

CLINICAL PROTOCOL

Protocol No.: PoArvi/PhIII_2017

Version: 2.0 of 30/05/2018

"A multicenter, prospective, randomized, double-blind, placebo-controlled parallel-group study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of acute respiratory viral infections (ARVI)"

Study Sponsor: NPO Petrovax Pharm LLC, Russia

Address: 1 Sosnovaya st., Pokrov village, Podolsk, Moscow Oblast, Russia, 142143

Confidentiality Statement

The confidential information contained herein is provided to you as the Principal Investigator or Consultant for review by you, your employees and the relevant Supervisory Board of the organization/Independent Ethics Committee. Your acceptance of this document means your consent to non-disclosure of the information contained in it to other persons without the written permission of the Sponsor/Representative of the Sponsor, except for the information necessary to obtain the Informed Consent from the persons participating in this study.

MOSCOW, 2018

1. PROTOCOL SYNOPSIS

Sponsor of the study	NPO Petrovax Pharm LLC, Russia
Study title	A multicenter, prospective, randomized, double-blind, placebo-controlled study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of ARVI.
Protocol No.	PoArvi/PhIII 2017
Date/Version No.	2.0 of 30/05/2018
Study phase	III (study of the product safety and efficacy in subjects with a particular disease)
Study product and Comparator	<p>Study product: Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia). Composition per 1 ml: Active ingredient: Azoximer bromide - 6 mg Excipients: mannitol - 1.8 mg, Povidone K 17 - 1.2 mg, purified water - up to 1.0 ml</p> <p>Placebo: nasal and sublingual spray (NPO Petrovax Pharm LLC, Russia). Composition per 1 ml: Excipients: mannitol - 1.8 mg, Povidone K 17 - 1.2 mg, purified water - up to 1.0 ml</p>
Study design	A multicenter, prospective, randomized, double-blind, parallel-group placebo-controlled Phase III study of efficacy and safety.
Posology and method of administration	<p>Study product: every day, at a daily dose of 0.15 mg/kg for 7 days: - for children aged 1 to 2 years: 1 spray x 2 times a day, sublingual; - for children aged 2 to 5 years: 1 spray x 2 times a day, intranasal into each nostril; - for children aged 5 to 8 years: 1 spray x 3 times a day, intranasal into each nostril; - for children aged 8 to 12 years: 2 sprays x 2 times a day, intranasal into each nostril.</p> <p>Placebo is administered the same way as the study product The first dose of study drug/placebo is administered at Visit 1 (or Visit 0, if it is combined with Visit 1). Subsequent doses are received at fixed time intervals: <u>12 ± 2 h</u> - with 2-times a day administration of the SP/placebo; <u>8 ± 1 h</u> - with 3- times a day administration of the SP/placebo</p>
Study design	A multicenter, prospective, randomized, double-blind, parallel group placebo-controlled Phase III study of efficacy and safety.

Study purpose	The main purpose of this study is to demonstrate the superiority of Polyoxidonium [®] , nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) therapeutic benefits over placebo in regards to therapy efficacy, when used as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI after 7 days of treatment.
Study objectives	<ol style="list-style-type: none">1. To demonstrate the superiority of Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) efficacy profile over placebo, when used as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI.2. To evaluate the safety of the study product Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) compared with placebo as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI.
Study duration	<p>Anticipated total duration of enrollment period will be up to 6 months in all clinical centers is; this means that the period from the date of inclusion of the first patient to the last visit of the last patient will be 6 months. According to the Protocol schedule, the duration of study participation will be at most 13 days for each subject. Furthermore according to Protocol the subject may be enrolled into the study only within 24 hours from the onset of ARVI manifestations. Due to the seasonal nature of the disease, the clinical part of the study is supposed to be carried out between September 2018 and February 2019.</p> <p>Visit 0 (screening) - Day -1... Day 0 (within 24 hours from the onset of ARVI symptoms).</p> <p>Visit 1 - Day 1 (randomization, Visit can be combined with Visit 0).</p> <p>Visit 2 - Day 3 - assessment of the clinical pattern dynamics, exclusion the need for the antibacterial therapy prescription.</p> <p>Visit 3 - Day 8 ± 1 - safety control, assessment of the clinical pattern dynamics, exclusion of the complications available.</p> <p>Visit 4 (telephone contact) - Day 12 ± 1 - follow-up period.</p> <p>Duration of study participation will be at most 13 days for each subject.</p> <p>Anticipated duration of the entire study will be approximately 9 months: Recruitment period will last for 6 months; data analysis and the Final Report preparation will last about 3 months.</p>

<p>Study population and the number of enrolled patients:</p>	<p>Patients with a clinically confirmed diagnosis of ARVI (ICD-10 code: J00, J02, J04, J06) will be randomized and assigned to one of two groups at the ratio 1:1: Group 1 - patients will receive the study product as part of complex therapy; Group 2 - patients will receive placebo as part of complex therapy.</p> <p>Calculation of the sample size is based on the following Formula:</p> $n = (Z_{\alpha} + Z_{\beta})^2 \cdot \frac{2 \cdot SD^2}{(\mu_o - \mu_p - \delta)^2}$ <p>where, Z_{α} and Z_{β} are critical values of the normal distribution corresponding to the established error levels α and β (α- and β-errors are 0.05 and 0.2, respectively), SD - a standard deviation [25 - 28].</p> <p>As a result of calculation based on the above values ($Z_{\alpha}=1.645$, $Z_{\beta}=0.842$, $SD=0.2$ day, $\delta=-0.52$ day, $\mu_o=2.6$ days, and $\mu_p=3.2$ days), the sampling size was obtained that ensures a statistical study power of at least 80%, equal to 78 patients in each group (156 subjects in total). Taking into account the possible dropout of 10% of patients, the sample size will be extended to 86 subjects in each group (172 subjects in total). Calculations were performed using the R v Statistics package. 3.4.3.</p> <p>Taking into account the possible dropout of patients at screening, it is planned to screen 210 patients in the study, of whom 172 will be randomized.</p>
<p>Study sites</p>	<p>Medical Technologies Limited Liability Company. Address: 6, Nevzorovoy st., Saint Petersburg, 192148.</p> <p>State Budgetary Institution of Public Health of Yaroslavl region "Regional Children's Clinical Hospital". Address: 27, Tutaevskoe chaussee, Yaroslavl, 150042.</p> <p>Municipal Children's Clinic No. 4. Address: 122/1, Dneprovsky per., Rostov-on-Don, 344065.</p> <p>Kurator, Limited Liability Company. Address: 125, Krasnoputilovskaya st., building A, room 13N, St. Petersburg, 196240.</p> <p>St. Petersburg State Budgetary Institution of Public Health "Children's Municipal Hospital No. 22". Address: 1, Zavodskoy prosp., Kolpino, Saint Petersburg, 196657.</p> <p>State Budgetary Institution of Public Health of Yaroslavl region "Municipal Children's Clinical Hospital No. 5". Address: 10 Soviet Army St., Perm, Russia, 614066.</p> <p>ArsVite Northwest Limited Liability Company. Address: 7, Constitution Square, lit. A., office 413, Saint Petersburg, 196191.</p>

	<p>MDP-Medical Group Limited Liability Company. Address: 7, Constitution Square, lit. A., office 413, Saint Petersburg, 196247. SHCI Yaroslavl Clinical Hospital No. 8. Address: 39, Suzdalskoe chaussee, Yaroslavl, 150030. KOROLEV MEDICINA LLC. Address: 8/1, Kalinina st., room 63, Naro-Fominsk, Moscow Oblast, 143300. Business place: 5, Oktyabrsky Boulevard, nonresidential premise No. 01, rooms 2-10, 14, 15, Korolev Moscow Oblast, 141077 ; Nebbiolo LLC. Address: 23, Ostrovsky Lane, Tomsk, 634009. FSBI Research Institute of Influenza at the Ministry of Health of the Russian Federation. Address: 15/17 prof. Popov st., Saint Petersburg, 197376. MedEstheticCenter Laboratory LLC. Address: 26, Karavaevskaya st., block 1, lit. A, Saint Petersburg, 192177 .</p>
Clinical Laboratory	Local laboratories of the clinical centers that are declared to conduct this study will be used to perform laboratory tests.
Eligibility criteria	<p>Inclusion criteria: Patients of both sexes at the age of 1 to 12 years inclusive. Diagnosis of ARVI [ICD-10 code: J00 - Acute nasopharyngitis (runny nose), J02 - Acute pharyngitis, J02.9 - Unspecified acute pharyngitis, Acute laryngitis and tracheitis - J04, J04.0 - Acute laryngitis, J04.1 - Acute tracheitis, J04.2 - Acute laryngitis, Acute upper respiratory tract infections of multiple and unspecified localization - J06, J06.0 - Acute laryngopharyngitis, J06.9 - Acute upper respiratory tract infection, unspecified] confirmed by physician's examination: axillary temperature ≥ 37.0 °C (measured at the moment of physical examination) and Symptom Assessment Scale total score ≥ 5 points, not less than 3 of which should be related to ENT-organs and upper respiratory tract affection (accord. the Symptom Assessment Scale [Appendix 1]). Not more than 24 hours from the onset of ARVI symptoms. Existence of an information sheet (Informed Consent Form) signed by one of the parents/adoptive parent of the child and a child (if aged ≥ 10 years). Non-inclusion criteria: Suspicion on pneumonia, bacterial infection (including meningitis, sepsis, otitis media, sinusitis, urinary tract infection, etc.) or the presence of a disease requiring the prescription of antibacterial drugs, starting from the first day of the disease.</p>

	<p>Suspicion on initial manifestations of diseases with symptoms similar to ARVI signs (other infectious diseases, flu-like syndrome at the debut of systemic connective tissue diseases and other pathology).</p> <p>Positive express test for influenza or streptococcal infection.</p> <p>Clinical symptoms of severe ARVI requiring hospitalization (fever $\geq 40^{\circ}\text{C}$, signs of respiratory obstruction, severe hemodynamic/neurological disorders).</p> <p>A history of or previously diagnosed primary and secondary immunodeficiency.</p> <p>Cancer.</p> <p>Acute infectious or non-infectious diseases (except for ARVI), as well as exacerbation or decompensation of chronic diseases (diabetes mellitus, infantile cerebral palsy, cystic fibrosis, primary ciliary dyskinesia, bronchopulmonary dysplasia, respiratory and ENT organ malformations, etc.) affecting the patient's ability to participate in a study.</p> <p>Sucrase/isomaltase deficiency, fructose intolerance, glucose-galactose malabsorption.</p> <p>A history of allergy/hypersensitivity to any component of products used in treatment (including sensitivity to paracetamol, propacetamol hydrochloride (paracetamol prodrug)).</p> <p>Use of drugs specified in Forbidden Therapy for 1 month prior to study entry.</p> <p>Patients whose parents/adoptive parents may fail to follow the observation requirements during the study or observe the mode of study product administration, in investigator's opinion.</p> <p>Participation in other studies of medicinal products within 3 months to screening visit.</p> <p>Pregnancy.</p> <p>Any other medical or social condition that may interrupt patient's study participation, investigator's opinion.</p>
Exclusion criteria:	<p>inability or refusal of the patient or his parents/adoptive parents to follow the Protocol's requirements.</p> <p>Informed Consent withdrawal by the patient or his/her parent/adoptive parent.</p> <p>Requirement for additional therapy which is not permitted under this Protocol.</p>

	<p>4. Serious adverse events or adverse events that do not meet the severity criteria, that are not categorized as «serious», in cases when further study participation may be pernicious for patients health or well-being, in investigator's opinion.. Requirement for surgical intervention. The patient is non-compliant with study procedures. Any patient's condition that reasonably requires withdrawal, in investigator's opinion.</p> <p>Subjects, who discontinued from the study due to AE/SAE will be under the follow up until total recovery or stabilization of AE.</p>
Study Methodology	<p>The study will be fully conducted on an outpatient basis. At the same time, Visits 0, 1 and 2 can be carried out by the physician's home visit to the patient.</p> <p><i>The study consists of the following stages:</i></p> <p><i>Screening (Visit 0)</i> - preassessment of patients (duration is less than 24 hours).</p> <p><i>Treatment and follow up period (Visit 1, Visit 2, Visit 3, Visit 4)</i> - on Visit 1 (can be combined with Visit 0) all patients who meet the inclusion criteria and do not meet any non-inclusion criteria will be randomized into two treatment groups in a 1:1 ratio. Patients in one group will receive the study product - Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) as part of complex therapy, and in the other group - placebo as part of complex therapy. On Visit 1 (Visit 0, if it is combined with Visit 1) in the Clinical Center or at home, the first administration of SP/placebo (depending on the group) in the sublingual area/nasal passages will be performed to the patient. A parent/adoptive parent will also be trained to use the study products and concomitant medications at home (only the parent/adoptive parent shall provide the therapy).</p> <p><i>Follow-up period (Visit 4).</i></p> <p>Screening, Visit 0 (Day -1... Day 0):</p> <p><i>Procedures:</i></p> <p>Signing an Informed Consent Form by one of the parents/adoptive parent of the child and by the child (if aged ≥ 10 years); Complaints and anamnestic data collection: duration of a disease, effect of the previous therapy, as well as data on concomitant therapy; Physical examination, demographic and anthropometric data collection;</p>

