITT, PP and safety; additionally: ITT_NV, PP_NV, ITT_NV_BE, PP_NV_BE.

Statistical data analysis will be carried out in the following populations of participants:

1. Population of all included and randomized participants (intention-to-treat, ITT): all randomized participants who were exposed to the study drug, regardless of the degree of protocol compliance during the study. This data set is the main one for the analysis of primary and secondary effectiveness parameters;
2. Population of participants who completed the study according to the protocol (per protocol, PP): all randomized subjects who completed participation in the study in accordance with the protocol (completed the prescribed period of treatment and follow-up without significant deviations from the protocol). This data set is additional for the analysis of primary and secondary effectiveness parameters;
3. Safety population: The data set analyzed for safety assessment is identical to the ITT data set. However, unlike the population depending on the prescribed treatment, participants are analyzed depending on the actual treatment (if it differs from the treatment that was prescribed by randomization). All types of safety analysis will be based on the use of a data set for security assessment;
4. Modified population of all included and randomized participants (intention-to-treat, ITT) not vaccinated against COVID-19: ITT_NV. This data set is additional for the analysis of the primary efficiency parameter;
5. Modified population of participants who completed the study according to the protocol (per protocol, PP), not vaccinated against COVID-19: PP_NV. This data set is additional for the analysis of the primary efficiency parameter;
6. Modified population of all included and randomized participants (intention-to-treat, ITT) not vaccinated against COVID-19 or vaccinated before inclusion in the study: ITT_NV_BE. This data set is additional for the analysis of the primary efficiency parameter;
7. Modified population of participants who completed the study according to the protocol (per protocol, PP), not vaccinated against COVID-19 or vaccinated before inclusion in the study: PP_NV_BE. This data set is additional for the analysis of the primary efficiency parameter.

Thus, the safety population will be used to present demographic data about participants, as well as for safety assessment. ITT will be considered the main sample for comparative analysis of performance parameters. The PP population will include only participants who completed the study without critical deviations from the protocol and will be formed as an additional sample to evaluate the effectiveness parameters in order to analyze the sensitivity of the results obtained in the ITT population. The modified populations will be used to perform sensitivity analysis when evaluating the primary endpoint.

The number of participants who must complete the study in accordance with the protocol is 286 in each group, or a total of 572 participants.

The number of randomized participants is 315 in each group or total of 630 participants.

The number of screened participants is up to 642.

5.6. Interim analysis

Not applicable.

6. TABLE PATTERNS

Table1. Distribution of subjects

Distribution of subjects	Group I (proportion, %)	Group II (proportion, %)
Included in the study (screened)	n/N (%)	
Of these: Excluded at the screening stage:	n/N (%)	
Randomized	n/N (%)	n/N (%)
Prematurely excluded, out of them:	n/N (%)	n/N (%)
Existence of exclusion criterion #X (description)	n/N (%)	n/N (%)
Population safety	n/N (%)	n/N (%)
ITT population	n/N (%)	n/N (%)
Population PP	n/N (%)	n/N (%)

Table2. Demographic and anthropometric characteristics of subjects at the time of inclusion (safety population)

Group	Parameter	Age (years)	Weight (kg)	Height (cm)	Smoking index (p/y)	Frequency of acute respiratory infections (amount/g)
GROUP I	n					
	M					
	CO					
	min.					
	max.					
	Me					
GROUP II	n					
	M					
	CO					
	min.					
	max.					
	Me					
p (between groups)						

Table3. Distribution of subjects by gender (safety population)

Gender	GROUP I	GROUP II
Male	n/N (%)	n/N (%)
Female	n/N (%)	n/N (%)
p (between groups)		

Table4. Distribution of subjects by race (safety population)

Race	GROUP I	GROUP II
Caucasian	n/N (%)	n/N (%)
Mongoloid	n/N (%)	n/N (%)
Negroid	n/N (%)	n/N (%)
p (between groups)		

Table5. Medical history (safety population)