	<p>Measurement of vital signs (HR, RR, body temperature) Symptom Assessment Scale completion by a physician; Clinical blood test; Common urine analysis; 12-lead ECG (only if there is a suspicion of cardiovascular pathology); pregnancy test for female patients with a history of menarche); Express test for influenza Express test for streptococcal infection with test strips Assessment of inclusion/non-inclusion criteria.</p> <p>Therapy period: Visit 1 (Day 1): <i>Office/home visit.</i> Re-assessment of inclusion/non-inclusion criteria; collection of patient's complaints; physical examination; measurement of vital signs (HR, RR, body temperature); Symptom Assessment Scale completion by a physician; randomization; the appointment, prescription and use of the first dose of the study product/comparator according to the randomization plan; issuance of antipyretic drugs, adverse events registration; training of one of the patient's parents/adoptive parents on a correct use of the SP/placebo and antipyretic drug; issuing and training on how to complete the patient's diary; invitation for the next visit. In the case of combining Visit 0 and Visit 1, the following procedures will not be repeated: collection of patient's complaints, physical examination, measurement of vital signs (HR, RR, body temperature), assessment of concomitant therapy.</p> <p>Visit 2 (Day 3): <i>Office/home visit.</i> Collection of patient's complaints; physical examination; measurement of vital signs (HR, RR, body temperature); Symptom Assessment Scale completion by a physician; checking the patient's diary completion at home; adverse events registration; evaluation of concomitant therapy; assessment of compliance with prescribed therapy, and assessment of exclusion criteria. Clinical signs of bacterial infection overlay should be evaluated by investigator at this visit. By the decision of investigator, the subject will be excluded from the study (if antibacterial therapy is required) or continue study participation and study treatment.</p> <p>. On Day 5 of therapy, the Symptom Assessment Scale form should be completed in the patient's diary ; this procedure should be performed by the patient's parent/adoptive parent at home.</p>
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	<p>Visit 3 (Day 8 ± 1): <i>Office visit.</i> Collection of patient's complaints; physical examination; measurement of vital signs (HR, RR, body temperature); assessment of inclusion criteria; Symptom Assessment Scale completion by a physician; checking the diaries completion at home; common urine analysis; evaluation of concomitant therapy; assessment of compliance with prescribed therapy; assessment of efficacy of the study treatment via IMOS scale performed by investigator and one of the the patient's parents/adoptive parents; product return.</p> <p>Visit 4 (Day 12 ± 1): <i>telephone contact.</i> Collection of patient's complaints; adverse events registration; evaluation of concomitant therapy; study completion.</p> <p>In the case of early patient withdrawal on the visit of the completion of study participation, all procedures provided for Visit 3 shall be carried out.</p>
Statistical methods	<p>According to the main study purposes (efficacy and safety assessment), the main tools for the analysis will be descriptive statistics and graphical representations.</p> <p>Continuous (quantitative) variables will be tabulated using such parameters of summary statistics as the amount of data, the amount of missing data, mean, standard deviation, median, Q₁ and Q₃, minimum and maximum values.</p> <p>For all the demographic and baseline data there will be presented descriptive statistics and tables. Baseline demographic characteristics, medical history and examination data - the latest data recorded before the first product administration. A comparative analysis of these data will be carried out in a population of patients who have undergone all the study procedures and completed it according to the Protocol (PP population).</p> <p>Based on the results of efficacy analysis, the comparative statistics will be presented. Comparison of quantitative indicators satisfying the conditions of normal distribution and equality of variances will be carried out by Student's t-test. Comparison of quantitative indicators not satisfying the conditions of normal distribution and equality of variances will be carried out by Mann-Whitney test. To compare the paired quantitative indicators satisfying the conditions of normal distribution and equality of variances, the paired Student's t-test will be used; for those not satisfying the conditions of normal distribution or equality of variances - the paired Wilcoxon test. A comparative analysis of qualitative variables will be carried out by Chi-square test; if more than 20% of the expected frequencies are less than 5, the exact Fisher's two-tail test will be used.</p>

	<p>The efficacy data analysis will be carried out in a population of patients who have undergone all the study procedures and completed it according to the Protocol (PP population).</p> <p>The safety population will consist of all patients who have received at least one dose of the study product, for which further safety surveillance data is provided (ITT population). The safety parameters evaluated during the study include the results of patient's general condition assessment, measurements of vital signs, a general physical examination, an assessment of the patient's complaints, a clinical blood test, and urinalysis (compared to baseline values on Visit 0).</p> <p>Throughout the study the following will be recorded:</p> <p>All cases of AE and SAE reported after the first use of the study product (quantity, severity).</p> <p>All cases of early study termination due to the development of AEs/SAEs associated with the study product (quantity, severity).</p> <p>Local adverse reactions (quantity, severity, connection with the product).</p> <p>Safety parameters will be studied descriptively for each group.</p> <p>The number of AEs and patients with AEs will be summarized by treatment groups, with a distribution by systems and selected terminology. Additional generalizations will be made on the severity, as well as the connection with the study product. Early withdrawn patients will be presented in the Patients List and summarized by the main reason for withdrawn, and by each treatment group. Indicators of physiological functions and laboratory analyzes at the baseline (Visit 0), as well as their changes from the baseline (Visit 3), will be summarized by treatment groups. In addition, the tables of changes in laboratory analyzes based on the classification of values as low, normal or high, relative to the norm limits, will be summarized and presented by treatment groups.</p> <p>Not available or missing data will not be replaced.</p> <p>In addition to the standard summary analysis, the Sponsor may conduct the additional analyzes, if deemed necessary.</p> <p>Interim analysis An interim analysis was not planned.</p> <p>Groups for analysis Safety analysis population and Per-Protocol Study Population.</p> <p><i>Efficacy data analysis</i></p>
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	<p>A superiority cut-off level $\delta = -0,52$ days was chosen to evaluate the principal efficacy parameter - fever duration. The choice is based on the results of earlier studies, which evaluated fever duration in similar cohorts of patients [4, 5].</p> <p>Therein, the following statistical hypotheses will be verified:</p> <ul style="list-style-type: none">- Null-hypothesis (H_0): efficacy of the study product does not exceed the efficacy of placebo: $H_0: \mu_o \geq \mu_p + \delta$, where, μ_o and μ_p - average fever and intoxication period in the main group (μ_o) and placebo group (μ_p);- Alternative hypothesis (H_A): therapy with the study product is better than placebo therapy: $H_A: \mu_o < \mu_p + \delta$ <p>A comparison of parameters between two groups of patients can be performed by calculating the 95% confidence interval for the difference between μ_o and μ_p. Efficacy of the study product is considered higher compared with the efficacy of placebo, if the upper limit of 95% confidence interval for the difference between μ_o and μ_p values is less than - (minus) 0.52 days.</p> <p>Safety data analysis</p> <p>Safety population will be evaluated for all types of safety analysis. Preferred terms of MEDDRA dictionary (Preferred Term) will be used for coding and presenting the Lists of adverse events and associated diseases. All adverse events in the aggregate, as well as serious adverse events, adverse events associated with the therapy, and on other significant adverse events (for example, on adverse events that led to the cancellation of study therapy) will be presented through descriptive statistics.</p> <p>Comparison of treatment groups by the incidence of AEs will be carried by Fisher's exact test.</p> <p>Clinical laboratory evaluations together with indication of changes from baseline will be presented through descriptive statistics for each visit. Laboratory deviations beyond normal values will be marked. Lists and summary descriptions of clinically significant hematological laboratory abnormalities will be presented.</p>
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	<p>Vital signs together with indication of changes from baseline will also be presented through descriptive statistics for each visit.</p> <p>For a statistical analysis of quantitative indicators, a preliminary assessment of compliance with the law of normal distribution according to the Shapiro-Wilk criterion will be made. When verifying statistical hypotheses, parametric criteria will be used for indicators with a normal distribution, and non-parametric criteria will be used for indicators which distribution differs from normal. Comparison of groups by quantitative indicators will be carried out by Student's t-test for independent samples in the case of a normal data distribution or the Mann-Whitney test in the case of a distribution other than normal. Comparison of indicators within the group between visits will be performed by T-test for related samples in the case of a normal data distribution, or the Wilcoxon test in the case of a distribution other than normal.</p> <p>To describe the quantitative variables, the use of the following characteristics is planned: mean, standard deviation, median, quartile, minimum, maximum, coefficient of variation.</p> <p>Qualitative variables will be analyzed by Pearson χ^2 test or Fisher's exact test (if the absolute frequency of the indicator is 5 or less in at least one of the subgroups). To describe categorical data, the use of percentages or shares is planned.</p> <p>Differences at $p < 0.05$ will be considered statistically significant.</p> <p>The selection of statistical analysis method will be determined by the type of source data, kind of distribution. The possibility of using a number of statistical methods will be assessed after the completion of data collection, since the nature of data distribution, sample homogeneity, etc. is unknown. In the course of the analysis, it is possible to expand the list of methods used, if it is necessary for high-quality data processing.</p>
<p>Efficacy criteria</p>	<p>Primary efficacy criterion:</p> <ul style="list-style-type: none"> Fever duration period¹ $\delta = -0.52$ days will be considered as a superiority cut-off level. Axillary body temperature level ≤ 36.9 °C confirmed by two consecutive measurements (morning-evening/evening-morning) will be considered as the end of fever. <p>Secondary efficacy criteria:</p>

¹ Axillary body temperature > 37.0 °C confirmed by two measurements (morning-evening/evening-morning)

	<p>The dynamics of intoxication symptoms in points by Days 3, 8 of treatment, assessed according to the Symptom Assessment Scale</p> <p>Assessment of the ongoing therapy efficacy by a physician at the end of treatment course (IMOS scale) - complete recovery (0 points), significant improvement (1 point), minor to moderate improvement (2 points), unchanged (3 points), worsening (4 points).</p> <p>Assessment of the ongoing therapy efficacy by the patient's parent/adoptive patient on the IMOS scale (excellent, good, satisfactory, not efficient) - scores from 0 to 3</p> <p>Number of cases of the antipyretic product (paracetamol) consumption for the entire study period</p> <p>Number of patients' dropout patients due to the need to prescribe the antibacterial products</p> <p>Number of patients (%) with body temperature normalization (presence of axillary body temperature ≤ 36.9 °C in two consecutive measurements (morning-evening/evening-morning) on Day 5 of therapy</p> <p>Number of patients (%) with clinical pattern normalization on Day 5 of therapy according to the Symptom Assessment Scale (total ≤ 3 points)</p>
<p>Safety assessment criteria</p>	<p>Safety and tolerability assessments will be conducted throughout the entire study (from the moment of the first use of the study product/placebo) on the following parameters:</p> <p>frequency of adverse events (AEs) occurrence, recorded according to the data of spontaneous patients' reports, presence of complaints, and also to physical examination data, clinically significant deviations of laboratory test indicators and instrumental methods of examination from baseline values;</p> <p>Conclusion on safety of the study product will be made after a statistical assessment of all AEs, including serious ones, which identified at least possible relation to the study product.</p>
<p>Ethical and legal aspects</p>	<p>The study will be conducted in accordance with:</p> <p>RF Constitution.</p> <p>Ethical principles of the World Medical Association's Declaration of Helsinki 1964, as amended in 2013.</p> <p><u>Federal Law:</u></p> <p>Federal Law No. 61-FZ "On Medicine Circulation" of 12/04/2010.</p> <p><u>RF Government Regulations:</u></p>

	<p>RF Government Regulation of 13/09/2010 No. 714 (revised on 15/10/2014) "On the approval of model rules of mandatory health and safety insurance for patients participating in a clinical drug study".</p> <p>RF Government Regulation of September 3, 2010 No. 683 "On the approval of Rules of accreditation of medical institutions for conducting clinical studies of medicinal products for human use".</p> <p><u>Orders:</u></p> <p>Order of the Federal Service for Supervision in Healthcare No. 1071 "On approval of procedure for pharmacovigilance" of February 15, 2017.</p> <p>Order of the Ministry of Health of the Russian Federation No. 200n "On approval of Rules of good clinical practices" of April 1, 2016.</p> <p>Appendix 13 to the Order of the Ministry of Industry and Trade of Russia No. 916 of 14/06/2013 (revised on 18/12/2015) "On approval of Rules of good manufacturing practices - medicinal products for clinical studies.</p> <p>Order of the Ministry of Health of the Russian Federation No. 137 "On the membership of the Ethics Board" of March 24, 2015."</p> <p>Order of the Ministry of Health of the Russian Federation No. 986n "On approval of Ethics Board Regulations" of 29/11/2012.</p> <p>Order of the Ministry of Health of the Russian Federation No. 1359n of 24/12/2012 "On invalidation of Order of the Ministry of Healthcare and Social Development of the Russian Federation No. 774n of 31/08/2010 "On Ethics Board".</p> <p>Order of the Ministry of Health of the Russian Federation No. 1106-Пп/12 of August 29, 2012 "On invalidation of Order of Federal Service for Surveillance in Healthcare and Social Development of the Russian Federation No. 2314-ПП/07 of August 17, 2007 "On Ethics Board".</p> <p>Order of the Ministry of Healthcare and Social Development of Russia No. 703n of August 23, 2010. "On approval of the reporting form of the completion, suspension or termination study for the medicinal product for human use".</p> <p>Order of the Ministry of Healthcare and Social Development of Russia No. 748 of August 26, 2010. "On approval of the Procedure for Issuance of a Permission to Conduct a Study of a Medicinal Product for Human Use" (as amended by the Order of the Ministry of Health of Russia No. 111n of 13/03/2015).</p> <p>Order of Roszdravnadzor No. 2314-Пп/07 of 17/08/2007 "On Ethics Board".</p> <p>Order of the Ministry of Health and Social Development of the Russian Federation No. 366n of April 16, 2012 "On approval of the Procedure for the provision of pediatric care."</p> <p>Order of the Ministry of Health and Social Development of the Russian Federation No. 521n of 05/05/2012 "On approval of the Procedure for the provision of pediatric care to children with infectious diseases".</p>
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	<p>Order of the Ministry of Health of the Russian Federation No. 798n of 09/11/12 "Standard of specialized pediatric care for children with acute respiratory diseases of moderate severity."</p> <p>Order of the Ministry of Health of the Russian Federation No. 1450n of 24/12/12 "Standard of specialized pediatric care with acute respiratory diseases of high severity."</p> <p>Order of the Ministry of Health of the Russian Federation No. 1654n of 28/12/12 "Standard of primary health care for children with acute nasopharyngitis, laryngitis, tracheitis and acute infections of the upper respiratory tract of mild severity"</p> <p><u>National Standard:</u> National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice".</p> <p><u>Guidelines:</u> Decision of the Council of the Eurasian Economic Commission No. 79 "On approval of the Rules of Good Clinical Practice of the Eurasian Economic Union" of 03/11/2016. ICH E11 (Guidance on the clinical studies of medicinal products in the pediatric population) European guidelines on ethical principles for conducting clinical studies of medicinal products in the pediatric population.</p>
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2. GENERAL INFORMATION AND SIGNATURES OF RESPONSIBLE PARTIES

Protocol No.	Protocol No.: PoArvi/PhIII 2017	
Date/Version No.:	2.0 of 30/05/2018	
Name of the study:	“A multicenter, prospective, randomized, double-blind, placebo-controlled study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of ARVI”.	
Sponsor of the study	NPO Petrovax Pharm LLC, Russia	
	Address:	1 Sosnovaya st., Pokrov village, Podolsk, Moscow Oblast, Russia, 142143
	Tel./Fax:	+7 (495) 926-21-07.
Sponsor’s Representative	Orekhova Olga Igorevna, 22, Krasnaya Presnya st., Moscow, 123022 Tel.: +7 (495) 730 75 45 (+147) Email: OrekhovaOI@petrovax.ru	
Name of a legal entity involved by the study Sponsor to the organization and conduction of a study	ClinPharmInvest LLC, Russia	
	Legal address:	68, Uglichskaya st., Yaroslavl, 150031
	Location address:	68, Uglichskaya st., Yaroslavl, 150031
	Tel.:	+7 (4852) 59-47-79
	e-mail:	aa_khokhlov@cphinvest.ru
Representative of a legal entity involved by the study Sponsor to the organization and conduction of a study	Full name: Alexander Alexandrovich Khokhlov Position: Director	

3. PROTOCOL'S SIGNATURE PAGE

INVESTIGATOR'S AGREEMENT

A multicenter, prospective, randomized, double-blind, placebo-controlled parallel-group study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of ARVI.