Parameter	Value	Group I (N =)	Group II (N =)
Diagnosis (chronic disease)	…	n/N (%)	n/N (%)
Diagnosis (according to anamnesis)	…	n/N (%)	n/N (%)
p (between groups)			

Table 6. Methods of nonspecific prevention (safety population)

Type	Frequency	GROUP I	GROUP II
Total subjects		**N =**	**N =**
Masks	Yes	n/N (%)	n/N (%)
	No	n/N (%)	n/N (%)
	Sometimes	n/N (%)	n/N (%)
Respirator	Yes	n/N (%)	n/N (%)
	No	n/N (%)	n/N (%)
	Sometimes	n/N (%)	n/N (%)
Gloves	Yes	n/N (%)	n/N (%)
	No	n/N (%)	n/N (%)
	Sometimes	n/N (%)	n/N (%)
Glasses	Yes	n/N (%)	n/N (%)
	No	n/N (%)	n/N (%)
	Sometimes	n/N (%)	n/N (%)
Surgical overalls	Yes	n/N (%)	n/N (%)
	No	n/N (%)	n/N (%)
	Sometimes	n/N (%)	n/N (%)
p (between groups)			

Table 7. Drug allergy (safety population)

	GROUP I	GROUP II
Total subjects	**N =**	**N =**
No	n/N (%)	n/N (%)
Yes	n/N (%)	n/N (%)
p (between groups)		

Table 8. Results of the assessment of the incidence rate at the end of the prevention period (ITT/PP/ITT_NV/PP_NV/ITT_NV_BE/PP_NV_BE population)

	GROUP I	GROUP II
Total subjects	**N =**	**N =**
ARVI	n/N (%)	n/N (%)
Not sick	n/N (%)	n/N (%)
p (between groups)		

Table 9. Results of the assessment of the incidence of COVID-19 at the end of the prevention period (ITT population, PP)

	GROUP I	GROUP II
Total subjects	**N =**	**N =**
COVID-19 (total)	n/N (%)	n/N (%)
Of these: COVID-19 confirmed	n/N (%)	n/N (%)

COVID-19 probable	n/N (%)	n/N (%)
COVID-19 suspicious	n/N (%)	n/N (%)
p (between groups)		

Table 10. Results of the assessment of the incidence rate at the end of the study (ITT population, PP)

	GROUP I	**GROUP II**
Total subjects	**N =**	**N =**
ARVI	n/N (%)	n/N (%)
Not sick		
p (between groups)		

Table 11. Results of the assessment of the incidence of COVID-19 at the end of the study (ITT population, PP)

	GROUP I	**GROUP II**
Total subjects	**N =**	**N =**
COVID-19 (total)	n/N (%)	n/N (%)
Of these: COVID-19 confirmed	n/N (%)	n/N (%)
COVID-19 probable	n/N (%)	n/N (%)
COVID-19 suspicious	n/N (%)	n/N (%)
p (between groups)		

Table 12. Results of the assessment of the frequency of complicated course (ITT population, PP)

	GROUP I	**GROUP II**
Total subjects	**N =**	**N =**
Complications (total)	n/N (%)	n/N (%)
Of these: …	n/N (%)	n/N (%)
…	n/N (%)	n/N (%)
p (between groups)		

Table 13. Results of evaluation of the frequency of different scores on the WHO scale at the end of the prevention period (ITT population, PP)

	GROUP I	**GROUP II**
Total subjects	**N =**	**N =**
0	n/N (%)	n/N (%)
1	n/N (%)	n/N (%)
2	n/N (%)	n/N (%)
3	n/N (%)	n/N (%)
4	n/N (%)	n/N (%)
5	n/N (%)	n/N (%)
6	n/N (%)	n/N (%)
7	n/N (%)	n/N (%)
8	n/N (%)	n/N (%)
p (between groups)		

Table 14. Results of evaluation of the frequency of different scores on the WHO scale at the end of the study (ITT population, PP)