Protocol No.: PoArvi/PhIII_2017, Version: 2.0 of 30/05/2018

I, the undersigned, am responsible for conducting a study at this Center and agree with the following:

- I understand the terms of the Protocol and will conduct the study in accordance with its requirements, all approved amendments to the Protocol, ICH GCP, and all applicable administrative and state regulations.
- I will not back out of the Protocol without the prior written Sponsor's permission and the following review and written approval by the Local Ethics Committee and/or the Ethics Board, unless necessary to prevent any immediate danger to the study subjects.
- I read and understood the rules for the use of study product according to this Protocol.
- I have enough time to correctly carry out the procedures stipulated by the Protocol and complete the study within a specified period of time, and I have a sufficient number of qualified employees and adequate equipment of the clinical center to conduct the study.
- I will take all actions to ensure that all personnel involved in conducting the study at my Center are adequately familiarized with the Study Product, the Protocol and their duties.

Clinical Site:

Address:

Telephone:

Principal Investigator

Tel:

Mobile:

E-mail:

Signature _____

Date _____

SIGNATURE PAGE FOR AND ON BEHALF OF THE SPONSOR

A multicenter, prospective, randomized, double-blind, placebo-controlled study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of ARVI.

Protocol No.: PoArvi/PhIII_2017, Version: 2.0 of 30/05/2018

The study will be conducted in accordance with the study protocol, principles of international good clinical practice (International Conference on Harmonization - Good Clinical Practice), and the requirements of the legislation of the Russian Federation and countries of the Eurasian Economic Union.

Approved by

Deputy Director General, Vice-President of Study, NPO Petrovax Pharm LLC:

Olga Igorevna Orekhova

Signature _____

Date _____

**SIGNATURE PAGE FOR AND ON BEHALF OF CONTRACT STUDY
ORGANIZATION**

**A multicenter, prospective, randomized, double-blind, placebo-controlled study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of ARVI.
Protocol No.: PoArvi/PhIII_2017, Version: 2.0 of 30/05/2018**

The study will be conducted in accordance with the study protocol, principles of international good clinical practice (International Conference on Harmonization - Good Clinical Practice), and the requirements of the legislation of the Russian Federation and countries of the Eurasian Economic Union.

Agreed by

Director of ClinPharmInvest LLC,
Alexander Alexandrovich Khokhlov

Signature _____

Date _____

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4. LIST OF ABBREVIATIONS

ICH	International Conference on Harmonization
IMOS	Integrated Medical Outcome Scale
ITT	Intent-To-Treat Exposed Population
IWRS	Interactive Web Response System
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
MEDDRA	Medical Dictionary for Regulatory Activities
PP	population of patients who completed the study protocol
CI	Confidence interval
DNA	Deoxyribonucleic acid
GIT	Gastrointestinal tract
BMI	Body Mass Index
SP	Study product
CRF	Case Report Form
CRO	Contract study organization
MP	Medicinal product
ICD	International Statistical Classification of Diseases
INR	International normalization ratio
LLC	Limited Liability Company
ARVI	acute respiratory viral infection
NPO	Scientific Production Association
AE/SAE	adverse event/serious adverse event
AR	adverse reaction
SOP	standard operating procedure
ESR	Erythrocyte sedimentation rate
COX	Cyclooxygenase
RR	Respiration rate
HR	Heart rate
ECG	Electrocardiogram

5. STUDY RATIONALE

5.1. Background

Polyoxidonium® is a physiologically active compound with a molecular mass of 60 to 100 kDa, which has a pronounced immunomodulating activity [1]. Polyoxidonium® belongs to a class of water-soluble derivatives of hetero-chain aliphatic polyamines. There is no analogues with a similar structure and characteristics in the world for this class of compounds [2]. Since 1983 the mechanism of action of Polyoxidonium® on all immune system components have been studied in detail by a group of authors led by R.V. Petrova [3]. It was established that this drug influences activation of nonspecific resistance of the body, phagocytosis, humoral and cellular immunity. One of the key biological properties of Polyoxidonium® is an ability to stimulate the anti-infective resistance of the body.

Previous experience showed that a majority of secondary immunodeficiency states, presenting in chronic, recurrent or indolent infectious and inflammatory diseases (skin and soft tissues, eyes, bronchopulmonary apparatus, gastrointestinal, urogenital), as well as acute bacterial and viral infections, may be treated with Polyoxidonium® (as part of complex treatment). Numerous clinical studies have proven its high efficacy and safety, dosage and treatment regimens have been developed for various diseases.

The Sponsor company "NPO Petrovax Pharm LLC", Russia, is planning to register a new dosage form of Polyoxidonium® in Russian Federation - nasal and sublingual spray for use in children aged 1 to 12 years -.

5.2. Name and description of the study products

The efficacy of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) in comparison with placebo for complex therapy of children aged 1 to 12 years with ARVI will be evaluated in this study. The hypothesis of the study product superiority over placebo will be used for efficacy assessment.

Study product - Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia).

Comparator - Placebo, nasal and sublingual spray, (NPO Petrovax Pharm, LLC, Russia) - similar to the study product, having an identical presentation, composition of excipients and appearance, but devoid of the active ingredient.

Below you can see basic information on the test product and the comparator relevant to this study.

5.2.1 Study product

Trade name: Polyoxidonium®

International non-proprietary name: Azoximer bromide

Pharmaceutical form: Nasal and sublingual spray.

Composition per 1 ml:

Component	Amount, mg
Active ingredient:	
Azoximer bromide	6.0
Auxiliary substances:	
Mannitol	1.8
Povidone K 17	1.2
Purified water	Up to 1.0

Appearance: clear, colorless or pale yellow solution.

Pharmacotherapeutic group: immunomodulating agent.

ATC: Immune potentiators.

ATC code: [L03]

Pharmacological effect:

Pharmacodynamics

Azoximer bromide has a complex action: immunomodulating, detoxifying, antioxidant, moderate anti-inflammatory.

The basis of The mechanism of immunomodulatory action of Azoximer bromide is based on a direct effect on phagocytic cells and natural killers, and also on stimulation of antibody formation and synthesis of interferon alpha and interferon gamma. Detoxification and antioxidant properties of Azoximer bromide are largely determined by the structure and high molecular weight of the drug. Azoximer bromide increases the body's resistance to local and generalized infections caused by bacteria, fungi, viruses. It restores immunity in secondary immunodeficiency states caused by various infections.

A characteristic feature of Azoximer bromide with topical (intranasal, sublingual) administration is the ability to activate early defense factors of the body against infection: the drug stimulates bactericidal properties of neutrophils, macrophages, enhances their ability to absorb bacteria, increases the bactericidal properties of saliva and the secretion of mucosa of the upper respiratory tract.

Azoximer bromide is well tolerated, does not have mitogenic, polyclonal activity, antigenic properties, it also does not have allergic, mutagenic, embryotoxic, teratogenic and carcinogenic effects. Azoximer bromide has no smell or taste, does not have a local irritant effect when applied on the mucosa of the nose and oropharynx.

Pharmacokinetics

Indications for use

It is used in adults and children from 1 year:

- For treatment of influenza and other ARVIs (at any moment from the onset of disease and during recuperation period);
- For prevention of influenza and other ARVIs (within 1 month before the expected seasonal increase in incidence);
- As part of complex therapy for treatment of acute bacterial and fungal infections of ENT organs (acute and chronic rhinitis, rhinosinusitis, adenoiditis);
- As part of complex therapy to prevent complications and recurrence of chronic ENT organ diseases (including tonsillitis, otitis, sinusitis);
- As part of complex therapy for acute and chronic allergic diseases (including pollinosis, allergic rhinitis) complicated by a bacterial, viral or fungal infection;
- For preoperative preparation of patients before surgical interventions on ENT organs, and also during postoperative period to prevent infectious complications and relapses of the disease.
- As part of complex therapy to enhance the regenerative processes of ENT organ mucosae after acute viral, bacterial and fungal infections;

Contraindications

- Increased individual sensitivity;
- Pregnancy, lactation;
- Children younger than 1 years old;

- Acute renal failure.

With caution

- chronic renal failure (used no more frequently than 2 times a week).

Posology and Administration

Polyoxidonium[®] route of administration: intranasal, sublingual.

Dose regimen, route of administration, the need and the frequency of subsequent therapy are chosen by the physician depending on the disease severity and the age of the patient.

Posology and administration in adults and children older than 12 years.

The drug is administered intranasal or in the sublingual area for 7-10 days at a daily dose of 6 mg:

Intranasal	In the sublingual region
1 spray into each nostril - 5 times a day	2 sprays - 5 times a day

Posology and administration in children aged 1 to 12 years.

The drug is administered intranasal or in the sublingual area for 7-10 days at a daily dose of 0.15 mg/kg:

Age	Intranasal	In the sublingual region
Aged 1 to 2 years	1 spray into each nostril - 1 time a day	1 spray - 2 times a day
Aged 2 to 5 years	1 spray into each nostril - 2 times a day	2 sprays - 2 times a day
Aged 5 to 8 years	1 spray into each nostril - 3 times a day	2 sprays - 3 times a day
Aged 8 to 12 years	2 sprays into each nostril - 2 times a day	4 sprays - 2 times a day

Side effects:

- An allergic reaction may develop in case of increased individual sensitivity to the product components.
- Possible body temperature elevation.

Overdose

No cases of overdose are recorded.

Interaction with other drugs

No drug–drug interactions have been identified.

Special warnings

If an allergic reaction is developed, immediately discontinue the use of Polyoxidonium® and consult a physician.

If the administration of a due dose is missed, the drug should subsequently be administered normally, as indicated in the prescribing information or recommended by the physician. Do not administer a double dose to compensate missed doses.

Do not use the drug in the presence of visual signs of its unsuitability (package defect, change in the product color).

Effect on the ability to operate vehicles and mechanisms

The use of Polyoxidonium® does not affect the ability to perform potentially dangerous activities requiring increased concentration of attention and speed of psychomotor reactions (including driving, working with moving mechanisms).

Presentation: Nasal and sublingual spray.

Per 10 ml in a dark glass vial. 1 vial with a sprayer and the Patient information leaflet in a carton.

Storage conditions: Store in the closed manufacturer's package away from direct sunlight, at 2 - 8 °C. Keep out of reach of children.

Shelf life: 2 years. Do not use after the expiration date.

5.2.2 Comparator

Trade name: Placebo.

Manufacturer: NPO Petrovax Pharm, LLC, Russia.

International non-proprietary name: N/A

Pharmaceutical form: Nasal and sublingual spray.

Composition: Composition per 1 ml:

Excipients: mannitol - 1.8 mg, Povidone K 17 - 1.2 mg, purified water - up to 1.0 ml.

Appearance: clear, colorless or pale yellow solution.

Presentation: nasal and sublingual spray.

Per 10 ml in a dark glass vial. 1 vial with a sprayer and the Patient information leaflet in a carton.

Storage conditions: Store in the closed manufacturer's package away from direct sunlight, at 2 - 8 °C. Keep out of reach of children.

5.3 Data of non-clinical and clinical studies. Published data

Non-clinical studies [13, 14, 15, 29, 30]

Preclinical studies of chronic toxicity showed no signs of general toxic and local irritant action after intranasal administration of Polyoxidonium spray solution at concentrations of 3 mg/ml or 6 mg/ml and doses up to 1 ml/kg to immature Wistar rats in the period before puberty, and also in the period of maturity. A study of Polyoxidonium, a lyophilisate for solution for injection and topical use of 3 mg and 6 mg, showed that the study product is safe in the range of therapeutic doses when administered SD to mature rats for 6 months, however the local and nephrotoxic effects were noted at the maximum dose used - 10 mg/kg (50-fold excess of the maximum single dose for humans).

When studying the acute toxicity of Polyoxidonium with its single intraperitoneal injection in high (1500 mg/kg and 2000 mg/kg) doses, a toxic effect on kidneys, liver, heart, lungs, thymus, spleen, adrenal glands, and brain was revealed. No pronounced dystrophic, necrobiotic, inflammatory reactions were found in the other examined organs.

Study of product non-toxic doses (0.005 mg/kg to 50 mg/kg) effect on the immune system functions of experimental animals (mice of different lines) showed that Polyoxidonium is an immunomodulator with a wide range of pharmacological action in a wide dose range. The immunopharmacological mechanisms of action of Polyoxidonium is based on the following product effects on specific units of immunogenesis:

- Polyoxidonium activates the three most important phagocytic subpopulations: motile tissue macrophages, circulating blood phagocytes, and resident reticuloendothelial phagocytes; it also significantly activates the macrophages migration, their ability to phagocytize and digest pathogenic bacteria, to capture and remove foreign microparticles from circulating blood; increases the body's immune resistance against a wide range of pathogens;

- Polyoxidonium leads to an increased intensity of antibody production in response to antigens of various nature, stimulates the antibody production in both high and low responsive genotypes;
- Polyoxidonium increases the efficiency of the cooperative interaction of T-and B-lymphocytes within the reactions of antibody production in response to foreign antigens; while stimulating immune reactions, the product does not violate the natural mechanisms of their inhibition;
- in the absence of an antigenic stimulus, Polyoxidonium does not induce any polyclonal transformation of B-lymphocytes, does not cause multiple cycles of B- and T-lymphocyte cell divisions, which distinguishes it from bacterial mitogens and plant lectins;
- stimulation of immunity with Polyoxidonium does not deplete the reserve capabilities of the hematopoietic system, stem hematopoietic cells, and retains their ability to proliferate and differentiate;
- Polyoxidonium significantly activates the immune responses in organisms with various types of severe immunodeficiency;
- administration of Polyoxidonium to experimental animals with inoculated tumour leads to a decrease in its growth;
- Polyoxidonium shows the antitoxic properties: it protects cell membranes against cytotoxic action, and reduces the toxicity of pharmacological drugs when administered together, protecting animals from death;

In the study of Polyoxidonium nasal spray, 0.6% solution pharmacological activity that was performed in rats with experimental acute rhinitis (n=52) the histologic pattern of nasal cavity and the semi-quantitative analysis of histopathological changes in the nasal cavity of rats that were intranasally treated for acute rhinitis with Polyoxidonium®, a 0.6% solution, for 5 days, showed a pronounced anti-inflammatory and anti-congestive (anti-edematous) effect of Polyoxidonium®, comparable with Derinat®, which is consistent with the clinical data of Polyoxidonium administration.

More detailed description of the results of non-clinical studies is given in the Investigator's Brochure.

Clinical studies [16, 17, 18, 19, 20].

Previous experience with Polyoxidonium showed its high clinical efficacy in the complex treatment of almost all secondary immunodeficiency states, which are manifested in chronic, recurrent, sluggish infectious-inflammatory processes: skin and soft tissues, eyes, bronchopulmonary apparatus, gastrointestinal and urogenital tracts, as well as in the treatment of acute bacterial and viral infections. Numerous clinical studies have proven its high efficacy and safety, and dosage and therapeutic regimens have been developed for various diseases. The immunomodulator restores the immune reactions in secondary immunodeficiency states caused by pathogens (bacterial, viral, fungal infections), surgical interventions complications, injuries, burns, cytostatic therapy, etc.

The combination of immunomodulating, antioxidant and detoxifying properties makes Polyoxidonium® one of the most effective immunomodulating agents with anti-inflammatory activity. The 15 years experience of using Polyoxidonium®, lyophilisate for solution for injection and topical use, in medical practice in adults and children from 6 months of age intravenously, intramuscularly, orally, sublingual and intranasal indicates its high efficacy and safety in the treatment of patients with primary and secondary immunodeficient conditions, allergic diseases, autoimmune processes. The use of Polyoxidonium® in complex therapy makes it possible to increase the efficacy of antibacterial, antifungal and antiviral medicinal products, shorten the treatment period and reduce the amount of consumed anti-infectious agents.

The results of in-depth studies of the product efficacy and safety showed that addition of Polyoxidonium in complex therapy of recurrent respiratory infections, chronic recurrent urogenital and herpes infections contributes to reduce in treatment period, relapses frequency and a number of complications (2-4 fold), reducing the time of rash re-epithelization, completely eliminating the causative agent from the pathological material, significantly reducing the inflammation and intoxication, and normalizing the indicators of immune status. A positive clinical effect has been achieved when Polyoxidonium was included in the complex therapy for chronic nonspecific lung diseases, tuberculosis in often and long-term sick children and adults.

The drug is available in three dosage forms: Lyophilizate for solution for injection and topical use (intranasal and sublingual) 3 and 6 mg, suppositories 6 and 12 mg, and tablets 12 mg. A new form of presentation of the drug has been developed - Polyoxidonium spray, which may be administered intranasal and sublingual.

This form is more convenient in use for the patient, resulting in an increased compliance. More detailed description of the results of clinical studies is provided in the Investigator's Brochure.

5.4 Brief description of known and expected risks and benefits for patients

study, A clinical benefit for patients is expected during this study. Monetary compensation is not provided to patients, but they will be able to receive free medical care within the procedures provided by this Protocol. In addition, as a result of the study conducted, patients will receive the reliable information about their state of health (as part of the study conducted), as well as information about the individual tolerance of the study product, which may be useful in the future. In case of detection of abnormalities in health status, patients will receive the detailed recommendations (if applicable) on elimination of health abnormalities and further treatment.

Physical, instrumental and laboratory examination methods, which will be conducted to patients within this study, are used in routine clinical practice for diagnosis and treatment of ARVI. All subjects will be tested for influenza and streptococcal infection using test strips, to avoid the presence of any pathogen that requires specific treatment.

The Investigator will closely monitor the patient's state throughout the study. If necessary, the use of the study product will be discontinued.

After taking the products used in this study, the adverse reactions may occur, as described in Sections 5.2.1, 5.2.3 and in the Investigator's Brochure attached hereto. In most cases, adverse reactions are of short duration and do not require additional treatment, however, the study physician should be ready to take all necessary measures to relieve them.

If significant clinical symptoms or suspicion on significant clinical symptoms appear in the course of the study, , an entire range of of tests should be performed immediately to provide an accurate diagnosis and to make decision on the required set of measures to eliminate them. If any significant reaction occurs, the subjects may come at the center on an unscheduled visit and receive the required medical care.

Since a product with a similar administration route (intranasal, sublingual) has already been registered and actively used in actual clinical practice for more than 20 years (Polyoxidonium®), a lyophilisate for solution for injections and topical use, NPO Petrovax Pharm, LLC, Russia), we can expect favorable safety profile of the study product.

Risks associated with the study procedures

Dizziness and/or asthenia may occur during or shortly after blood samples collection.

Taking a smear from the oral cavity could lead to the development of unpleasant sensations, coughing attack and possible gag reflex.

Examination of the oral cavity can carry some discomfort associated with the use of a spatula and a flashlight.

An ECG (if necessary) requires the application of a special gel or wet tampons on the skin, which can lead to unpleasant tactile sensations, as well as hyperemia and irritation at the site of application.

Some of the inconveniences listed above can be counterbalanced by involving the experienced and qualified personnel in the study procedures.

All patients will receive the SP/Placebo in addition to complex treatment for ARVI in accordance with the clinical guidelines and standards of care for this disease.

Taking into account the above information, we can conclude that the study benefits definitely outweigh the potential risk for the study subjects. In addition, the risks of study procedures will be minimized by engaging the experienced medical personnel to monitor the patient's health and to perform laboratory and instrumental examinations.

5.5 Justification of the administration route, dosage, dose regimen, and treatment duration

The route of administration, strength, dose regimen and duration of the therapy course with the study product were determined on the basis of use of the registered product Polyoxidonium®, a lyophilisate for solution for injections and topical use (NPO Petrovax Pharm LLC, Russia).

According to the patient information leaflet for Polyoxidonium® (a lyophilisate for solution for injections and topical use), for intranasal and sublingual use, the product is prescribed at a daily dose of 0.15 mg/kg of body weight.

Calculation of the dosage regimen of "Polyoxidonium® - spray" for children aged 1 to 12 years was carried out at the rate of the product daily dose per 1 kg of weight (0.15 mg/kg). A single dose of Polyoxidonium® spray contains 0.6 mg of Azoximer bromide.

Since the product (Polyoxidonium®, lyophilisate for solution for injection and topical use, NPO Petrovax Pharm LLC, Russia) with a similar administration route (intranasal, sublingual) and strength has been registered and actively used in actual clinical practice for more than 20 years, we can expect favorable safety profile of the new medicinal product. The new dosage form (spray) does not require a procedure for preparing a solution that is associated with a number of difficulties, new form also will allow to perform more accurately dosing; therefore, the use of a spray will be preferable for patients, especially in cases of outpatient-based treatment.

The 7-day treatment duration is determined by efficacy data obtained from clinical studies [5]. It is assumed that a 7-day course of treatment should provide the necessary therapeutic effect.

Adjunctive therapy

, According to the existing standards of ARVI treatment, the use of only two drugs is recommended to keep the fever down in children - Paracetamol up to 60 mg/kg/day or Ibuprofen up to 30 mg/kg/day [7, 10, 11].

Efferalgan (INN: Paracetamol), syrup for children 30 mg/5 ml (UPSA SAS, France), will be used as an antipyretic agent. The selection of this product is based on the fact that it is the original product of paracetamol in this dosage form which can be used as an antipyretic for ARVI in children aged 1 month to 12 years, weight from 4 to 32 kg, as indicated in the patient information leaflet [6]. This product will be provided to patients within a study free of charge for the entire period of treatment.

Efferalgan (INN: Paracetamol), syrup for children 30 mg/5 ml ***is prescribed once per set dose only in cases of febrile temperature ($\geq 38.5^{\circ}\text{C}$) presence. The next intake of the product is possible in cases of febrile temperature presence but it may be performed no earlier than at 4-6 hours from the first intake. It is necessary to warn the unnecessary prescription of any antipyretic drug, to exclude its effect on the study results interpretation. The number of antipyretic drug intakes by the patient should be recorded in the primary documentation.***

5.6 Legislative and regulatory framework

The study shall be conducted in strict accordance with this Study Protocol, the RF Constitution, and current legislation of the Russian Federation:

- Ethical principles of the World Medical Association's Declaration of Helsinki 1964, as amended in 2013.

Federal Law:

- Federal Law No. 61-FZ “On Medicine Circulation” of 12/04/2010.

RF Government Regulations:

- RF Government Regulation of 13/09/2010 No. 714 (revised on 15/10/2014) “On the approval of model rules of mandatory health and safety insurance for patients participating in a clinical drug study”.
- RF Government Regulation of 3/09/2010 No. 683 “On the approval of Rules of accreditation of medical institutions for conducting clinical studies of medicinal products for human use”.

Orders:

- Order of the Ministry of Health of the Russian Federation No. 200n "On approval of Rules of good clinical practice" of 1/04/2016.
- Appendix 13 to the Order of the Ministry of Industry and Trade of Russia No. 916 of 14/06/2013 (revised on 18/12/2015) "On approval of Rules of good manufacturing practices - medicinal products for clinical studies.
- Order of the Ministry of Health of the Russian Federation No. 137 "On the membership of the Ethics Board" of 24/03/2015.
- Order of the Ministry of Health of the Russian Federation No. 986n “On approval of Ethics Board Regulations” of 29/11/2012.
- Order of the Ministry of Health of the Russian Federation No. 1359n of 24/12/2012 “On invalidation of Order of the Ministry of Healthcare and Social Development of the Russian Federation No. 774n of 31/08/2010 “On Ethics Board”.
- Order of the Ministry of Health of the Russian Federation No. 1106-Пп/12 of 29/08/2012 “On invalidation of Order of Federal Service for Surveillance in Healthcare and Social Development Russian Federation No.2314-ПП/07 of 17/08/2007 “On Ethics Board”.
- Order of the Ministry of Healthcare and Social Development of Russia No. 703n of 23/08/2010. "On approval of the reporting form of the completion, suspension or termination of study for the medicinal product for human use".

- Order of the Ministry of Healthcare and Social Development of Russia No. 748 of 26/08/2010. "On approval of the Procedure for Issuance of a Permission to Conduct a Study of a Medicinal Product for Human Use" (as amended by the Order of the Ministry of Health of Russia No. 111n of 13/03/2015).
- Order of Roszdravnadzor No. 2314-Пп/07 of 17/08/2007 "On Ethics Board".
- Order of the Ministry of Health and Social Development of the Russian Federation No. 366n of 16/04/2012 "On approval of the Procedure for the provision of pediatric care."
- Order of the Ministry of Health and Social Development of the Russian Federation No. 521N of 05/05/2012 "On approval of the Procedure for the provision of pediatric care to children with infectious diseases".
- Order of the Ministry of Health of the Russian Federation No. 798n of 09/11/12 "Standard of specialized pediatric care for children with acute respiratory diseases of moderate severity."
- Order of the Ministry of Health of the Russian Federation No. 1450n of 24/12/12 "Standard of specialized pediatric care with acute respiratory diseases of high severity."
- Order of the Ministry of Health of the Russian Federation No. 1654n of 28/12/12 "Standard of primary health care for children with acute nasopharyngitis, laryngitis, tracheitis and acute infections of the upper respiratory tract of mild severity"
- Order of Roszdravnadzor No. 1071 of 15/02/2017 "On approval of procedure for pharmacovigilance".

National Standard:

- National Standard of the Russian Federation GOST P 52379-2005 "Good Clinical Practice".

Guidelines:

- Decision of the Council of the Eurasian Economic Commission No. 79 "On approval of the Rules of Good Clinical Practice of the Eurasian Economic Union" of 03/11/2016.
- ICH E11 (Guidance on the clinical studies of medicinal products in the pediatric population).
- European guidelines on ethical principles for conducting clinical studies of medicinal products in the pediatric population.

The Investigator must be familiar with current legislation and ICH GCP guidelines and should conduct the study in accordance with them.