	GROUP I	GROUP II
Total subjects	**N =**	**N =**
0	n/N (%)	n/N (%)
1	n/N (%)	n/N (%)
2	n/N (%)	n/N (%)
3	n/N (%)	n/N (%)
4	n/N (%)	n/N (%)
5	n/N (%)	n/N (%)
6	n/N (%)	n/N (%)
7	n/N (%)	n/N (%)
8	n/N (%)	n/N (%)
p (between groups)		

Table 15. Duration of symptoms of the disease (ITT population, PP)

Evaluation period	Parameter	GROUP I	GROUP II
At the end of the prevention period (28 days)	n		
	M		
	CO		
	min.		
	max.		
	Me		
At the end of the study (2 months)	n		
	M		
	CO		
	min.		
	max.		
	Me		
p (between groups)			

Table 16. Distribution of the nature of the symptoms of the disease (ITT population, PP)

Group	Symptom	Number of patients, percentage (%)
GROUP I		n/N (%)
GROUP II		n/N (%)
p (between groups)		

Table 17. Assessment of vital signs (safety population)

Visit	Group	Parameter	SBP (mmHg)	DBP (mmHg)	HR (beats/min)	RR (/min)	Temperature (°C)	Oxygenation (SpO_2)
B0	GROUP I	n						
		M						
		CO						
		min.						
		max.						
		Me						
	GROUP II	N						
		M						
		CO						

Visit	Group	Parameter	SBP (mmHg)	DBP (mmHg)	HR (beats/min)	RR (/min)	Temperature (°C)	Oxygenation (SpO_2)
		min.						
		max.						
		Me						
p (between groups)								
B3	GROUP I	N						
		M						
		CO						
		min.						
		max.						
		Me						
	GROUP II	N						
		M						
		CO						
		min.						
		max.						
		Me						
p (between groups)								

Table 18. Total number of AE, SAE in groups (safety population)

Group	AE	SAE
GROUP I	n/N (%)	n/N (%)
GROUP II	n/N (%)	n/N (%)
p (between groups)		

Table 19. Number of subjects with reported adverse events (safety population)

Group	AE+	AE-
GROUP I	n/N (%)	n/N (%)
GROUP II	n/N (%)	n/N (%)
p (between groups)		

Table 20. Adverse events that developed in the study group participants (safety population)

N	Mild AE		Moderate AE		Severe AE		Total		Total
Organ system / AE	C	HC	C	HC	C	HC	C	HC	C + HC
Organ system x	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
AE x	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX

Note: the table shows all the AE that chronologically occurred in the group after at least one use of the study drug.
C – related to the study drug
HC – not related to the drug under study
NNx – participant's number with the corresponding AE

Table 21. Adverse events that have developed in the subjects of the control group (safety population)

N	Mild AE	Moderate AE	Severe AE	Total

Organ system / AE	C	HC	C	HC	C	HC	C + HC
Organ system x	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
AE x	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX	NN1 NN2 NNX

Note: The table shows all AE that occurred in the control group at any time after randomization into the study.
NNx – participant's number with the corresponding AE

Table 22. Adverse events by nosology (safety population)

SOC	PT	Group 1	Group X
Category SOC 1	Category PT 1	n/N (%)	n/N (%)
	Category PT x	n/N (%)	n/N (%)
Category SOC x	Category PT 1	n/N (%)	n/N (%)
	Category PT x	n/N (%)	n/N (%)

Table 23. Severity of AE (safety population)

Group	Mild	Moderate	Severe
GROUP I	n/N (%)	n/N (%)	n/N (%)
GROUP II	n/N (%)	n/N (%)	n/N (%)

Table 24. Results of comparison of groups by vaccination status against COVID-19 (ITT/PP/ITT_NV/PP_NV/ITT_NV_BE/PP_NV_BE population)

	GROUP I	GROUP II
Total subjects	**N**	**N**
Not vaccinated	n/N (%)	n/N (%)
Vaccinated	n/N (%)	n/N (%)
p (between groups)		