Before starting the study, the Sponsor should obtain a Permission to conduct a study from the relevant regulatory authorities, in accordance with all requirements applicable in the Russian Federation.

Before starting a study, the Principal Investigator should fully review this Protocol and the Investigator's brochure attached to it, which should be documented in the appropriate forms of the organization conducting this study.

5.7 Rationale for the patient population

The selection of patient population is determined by the requirements of the Federal Law No. 61-FZ "On Medicine Circulation" and GOST R52379-2005 "Good Clinical Practice".

Rationalization for the population selected for the study is provided by the purpose of this study: proving the advantages of using Polyoxidonium® spray over placebo as part of complex therapy in children aged 1 to 12 years with ARVI.

5.8 Criteria for diagnosis

Acute respiratory viral infection (ARVI) is an acute, local (in most cases) respiratory tract infection presenting with catarrhal inflammation of the upper respiratory tract and proceeding with fever, runny nose, sneezing, cough, sore throat, a violation of the general condition of different manifestations.

The patient or parents (legal representatives) may complain of acute rhinitis and / or cough and / or conjunctival hyperemia (catarrhal conjunctivitis) in combination with symptoms of rhinitis, pharyngitis. The disease usually begins acutely, often accompanied by an increase in body temperature to subfebrile values (37.5 °C — 38.0 °C). Febrile fever is more typical for influenza, adenovirus infection, and enterovirus infections. Elevated temperature in 82% of patients is reduced by the 2-3rd day of the disease; longer (up to 5-7 days) febrile is maintained during influenza and adenovirus infection [7]. An increase of fever intensity during the disease period, or appearance of severe intoxication symptoms may indicate the accession of a bacterial infection. Repeated raise of temperature after a short-term improvement often related to development of acute otitis media following the long-lasting runny nose.

Nasopharyngitis is characterized by complaints of nasal congestion, discharge from the nasal passages, nasopharynx discomfort: burning, tingling, dryness, often accumulation of mucous discharge, which in children, flowing down the posterior pharyngeal wall, can cause a productive cough. When inflammation spreads to the mucosa of auditory tubes (Eustachitis), clicking, noise and ear pain may occur, and a sense of hearing may decrease. Clinical course of nasopharyngitis has the following age features: in infants - fever, discharge from the nasal passages, sometimes - anxiety, difficulty in feeding and falling asleep. In older children, the typical manifestations are rhinitis symptoms (peak on day 3, duration up to 6-7 days), in 1 / 3-1 / 2 patients - sneezing and / or cough (peak on day 1, average duration - 6-8 days), rarely - headache (20% in the 1st and 15% - up to the 4th day) [8].

The symptom, allowing to diagnose laryngitis, is hoarseness. In this case, there is no respiratory affection, other signs of laryngeal stenosis. Hyperemia and edema of the posterior pharyngeal wall, and its granularity caused by hyperplasia of lymphoid follicles may be found in patients with pharyngitis. A small amount of mucus (catarrhal pharyngitis) may be noticeable on the posterior pharyngeal wall [8], pharyngitis is also characterized by unproductive, and often obsessive cough. This symptom causes the anxiety of parents, gives the child an unpleasant feeling, since coughing can be very frequent. Such a cough does not respond to treatment with bronchodilators, mucolytics, inhaled glucocorticosteroids. Laryngitis, laryngotracheitis are characterized by rough cough, hoarseness. The cough can be intrusive, frequent and exhausting patients with tracheitis. Laryngeal stenosis and respiratory depression are not observed as distinct from the croup syndrome (obstructive laryngotracheitis). On average, ARVI symptoms can last for up to 10-14 days [9].

Thus, the following typical clinical signs of respiratory diseases can be distinguished:

1. Nasopharyngitis is characterized by complaints of nasal congestion, discharge from the nasal passages, nasopharynx discomfort: burning, tingling, dryness, often accumulation of mucous discharge, which in children, flowing down the posterior pharyngeal wall, can cause a productive cough. Possible increase in body temperature to subfebrile values (37.5 °C — 38.0 °C)
2. With pharyngitis, Hyperemia and edema of the posterior pharyngeal wall, and its granularity caused by hyperplasia of lymphoid follicles may be found in patients with pharyngitis. A small amount of mucus (catarrhal pharyngitis) may be noticeable on the posterior pharyngeal wall, pharyngitis is also characterized by unproductive, often obsessive cough.
3. Laryngitis is characterized by hoarseness, without any respiratory difficulty or other signs of laryngeal stenosis.

4. The cough can be intrusive, frequent and exhausting patients with tracheitis. Unlike croup syndrome (obstructive laryngotracheitis), laryngeal stenosis is not observed, there is no respiratory depression.

5. Laryngotracheitis is characterized by rough cough, hoarseness.

Laboratory diagnosis

Leukopenia, characteristic of influenza and enterovirus infections, is usually absent in other ARVIs. Respiratory syncytial viral infection is characterized by lymphocytic leukocytosis, which can exceed $15 \times 10^9/L$. In case of adenovirus infection, leukocytosis can reach a level of $15 - 20 \times 10^9/L$ and even higher, with the possible neutrophilia of more than $10 \times 10^9/l$ [7, 8, 9].

6. STUDY PURPOSES AND OBJECTIVES

6.1 Study purpose

The main purpose of this study is to demonstrate the superiority of Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) therapeutic benefits over placebo in regards to therapy efficacy, when used as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI after 7 days of treatment.

6.2 Study objectives

1. To demonstrate the superiority of Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) efficacy profile over placebo when used as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI.
2. To evaluate the safety of the study product of Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) compared with placebo as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI.

7. STUDY DESIGN

7.1 Parameters evaluated during the study

This study assesses the efficacy and safety of nasal and sublingual spray Polyoxidonium[®] (active ingredient of Azoximer bromide) compared with placebo, as part of complex therapy for ARVI not requiring hospitalization in children aged 1–12 years.

Primary efficacy criterion:

- Fever duration period² $\delta = -0.52$ days will be considered as a superiority cut-off level. Axillary body temperature level ≤ 36.9 °C confirmed by two consecutive measurements (morning-evening/evening-morning) will be considered as the end of fever.

Secondary efficacy criteria:

- The dynamics of intoxication symptoms by Days 3, 8 of treatment, assessed according to the Symptom Assessment Scale.
- Assessment of the ongoing therapy efficacy by a physician at the end of treatment course (IMOS scale) - complete recovery (0 points), significant improvement (1 point), minor to moderate improvement (2 points), unchanged (3 points), worsening (4 points).
- Assessment of the ongoing therapy efficacy by the patient's parent/adoptive patient (IMOS scale) - excellent, good, satisfactory, not efficient - scores from 0 to 3.
- Number of cases of the antipyretic product (paracetamol) consumption for the entire study period.
- Number of patients' dropout patients due to the need to prescribe the antibacterial products.
- Number of patients (%) with body temperature normalization (presence of axillary body temperature ≤ 36.9 °C in two consecutive measurements (morning-evening/evening-morning) on Day 5 of therapy.
- Number of patients (%) with clinical pattern normalization on Day 5 of therapy according to the Symptom Assessment Scale (total ≤ 3 points)

Safety endpoints

Safety and tolerability assessments will be conducted throughout the entire study (from the moment of the first use of the study product/ placebo) on the following parameters:

² Axillary body temperature > 37.0 °C confirmed by two measurements (morning-evening/evening-morning)

- frequency of AEs occurrence recorded according to the data of spontaneous patients' reports, presence of complaints, and also to physical examination data, clinically significant deviations of laboratory and instrumental methods of examination from baseline values;

Conclusion on safety of the study product will be made after a statistical assessment of all AEs, including serious ones, which identified at least possible relation to the study product.

7.2 Description of the study design

This phase III study (study of the product safety and efficacy in individuals with a specific disease) will be conducted as a multicenter, prospective, randomized, double-blind, placebo-controlled study of the efficacy and safety of study product in children aged 1 to 12 years with a diagnosis of ARVI not requiring hospitalization.

The collection of data from patients during the treatment period of 7 days with a planned visit to monitor the therapy efficacy and safety on Day 8 after the start of treatment with the study product as part of complex therapy, as well as telephone contact on Day 12 ± 1 are sufficient to assess the efficacy and safety profile of study product compared with placebo.

The study will be fully conducted on an outpatient basis. At the same time, Visits 0, 1 and 2 can be carried out by the physician's home visit to the patient.

A total of 4 or 5 patient's visits are expected: Visit 0 (Day -1 - screening), Visit 1 (Day 1 - randomization), Visit 2 (Day 3), Visit 3 (Day 8 ± 1) and Visit 4 (Day 12 ± 1 - telephone contact) (Figure 1). Detailed description of the visits is provided in Section 9.

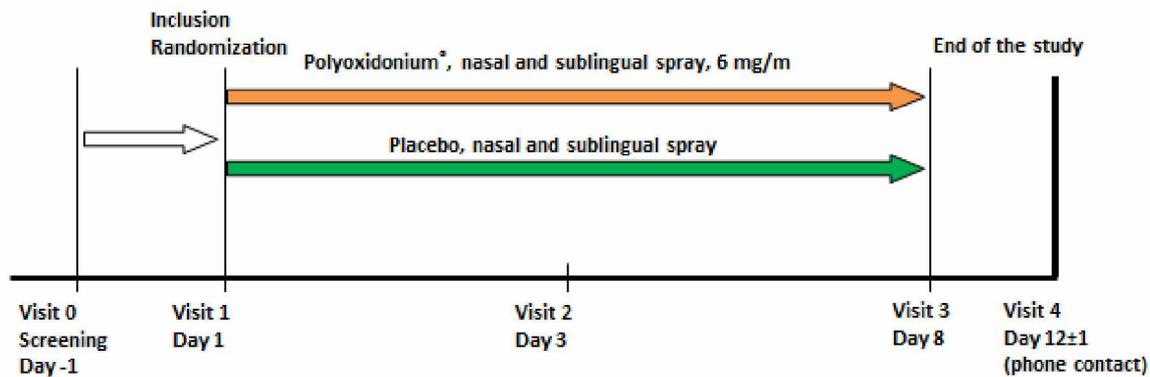


Figure 1. Study flow chart

Signing the informed consent form by one of the child's parents/adoptive parents, and by the child himself/herself (if the child's age is ≥ 10 years old), laboratory tests and assessment of compliance with the requirements of inclusion criteria, non-compliance with non-inclusion criteria will be performed at Visit 0 (Screening). Compliance with the inclusion/non-inclusion criteria requirements will be reassessed at the Visit 1 (Day 1) (may be combined with Visit 0).

At Visit 1 (Day 1) all patients who meet the inclusion criteria and do not meet any non-inclusion criteria will be randomized to two treatment groups in a 1:1 ratio, according to assigned randomization number. One group of patients will receive the study product - Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia), and the other group will receive Placebo, nasal and sublingual spray (NPO Petrovax Pharm, LLC, Russia). The duration of therapy will be 7 days. First administration of SP/placebo (depending on the group) in the sublingual area/nasal passages will be performed at the Visit 1 (Visit 0, if it is combined with Visit 1) in the Clinical Center or at home. During the visit, one of the parents/adoptive parents will be issued and trained how to independently use The study product and antipyretic drugs will be administered at the visit, one of the parents/adoptive parents will be trained for the correct use of dispensed medications at home. Administration of medications to the patient at home will be performed only by one of the parents/adoptive parents.

Visit 2 (day 3) will be conducted at Day 3 of therapy. Clinical signs of bacterial infection overlay should be evaluated by investigator at this visit. By the decision of investigator, the subject will be excluded from the study (if antibacterial therapy is required) or continue study participation and previously prescribed study treatment.

Visit 3 (day 8 ± 1) will be conducted at Day 7 of therapy. Treatment with the study product/placebo will be ended. The visit will include procedures to evaluate efficacy and monitor the safety of treatment.

Visit 4 (day 12 ± 1) is a follow-up visit, it will be performed for safety assessment by the end of the study via a telephone contact. After completion of all Visit 4 procedures the patient will complete study participation.

Throughout the study, the patient is under medical supervision. During this period, the safety and tolerability of the study product/placebo are assessed. Summary schedule of visits and study procedures is given in Appendix 5.

7.3 Minimizing subjectivity

Randomization procedures are used to minimize the possibility of systematic biases and to provide comparability of patients' initial data at the start of treatment and over the whole period of treatment.

7.3.1. Blinding procedure

The whole study will be performed under the conditions of double blinding scenario. The product or placebo in the labeled package (primary and secondary package of products do not differ) is given by the Investigator to the parents/adoptive parents. Product codes are known only to the responsible representative of the Sponsor and the medical representative of the Sponsor.

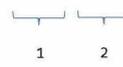
Product codes remain unknown to the Investigator and statisticians until the database lock. Disclosure of the corresponding code is possible only in the case of the registration of any study product related AEs.

7.3.2 Screening and randomization

On Visit 0 (Screening), all patients who previously meet the inclusion criteria and/or the child's parents/adoptive parents receive the detailed information about the study. After signing the Patient Information Sheet with an informed consent form, each patient is assigned a unique four-digit screening number.

Screening No. structure:

• • • • 1 - serial number of the clinical center according to the permission to conduct a study issued by the Ministry of Health of the Russian Federation.



For example: 2 - number reflecting the order of priority of patients' inclusion at each specific clinical center.

In the clinical center No. 2, one out of five patient was enrolled. This study subject shall be assigned a screening number **0205**, where 02 is the center number, 05 is a serial number of the patient enrolled to the study at this clinical center. On Visit 1, all patients who meet all inclusion criteria and do not meet any non-inclusion criteria will be randomized and assigned a three-digit random number.

The distribution of patients into 2 groups in a 1:1 ratio will be conducted according to the randomization scheme of the study protocol.

The randomization scheme will be generated by a separate document and will not be attached to the Study Protocol.

Treatment groups:

Group A: Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia).

Group B: Placebo, nasal and sublingual spray (NPO Petrovax Pharm, LLC, Russia).

Randomization using the electronic system (IWRS).

Each patient will be assigned a randomization number using a special interactive system with Internet access. To gain skills in working with the system, users will be trained and will receive a user manual.

The study will use a competitive set of patients. The number of patients included on the basis of each specific clinical center is not regulated. The recruitment of patients is terminated simultaneously in all centers after randomization of the 172nd patient, whereof the study physicians will be immediately notified.

If a patient early terminates the study, **his/her randomization number will not be reused**, and the discontinued patient cannot be included in the study afterwards. For patients who early terminated the study, the Investigator shall complete the appropriate CRF section.

7.4 Use of the study products. Description and labeling

All study products will be supplied with Certificates of Analysis. Packaging and labeling will be carried out in accordance with the legislation of the Russian Federation on medicinal products and the requirements of Good Manufacturing Practice (GMP). Labels will be made in Russian separately for primary and secondary packaging and contain the following information:

Name of the product: Polyoxidonium[®]/Placebo

Nasal and sublingual spray

Dose number per pack

Protocol code

Randomization patient's ID

Pack or vial No.

Storage conditions

Sponsor's name and address

Study Center No.

Full name of the Principal Investigator:

Product batch and shelf life

Inscription: "For clinical trial use only"

Additionally, the name "N" or "X" will be indicated on the primary and secondary package of study products/placebo.

The Sponsor will pre-label the study products and transfer it to the Clinical Centers.

Study product/placebo dose method:

When using a study product/placebo, the study physicians shall follow the instructions provided below. On Visit 1 (Visit 0, if it is combined with Visit 1) in the Clinical Center conditions/at home, the first administration of SP/placebo (depending on the group) in the sublingual area/nasal passages will be performed to the patient. At the same time, a parent/adoptive parent will also be trained to use the study products by himself/herself at home.

First administration of the SP/placebo is performed on Visit 1 (or Visit 0, if it is combined with Visit 1).

Subsequent administration (if provided) is performed at regular intervals:

12 ± 2 h - with 2-fold administration of the SP/placebo

8 ± 1 h - with 3-fold administration of the SP/placebo

Required dosages of the study product/placebo

Every day, at a daily dose of 0.15 mg/kg for 7 days.

- for children aged 1 to 2 years: 1 spray x 2 times a day, sublingual;
- for children aged 2 to 5 years: 1 spray x 2 times a day, intranasal into each nostril;
- for children aged 5 to 8 years: 1 spray x 3 times a day, intranasal into each nostril;
- for children aged 8 to 12 years: 2 sprays x 2 times a day, intranasal into each nostril.

Use of the concomitant therapy product - Efferalgan®.

Average single dose of the product depends on the child's body weight and is **10-15 mg/kg** of body weight. Maximum daily dose shall not exceed **60 mg/kg** of body weight. Minimum interval between doses of the product shall be 4 hours. For convenience and accuracy of dosing, it is necessary to use a measuring spoon.

On the measuring spoon there are graduations indicating the child's body weight: 4, 6, 8, 10, 12, 14 or 16 kg. Unmarked graduations correspond to intermediate body weight: 5, 7, 9, 11, 13 or 15 kg.

The product can be given to the child both without dilution, and after dilution (with water, milk or juice).

Duration of treatment with Efferalgan®:

3 days as an anti-febrile agent. The product is prescribed only in the case of body temperature rise up to 38.5 °C and above.

7.5 Anticipated study duration

The duration of the study participation in the study will be at most to 13 days, including the screening period (maximum 1 day), the period of therapy with the study product or placebo for 7 days, and the follow up period (telephone contact) at day 12 ± 1 after the therapy initiation.

The anticipated total duration of the study will be approximately 9 months: 6 months of patient enrollment; up to 13 days of each patient's participation in the study; 2.5 months to process the results and prepare the final report.

7.6 Suspension, termination of the study, dropout of individual patients. Study completion

The Sponsor reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) issues of safety, ethics, or significant protocol violations.

In addition, the Sponsor reserves the right to discontinue the study at any time, if the study objectives are not achieved, or for administrative reasons. In this case, the Sponsor shall notify the Investigator or the medical institution management, the local ethics committee of the temporary suspension or early termination of the study in writing or through the organization conducting the study.

If the study is suspended or terminated for safety reasons, the Sponsor shall immediately notify all Investigators, as well as regulatory authorities, and ethical committees.

The Ministry of Health of the Russian Federation may temporarily or completely discontinue the study if, in its opinion, the conditions presented in the Application are not fulfilled, or the regulator has at its disposal data that challenge the safety of patients or the scientific rationale of the study. The regulator shall notify the Sponsor, the Investigator of his/her decision and the reason for its adoption.

In those cases, when the Investigator discontinues the study before it ends in his/her clinical center, he or she shall immediately notify the Sponsor of the termination and explain in writing the reasons.

In all cases, the Investigator is obliged to immediately inform the study subjects on the termination/suspension of the study, to ensure the appropriate monitoring of their state prior to the procedures of the final visit).

The Investigator is obliged to discontinue the patient's participation in the study, when he/she complies with the exclusion criteria.

After study completion in each clinical center, the organization conducting the study shall notify the study Sponsor whereof, after which the study Sponsor shall notify the Ministry of Health of the Russian Federation of the study completion within 5 working days, according to Order of the Ministry of Healthcare and Social Development of Russia No. 703n of August 23, 2010.

7.7 Handling the study product

The quality of study products is the Sponsor's responsibility.

The study product and placebo, according to the patient information leaflet of the study product - Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia), shall be stored in the manufacturer's closed package away from direct sunlight, at 2 to 8 °C, out of reach of children.

The study product and placebo for the study will be delivered by the Sponsor/organization conducting the study to the clinical centers conducting the study, under temperature control, accompanied with a consignment note confirming the delivery of products.

Delivery of the study product/comparator shall be documented by the Investigator or other responsible persons in protocol-specific forms indicating the delivery date, quantity, batches, and shelf life of the product being transferred. These forms will be transferred to each clinical center by the organization conducting the study before the actual study initiation. Acceptance Certificates of the product delivery and return shall be signed by the responsible person, the Certificates shall indicate the quantity, shelf life, and a batch of the product being transferred. Accounting for the study product/comparator shall be documented throughout the study.

Any products delivered to clinical centers will be used only for the purpose of conducting this study in strict accordance with the Study Protocol.

The Investigator or other authorized persons will keep records of the product account. The Investigator shall be responsible for the fact that the study product/placebo, as well as the antipyretic drug Efferalgan® is:

- used only by this study subjects;
- stored in a locked and safe place, under temperature and humidity monitoring, where only authorized employees who participate in the study organization have access;
- strictly controlled, the product use procedures shall be registered in the forms provided by the organization conducting the study, indicating the patient to whom the product was issued, the date of issue, the number of products issued and returned by the patient. The unused study products, and the remainings of the used products shall be returned to the Investigator by the patient on Visit 3 (Day 8 ± 1, saved and transferred to the Sponsor).

If the study product was issued to the patient at home, it will be transported using thermal containers that ensure proper storage conditions of the product during delivery. Delivery temperature will be recorded with special sensors.

Prior to the study, all Investigators responsible for the product circulation will be additionally instructed on the rules for product transportation in the study, on the use of thermal containers and temperature sensors.

7.8 Primary data

Primary data means all the information contained in the original medical records and their certified copies, describing the results of clinical observations, examinations and other activities, allowing you to restage the study and assess it. Patient's diaries are also primary data.

Data from any primary documents will be transferred to the CRF for each study subject.

The Investigator's file shall contain the complete information on the study, indicating all events and the time at which they occurred.

8. PATIENT SELECTION AND STUDY WITHDRAWAL

All patients, after signing the Patient Information Sheet with the Informed Consent Form by the child's parents/adoptive parents and the child itself (if the child is ≥ 10 years old), shall be screened (Visit 0), which is described in detail in section 9.1.1 of this Protocol.

Only patients who meet all inclusion criteria and do not meet any non-inclusion criteria can be randomized to the study.

8.1 Inclusion criteria

A patient shall meet the following inclusion criteria:

1. Patients of both sexes aged 1 to 12 years inclusive.
2. Diagnosis of ARVI [ICD-10 code: J00 - Acute nasopharyngitis (runny nose), J02 - Acute pharyngitis, J02.9 - Unspecified acute pharyngitis, Acute laryngitis and tracheitis - J04, J04.0 - Acute laryngitis, J04.1 - Acute tracheitis, J04.2 - Acute laryngitis, Acute upper respiratory tract infections of multiple and unspecified localization - J06, J06.0 - Acute laryngopharyngitis, J06.9 - Acute upper respiratory tract infection, unspecified] confirmed by physician's examination: axillary temperature ≥ 37.0 °C (measured at the moment of physical examination) and Symptom Assessment Scale total score ≥ 5 points, not less than 3 of which should be related to ENT-organs and upper respiratory tract affection (accord. the Symptom Assessment Scale [Appendix 1]).
3. Not more than 24 hours from the onset of ARVI manifestations.
4. Signing an Informed Consent Form by one of the parents/adoptive parent of the child and the child him/herself (if aged ≥ 10 years);

8.2 Non-inclusion criteria

A patient will not be enrolled, if he/she meets at least one of the following criteria:

1. Suspicion on pneumonia, bacterial infection (including meningitis, sepsis, otitis media, sinusitis, urinary tract infection, etc.) or the presence of a disease requiring the prescription of antibacterial drugs, starting from the first day of the disease.
2. Suspicion on initial manifestations of diseases with symptoms similar to ARVI signs (other infectious diseases, flu-like syndrome at the debut of systemic connective tissue diseases and other pathology).
3. Positive express test for influenza or streptococcal infection.
4. Clinical symptoms of severe ARVI requiring hospitalization (fever ≥ 40 °C, signs of respiratory obstruction, severe hemodynamic/neurological disorders).
5. A history of or previously diagnosed primary and secondary immunodeficiency.
6. Cancer.
7. Acute infectious or non-infectious diseases (except for ARVI), as well as exacerbation or decompensation of chronic diseases (diabetes mellitus, infantile cerebral palsy, cystic fibrosis, primary ciliary dyskinesia, bronchopulmonary dysplasia, respiratory and ENT organ malformations, etc.) affecting the patient's ability to participate in a study.
8. .Sucrase/isomaltase deficiency, fructose intolerance, glucose-galactose malabsorption.
9. A history of allergy/hypersensitivity to any component of products used in treatment (including sensitivity to paracetamol, propacetamol hydrochloride (paracetamol prodrug)).
10. Use of drugs specified in Forbidden Therapy for 1 month prior to study entry.
11. Patients whose parents/adoptive parents, from the point of view of the study, will not fulfill the observation requirements during the study or observe the mode of study product administration.
12. Participation in other clinical studies of medicinal products for less than 3 months to the screening visit.
13. Pregnancy.
14. Any other medical or social condition that, in the opinion of the study physician, prevents the child from this study participation.

8.3 Patients' Exclusion

The patient and/or one of the child's parents/adoptive parents may refuse to continue the study participation at any time without explaining the reason and without consequences for the patient's treatment in the future. In this case, the Investigator is obliged to ask the patient to come to the clinical center for the procedures provided for Visit 3 in case of early withdrawal, and also to complete fully, as far as possible, the relevant primary documents and the CRF.

The patient should be excluded from the study directly by the Investigator for the following reasons:

1. Inability or refusal of the patient, his parents/adoptive parents to follow the Protocol's requirements.
2. Informed Consent withdrawal by the patient or his/her legal representative.
3. Requirement for additional therapy is not permitted under this Protocol.
4. Serious adverse events or adverse events that do not meet the severity criteria, that are not categorized as «serious», in cases when further study participation may be pernicious for patients health or well-being, in investigator's opinion.
5. Requirement for surgical intervention.
6. The patient is non-compliant with study procedures.
7. Any patient's condition that reasonably requires withdrawal, in investigator's opinion.

Subjects, who discontinued from the study due to AE/SAE will be under the follow up until total recovery or stabilization of AE.

The emergence of non-inclusion criteria during the study, in general, is not a reason for excluding the patient from the study, as well as new or associated diseases that may affect the course of the study. In these cases, the Investigator must inform the Sponsor / organization conducting the study, which must decide, either alone or with the Investigator, whether to exclude the patient from the study. The patient is eventually excluded from the study or not, the circumstances of exclusion or interruption of participation should be recorded in detail in the primary documentation and in the CRF.

In case of early termination of the study the Investigator should make every effort to ensure the visit of the Completion of the study, which corresponds to the Visit 3 procedures (the visit procedures are described in detail in Section 9.1.4 Visit 3 (end of therapy, day 8 ± 1)).

9. STUDY PROCEDURES AND THEIR SCHEDULE

9.1 Description of study visits

A total of 5 patient's visits are expected: Visit 0 (Screening, Day 1), Visit 1 (Day 1, can be combined with Visit 0), Visit 2 (Day 3), Visit 3 (Day 8 ± 1), Visit 4 (Day 12 ± 1).

Inclusion / non-inclusion criteria should be assessed on Visit 0 (Screening) and Visit 1 (Randomization), then the patient is randomized into one of the groups and begins treatment with the study product or comparator. The whole study shall take place on an outpatient basis. At the same time, Visits 0, 1 and 2 can be carried out by the physician's home visit to the patient. This is due to the fact that in actual clinical practice, often parents / adoptive parents call a physician to a house, without burdening themselves with a visit to a clinical center that involves a number of difficulties (this is especially true for children of the younger age group) and the risk of infection with a secondary infection. Visiting patients at home is regulated by the internal routine of the clinical center and can be carried out as part of the provision of medical care in accordance with modern standards. Visit 4 is carried out in order to monitor the safety and efficacy of the therapy, carried out by means of a telephone contact on Day 12 ± 1 after the start of therapy. A detailed description of study visits is provided below.

9.1.1. Visit 0 (Screening, Day -1)

Visit 0 (screening) is held at the clinical center, or during a visit to the patient by a physician at home. On Visit 0 (screening), the Investigator is obliged to provide the patient and / or parent / adoptive parent of the child with information about the study ("Patient Information Sheet with Informed Consent Form") in Russian. The procedure for signing informed consent is detailed in Section 15.4.

Prior to the provision of a signed written "Informed Consent", no study-related procedures should be conducted.

In accordance with the Federal Law of the Russian Federation No. 61-FZ “On Medicine Circulation” and the Rules for Mandatory Life Insurance of a Patient participating in clinical studies of a medicinal product, approved by the RF Government Regulation No. 714 of September 13, 2010, after signing the Patient Information Sheet with the Informed Consent Form, each patient must be issued a life and health insurance policy to be insured against the harm that may be caused to him/her during a study of drugs. The original policy, as well as one copy of the signed and dated Patient Information Sheet with the informed consent form, shall be handed out to each patient, a copy of the insurance policy will be stored along with the primary documentation for each patient included in the study. In this study, all patients will be insured by the insurance company IPJSC Ingosstrakh. In the Insurance Policy and the “Patient Information Sheet with the Informed Consent Form” the patient identification code shall be entered, which is formed on the following data:

Table 1. Patient’s ID

<i>Permission of the Ministry of Health of Russia No. (3 sections)</i>	<i>Permission’s date of issue DD.MM.YYYY (8 sections)</i>	<i>Serial number of the medical organization specified in the Permission (3 sections)</i>	<i>Patient’s initials, full name, in Russian (3 sections)</i>	<i>Patient’s date of birth DD.MM.YYYY (8 sections)</i>	<i>The code is assigned by the Clinical Center (4 sections)</i>	<i>Patient’s screening No. (4 sections)</i>

The study design envisages the inclusion of up to 210 patients in the study whose parents / adoptive parents, as well as the child him-/herself (if the child is ≥ 10 years old) must sign the Patient Information Sheet with an Informed Consent Form and the patient must undergo screening procedures to consider the possibility of including them in the study.

Screening is carried out to determine whether patients comply with the inclusion criteria and do not comply with non-inclusion criteria.

This visit must be held within 24 hours from the onset of the first ARVI symptoms.

Before conducting any screening visit procedures, you must have a signed Informed Consent Form by one of the parents/adoptive parent of the child, as well as the child himself (if the child is ≥ 10 years old) and the Investigator.

In order to determine the patient's compliance with the required inclusion criteria and non-inclusion criteria, it is necessary to conduct a clinical assessment of the patient's health, which will include the following procedures:

- Physical examination, demographic and anthropometric data collection;
- Measurement of major vital signs (HR, RR, body temperature);
- Symptom Assessment Scale completion;
- Express test for influenza;
- Express test for streptococcal infection;
- Complaints and anamnestic data collection: disease duration, effect of the previously received therapy, as well as data on concomitant therapy;
- Clinical blood test;
- Common urine analysis;
- pregnancy test (for female patients with a history of menarche);
- 12-lead ECG (only if there is a suspicion of cardiovascular pathology);
- Assessment of inclusion/exclusion criteria;
- Establishment of a clinical diagnosis;

The Investigator will assess the results obtained to determine the patient's compliance with the required inclusion criteria and non-inclusion criteria. If a patient meets all inclusion criteria, and does not meet any non-inclusion criteria, he/she can be enrolled and admitted to Visit 1 (which can be combined with Visit 0 (Screening)).

9.1.2 Visit 1 (Randomization, Day 1). Therapy period.

Visit 1 (Randomization, Day 1) can be combined with Visit 0 (Screening) held at the clinical center/at home. On Visit 1, the patient's compliance with all inclusion and non-inclusion criteria shall be reassessed. This assessment is carried out through the following procedures.

- Assessment of concomitant therapy

- Collection of patient's complaints
- Physical examination;
- Measurement of vital signs (HR, RR, body temperature)
- Symptom Assessment Scale completion

If the patient meets the requirements of inclusion/non-inclusion criteria, a randomization procedure shall be performed. It can be carried out prior to obtain the laboratory study results. After this, the following actions are performed:

- Prescription and administration of the first dose of study product/comparator, according to the randomization plan
- Adverse events registration
- Issuance of the SP/placebo and training of parents/adoptive parents how to take the products
- Issuance of antipyretic drug (Efferalgan®) and training of parents/adoptive parents how to take it
- Issuance and training of parents/adoptive parent how to complete the patient's diary
- Invitation to the next visit

After the first administration of the product, the physician will monitor the patient for one hour in order to register possible adverse events.

In the case of combining Visit 0 and Visit 1, the following procedures: collection of patient's complaints, physical examination, measurement of vital signs (HR, RR, body temperature), assessment of inclusion/non-inclusion criteria, assessment of concomitant therapy - will not be repeated.

On this visit, the parent/adoptive parent will be given for use at home the study product or a placebo (according to the drug code obtained by the Investigator during randomization), as well as antipyretic drugs - Efferalgan®, syrup for children 30 mg / ml (UPSA SAS, France). The drugs must be given in sufficient quantities, taking into account the stock, for the entire course of therapy, but no more (the calculation of the Efferalgan® amount is based on the maximum daily dosage of the drug according to the current instruction - 60 mg / kg per day, multiplied by 3 days).

The Investigator shall inform the patient about the product administration route (described in detail in section 7.4 of Protocol). The Investigator shall record the amount of product issued in the form of study product control.

Upon the completion of all the procedures of Visit 1, the Investigator shall inform the patient about the next visit - Visit 2 (Day 3), which will be held on Day 3 of therapy. The Investigator shall discuss with the patient a convenient time for visit.

9.1.3 Visit 2 (Day 3)

Visit 2 shall be held at the clinical center/at home. The Investigator needs to conduct the following study procedures:

- Collection of patient's complaints;
- Physical examination;
- Measurement of major vital signs (HR, RR, body temperature);
- Symptom Assessment Scale filling out
- Checking the diaries completion at home;
- Adverse events registration
- Assessment of concomitant therapy
- Assessment of compliance with prescribed therapy;
- Assessment of exclusion criteria.

Clinical signs of bacterial infection overlay should be evaluated by investigator at this visit. By the decision of investigator, the subject will be excluded from the study (if antibacterial therapy is required) or continue study participation and study treatment.

Upon the completion of all the procedures of Visit 2, the Investigator shall inform the patient about the next visit - Visit 3 (Day 8 ± 1), which will be held at the clinical center.

On Day 5 of therapy, in the patient's diary the Symptom Assessment Scale shall be filled in; this procedure will be performed by the parent/adoptive parent at home. To carry out this procedure on Visit 2, parents/adoptive parents shall be instructed on how to fill out this scale.

9.1.4 Visit 3 (End of the treatment, Day 8 ± 1)

Visit 3 (End of the treatment, Day 8 ± 1) shall be held at the clinical center. The Investigator needs to conduct the following study procedures:

- Collection of patient's complaints;
- Physical examination;
- Measurement of major vital signs (HR, RR, body temperature)
- Symptom Assessment Scale completion

- Checking the diaries completion at home
- Adverse events registration
- Clinical blood test
- Common urine analysis
- Assessment of concomitant therapy
- Assessment of exclusion criteria
- Assessment of compliance with prescribed therapy
- Assessment of the ongoing therapy efficacy by a physician (IMOS scale)
- Assessment of the ongoing therapy efficacy by a parent/adoptive patient (IMOS scale)

On this visit, the patient shall return to the Investigator all the unused and used products. The Investigator shall calculate the returned product, including the antipyretic drug Efferalgan®, and fill in the appropriate form for accounting the study products.

The Investigator, on the basis of data obtained during this Visit, shall make a conclusion about the patient's condition.

If the patient has early terminated the study, he/she should undergo all the procedures provided for this Visit. Upon the completion of all the procedures of Visit 3, the Investigator shall inform the patient about the next visit - Visit 4 (Day 12 ± 1), which will be held through the telephone contact. For the visit, the study physician needs to determine a time convenient for the patient and/or the patient's parents/adoptive parents.

9.1.5 Visit 4 (Study completion, Day 12 ± 1)

Visit 4 (Study completion, Day 12 ± 1) shall be held by telephone contact at a time convenient for the patient and/or parents/adoptive parents. The Investigator needs to conduct the following study procedures:

- Collection of patient's complaints
- Adverse events registration
- Assessment of concomitant therapy
- Study completion.

Upon the completion of all the procedures for Visit 4, the patient, as decided by the Investigator (in the absence of unresolved adverse events), completes the study.

9.1.6. Description of study procedures

Demographic and anthropometric data collection

Demographic data include date of birth, age (number of full years at the time of participation in the study), gender and race. Anthropometric data include weight and height.

Medical history collection

The medical history data includes a description of the underlying disease, including the duration and effect of previously received therapy, a description of previous and concurrent diseases. In addition, information about concomitant therapy shall be collected: INN, trade name, strength, presentation, single and daily dose, date of therapy initiation and termination.

Physical examination

Physical examination includes an examination of the following organs and systems:

- Skin, hair, nails
- Endocrine system
- Cardiovascular system
- Respiratory system, state of nasal passages, character of discharge
- Gastrointestinal tract, including oral examination using a spatula and flashlight
- Nervous system
- Musculoskeletal system
- Reproductive system
- Urinary system

Measurement of vital signs

Measurement of HR, RR shall be performed by qualified medical personnel in accordance with the standards adopted at the study site.

The study is conducted as part of the safety assessment of study subjects.

Body temperature measurement.

It is conducted at screening visits, Visit 1, 2 and 3 by medical personnel, and at home by parents/adoptive patients.

Algorithm for measuring body temperature:

1. Wash your hands with warm water and soap
2. Inspect the armpit, and wipe it dry

3. Take a thermometer and shake off mercury below 35 °C
4. Position the thermometer in the armpit so that the measuring tank is in contact with the body from all sides
5. Measure the temperature for 10 min
6. Pay attention to between the body and the thermometer was no linen
7. Remove the thermometer and record the digital data
8. Shake the thermometer

Parents/adoptive parents should be instructed on how to conduct thermometry at Screening.

ECG

It shall be conducted at suspicion on cardiovascular disease. At least an hour before the procedure, it is necessary to exclude the outdoor games and emotional stress of the child. No less than 1.5 hours shall pass after the meal. In young children, special electrodes are used, which are tightly fixed on the skin without damaging it. Record at least 10–15 cardiac cycles, and if they are suspicion on of arrhythmia, there may be more cycles.

The study is conducted as part of the safety assessment of study subjects.

Laboratory examination

Each clinical center will use its own clinical laboratory to conduct all tests.

Evaluation of the result of a particular indicator will occur taking into account the reference values of local laboratory in each study center.

During the study, the blood and urine samples will be taken to determine the following indicators:

Name of laboratory test	Test items			
Clinical blood test (capillary blood)	Hemoglobin Hematocrit	RBC Platelets	Leukocytes (total and WCC) ESR	
Common urine analysis	Color Clarity	pH Specific weight	Protein Glucose Bacteria	Leukocytes RBC

Express test (on screening only)	<ul style="list-style-type: none">• Influenza virus• Streptococcal infection
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Biological samples will be collected according to the procedures and standards of the clinical center. In the case of taking biological samples at home, the biomaterials will be delivered to the clinical center laboratory under appropriate conditions, using thermal containers with temperature control. The Investigators will be instructed on the rules for transporting biological samples in this study.

The tests shall be conducted as part of the safety assessment of study subjects.

In modern clinical studies practice, in addition to the above laboratory blood tests for the safety assessment of the therapy being conducted, an assessment of biochemical blood parameters shall be performed. In this study, the blood chemistry is impractical for a number of reasons related to the difficult procedure for venous blood collection in patients of the pediatric population, and ethical principles. Due to the fact that Polyoxidonium has been used in pediatric practice for more than 20 years, the accumulated experience of its use suggests that, in the doses used, the product will not have a negative effect on the patient's body.

Urine pregnancy test

The test is carried out on a screening visit and applicable only to female patients with a history of menarche using the certified test strips. The study is conducted as part of the safety assessment of study subjects.

Each clinical center will use its own clinical laboratory to conduct all other tests.

Evaluation of the result of a particular indicator will occur taking into account the reference values of local laboratory in each study center.

Express test for influenza

The test is performed on a screening visit for all patients using certified test strips.

To perform the test, it is necessary to collect biological material that must be examined for influenza virus. This is done by taking the nasal mucus. Use a sterile cotton swab take a smear of nasal epithelium, inserting it into the nasal passage and slightly rotating. Then, follow the patient information leaflet attached to the test system.

The test is conducted as part of the exclusion of influenza virus, which requires specific treatment.

Express test for streptococcal infection

The test is performed on a screening visit for all patients using certified test strips.

To perform the test, it is necessary to collect biological material that must be examined for the streptococcus. To do this, take a swab from the surface of tonsils and the posterior pharyngeal wall using the cotton wool stick supplied with the test system; it is not allowed to touch the tongue, gums, the palate, teeth (with a cotton wool stick (it is sterile). Then, follow the patient information leaflet attached to the test system.

The test is conducted as part of the exclusion of streptococcal infection, which requires specific treatment.

Assessment of compliance with prescribed therapy

Assessment of compliance with prescribed therapy will be conducted on Visits 2 and 3 by checking the Patient's Diary with notes on the amount of product used. A sufficient level of compliance is considered to be the level of compliance with prescriptions over 80% (for more details on tolerances in the treatment regimen, see section 9.4).

9.2 Diagnostic Scales and Patient's Diary

During the study, the patient's condition and the therapy efficacy will be evaluated using the following parameters: 1) "Symptom Assessment Scale" (Appendix 1) - completed by the physician, 2) IMOS scale completed by the physician (Appendix 2) and also by the parent / adoptive parent (Appendix 3).

Symptom Assessment Scale completion will be conducted on Visit 0, Visit 1, Visit 2 and Visit 3. Also, on Day 5 of therapy, in the patient's diary the Symptom Assessment Scale shall be filled in; this procedure will be performed by the parent/adoptive parent. IMOS scale completion (Appendix 3) and assessment of the ongoing therapy efficacy by the patient's parent/adoptive patient (excellent, good, satisfactory, not efficient) will be held on Visit 3.

In addition, parents / adoptive parents of patients will be given a diary to record the patient's body temperature (twice a day: morning and evening), the time of taking the study product / placebo, the time and amount of taking antipyretic (paracetamol) and other drugs and their dosage and method of taking patients' complaints.

The diary and the diagnostic scales completed by the physician are the primary documentation; upon completion of the examination by the patients, they should be collected and kept together with the patient's medical record. When using electronic diaries, the data downloaded from them will be stored in the Investigator's file.

When conducting Visit 1 procedures, the Investigator must train the parents / adoptive parent to fill out a diary. At each visit, the Investigator must verify the correctness and timeliness of filling the diary with the patient's parent / adoptive parent.

9.3 Concomitant therapy

The use of drugs other than those studied (with the exception of the fever-reducing drug Efferalgan®) will be considered as concomitant therapy and will be recorded in primary documentation and in the CRF. The concomitant therapy can include forbidden therapy and authorized therapy.

9.3.1 Forbidden Therapy

The concomitant use of the following medicinal products and/or procedures will lead to the patient's exclusion:

- antiviral drugs;
- immunomodulators (except for the study product);
- antimicrobial agents;
- centrally acting antitussives (butamirate);
- local and systemic glucocorticoids;
- physiotherapeutic treatment.

In the case of taking drugs included in the section "Forbidden therapy", the patient's study participation will be terminated and treatment will continue according to the standard of care for this nosology (treatment will be similar to real clinical practice).

9.3.2 Authorized Therapy

Combined with the intake of a study product, by decision of a study physician; the following products for the symptomatic treatment of acute respiratory infections may be prescribed to this study subjects:

- Ascorbic Acid (Vitamin C)
- Adrenomimetics (intranasal)
- Antipyretic agents at temperatures above 38.5 °C (Efferalgan®).
- Expectorant drugs (Codelaс Broncho)
- Mucolytic drugs (Acetylcysteine)
- Fenspirid

Information about the antipyretic used in this study is provided below.

Trade name: Efferalgan®

International non-proprietary name Paracetamol

Pharmaceutical form: oral solution [for children]

Composition:

100 ml of the product contains:

Active ingredient: paracetamol 3.000 g

Excipients: macrogol 6000 - 20.000 g; sugar syrup (sucrose, water) - 50.000 g; saccharinum naticum - 0.150 g; potassium sorbate - 0.400 g; caramel vanilla flavoring* - 0.200 g; citric acid - 0.107 g; purified water - up to 100 ml.

* *Composition of caramel vanilla flavoring:* butanedione, acetylmethyl carbinol, benzaldehyde, propylene glycol, gamma heptalactone, benzyl alcohol, triacetin, piperronal, amyl cinamate, vanillin, acetyl vanillin.

Appearance

Brown slightly viscous solution with caramel-vanilla smell.

Pharmacotherapeutic group: analgesic non-narcotic agent.

ATC code: N02BE01.

Pharmacological properties

(Na⁺ and water retention) and mucosa of the gastrointestinal tract.

Pharmacokinetics

Paracetamol absorption after oral administration is complete and rapid. Maximum plasma concentration is reached in 30-60 minutes after administration. Paracetamol distribution in tissues occurs rapidly. Distribution volume in children is 0.7-1.01 l/kg.

Indications for use

Efferalgan® is used in children from the age of 1 month to 12 years (with a body weight of 4 to 32 kg) as an antipyretic for acute respiratory diseases, flu, childhood infections, post-vaccination reactions and other conditions accompanied by fever.

The drug is also used as an analgesic for pain syndrome of weak or moderate intensity, including: headache, toothache, muscle pain, neuralgia, pain in injuries and burns.

Contraindications

- hypersensitivity to paracetamol, propacetamol hydrochloride (paracetamol prodrug) or other components of the drug;
- severe liver dysfunctions or decompensated hepatic disorder at the active stage;
- aged up to 1 month;
- Sucrase/isomaltase deficiency, fructose intolerance, glucose-galactose malabsorption.

With caution

Severe renal failure (creatinine clearance < 30 ml / min), liver failure, chronic alcoholism, anorexia, bulimia, cachexia, hypovolemia, dehydration, deficiency of glucose-6-phosphate dehydrogenase.

Posology and administration

Average single dose of the product depends on the child's body weight and is **10-15 mg/kg** of body weight. Maximum daily dose shall not exceed **60 mg/kg** of body weight. Minimum interval between doses of the product shall be 4 hours. For convenience and accuracy of dosing, it is necessary to use a measuring spoon supplied with the product. The product can be given to the patient both without dilution, and after dilution (with water, milk or juice).

The product is prescribed only with febrile temperature ($\geq 38.5^{\circ}\text{C}$) once per set dose. The next intake of the product is possible no earlier than at 4-6 hours, subject to the presence of febrile temperature.

Side effect

Diarrhea, abdominal pain, nausea, vomiting, tenesmus, decreased or increased prothrombin index and the international normalized ratio (INR), blood pressure reduction (as anaphylaxis symptom), thrombocytopenia, leukopenia, neutropenia, allergic skin and subcutaneous tissue reactions (skin rash, pruritus, urticaria, angioedema, anaphylactic shock, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis) are possible.

Overdose

In case of overdose, intoxication is possible, especially in children, patients with liver diseases (caused by chronic alcoholism), in patients with malnutrition, as well as in patients taking inducers of microsomal liver enzymes, in which fulminant hepatitis, hepatic insufficiency, cholestatic hepatitis can develop, cytolytic hepatitis, in the above cases - sometimes fatal.

The clinical picture of acute overdose develops within 24 hours after taking paracetamol.

Symptoms: gastrointestinal disorders (nausea, vomiting, loss of appetite, feeling of abdominal discomfort and / or abdominal pain), skin pallor. With simultaneous use in adults of 7.5 g or more or in children of over 140 mg/kg, cytolysis of hepatocytes occurs with complete and irreversible liver necrosis, development of liver failure, metabolic acidosis and encephalopathy, which can lead to coma and death. 12-48 hours after intake of paracetamol, there is an increase in the activity of "hepatic" transaminases, lactate dehydrogenase, bilirubin concentration and a decrease in the content of prothrombin.

Clinical symptoms of liver damage occur 1–2 days after drug overdose and reach a maximum of 3–4 days.

Treatment:

- Immediate hospitalization;
- Assay of blood plasma paracetamol before starting treatment at the earliest possible time after an overdose;
- Introduction of SH-group donors and precursors of the synthesis of glutathione - methionine and acetylcysteine within 10 hours after an overdose. The need for additional therapeutic measures (further introduction of methionine, intravenous introduction of acetylcysteine) is determined depending on the blood paracetamol concentration, as well as the time elapsed after its introduction;
- Symptomatic treatment;
- Liver function tests should be performed at the beginning of treatment and then - every 24 hours. In most cases, the activity of hepatic transaminases is normalized within 1 -2 weeks.

In very severe cases, a liver transplant may be required.

Interaction with other drugs

Phenytoin reduces the efficacy of paracetamol and increases the risk of hematotoxicity. Patients taking phenytoin should avoid frequent use of paracetamol, especially in high doses.

Probenecid almost twice reduces paracetamol clearance, inhibiting the process of its conjugation with glucuronic acid. In case of simultaneous prescription paracetamol dose reduction should be considered.

Care should be taken when using paracetamol and liver microsomal enzyme inducers (eg, ethanol, barbiturates, isoniazid, rifampicin, carbamazepine, anticoagulants, zidovudine, amoxicillin + clavulanic acid, phenylbutazone, tricyclic antidepressants).

Prolonged use of barbiturates reduces the efficacy of paracetamol. Salicylamide increases the half-life of paracetamol.

The INR should be monitored during and after the end of simultaneous use of paracetamol (especially in high doses and / or for a long time) and coumarins (for example, warfarin), since paracetamol when taken in a dose of 4 g for at least 4 days may enhance the effects of indirect anticoagulants.

Effects on ability to drive and use machines.

Effects on ability to drive and use machines have not been studied. If a patient experiences dizziness, psychomotor agitation and disorientation of orientation in space and time, he is not recommended to drive a car and other mechanisms during treatment with the drug.

9.4 Methods for monitoring compliance with procedures

Compliance of the study product / placebo (adherence to therapy) will be assessed at Visits 2 and 3 according to the patient's electronic diary by checking the data entered by the patient's parent about taking the drug.

On Visit 1, one bottle of the prescribed drug will be given to the patient's parent / adoptive parent.

At Visit 3, the vial of the prescribed drug must be returned by the patient's parent / adoptive parent to the study center.

Monitoring compliance with the protocol procedures during the study is carried out by the investigator

According to the draft Patient information leaflet for Polyoxidonium, during therapy, patients from 1 to 2 years should receive the drug by 1 injection x 2 times per day sublingual (14 drugs in total / 14 doses), patients from 2 to 5 years - intranasal 1 injection in each nasal passage x 2 times a day (14 applications total / 28 doses), patients from 5 to 8 years old - intranasal 1 injection in each nasal passage 3 times a day (21 applications total / 42 doses), patients from 8 to 12 years old - intranasal for 2 injections per each nasal passage 2 times a day (14 applications in total / 56 doses). Possible omissions of taking the drug during the study:

No more than two misses with 2-fold SP / placebo.

No more than four passes - with 3-fold use of SP / placebo.

These conditions will allow maintaining the level of compliance not lower than 80% [21 - 24].

If compliance is less than 80%, patient data will not be included in the efficacy analysis.

Dosage of antipyretic drugs will be assessed during the study according to the Patient's Diary - by checking the completed data by the patient's parent about taking the drug on visits 2 and 3.

On Visit 1, one vial of the prescribed antipyretic drug will be given to the patient's parent / adoptive parent.

On Visit 3, the vial of the prescribed antipyretic drug must be returned by the patient's parent / adoptive parent to the study site.

10. EFFICACY ASSESSMENT

In this study, the efficacy will be assessed based on the body temperature changes recorded in the patient's diaries at home by the parent / adoptive parent of the child; based on the Symptom Assessment Scale, IMOS scale, evaluation of the efficacy of the patient's parent / adoptive therapy, the number of cases of consumption of the antipyretic drug, the number of cases of dropout of patients due to the need to prescribe antibacterial drugs.

The multiplicity and rules for the use of these diagnostic scales are described in detail in the protocol section 9.2 "Diagnostic scales and Patient's diary".

Primary efficacy criterion:

- Fever duration period³ $\delta = -0.52$ days will be considered as a superiority cut-off level. Axillary body temperature level ≤ 36.9 °C confirmed by two consecutive measurements (morning-evening/evening-morning) will be considered as the end of fever.

Secondary efficacy criteria:

- The dynamics of intoxication symptoms by Days 3, 8 of treatment, assessed according to the Symptom Assessment Scale .
- Assessment of the ongoing therapy efficacy by a physician at the end of treatment course (IMOS scale) - complete recovery (0 points), significant improvement (1 point), minor to moderate improvement (2 points), unchanged (3 points), worsening (4 points).
- Assessment of the ongoing therapy efficacy by the patient's parent/adoptive patient (excellent, good, satisfactory, not efficient) - scores from 0 to 3.
- Number of cases of the antipyretic product (paracetamol) consumption for the entire study period.
- Number of patients' dropout patients due to the need to prescribe the antibacterial products.
- Number of patients (%) with body temperature normalization (presence of axillary body temperature ≤ 36.9 °C in two consecutive measurements (morning-evening/evening-morning) on Day 5 of therapy.
- Number of patients (%) with clinical pattern normalization on Day 5 of therapy according to the Symptom Assessment Scale (total ≤ 3 points).

11. SAFETY ASSESSMENT

The safety of compared drugs will be assessed throughout the study on the occurrence and development of adverse events (AE) recorded primarily on the complaints of patients, as well as on the data of physical examination and the results of laboratory and instrumental examination.

Adverse event - any medically unfavorable event observed in the subject of the study after the use of the medicinal product, which may not have a causal relation with its use.

³ Axillary body temperature > 37.0 °C confirmed by two measurements (morning-evening/evening-morning)

Thus, an adverse event (AE) can be any unfavorable symptom (including deviation of the laboratory value from the norm), a complaint or a disease, the time of occurrence of which does not exclude a causal relationship with the use of the medicinal (test) product, regardless of the presence or absence of such communication.

The severity of AE is established in accordance with the following classification:

- Grade 1 (mild AE): an adverse event easily tolerated by the patient, causing minimal discomfort and not interfering with daily activities;
- Grade 2 (moderate AE): an adverse event that causes discomfort that interferes with daily activities;
- Grade 3 (severe AE): an adverse event that interferes with normal daily activities.

The AE relation to the product prescription is determined by the WHO scale:

Certain. Clinical manifestation of AEs, laboratory findings deviations occur during the period of administration of the product are unlikely to be explained by the presence of existing diseases and other factors. Manifestations of AEs regress after the product discontinuation and occur again after repeated administration.

Probable. Clinical manifestations of AEs, laboratory findings deviations have temporal association with the product administration, are unlikely to have any association with concurrent diseases or other factors, and which regress upon cancellation of the product. Response to the drug re-challenge is unknown.

Possible. Clinical manifestation of AEs, changes in laboratory findings have temporal association with the product administration, but they can be explained by the presence of concomitant diseases or administration of other medicinal products and the influence of chemical compounds. Information on drug withdrawal response is unclear.

Questionable. Clinical manifestation of AEs, changes in laboratory findings manifest without a clear temporal association with the product administration; other factors are present (medicinal products, diseases, chemical compounds, medical manipulations), which may have caused them.

Unlikely. Clinical manifestation of AEs, abnormal laboratory findings related to AEs, are hard to assess. Necessary additional data for the assessment, or the same date are presently analyzed.

Unclassified. Reports on suspected AEs cannot be assessed as there are no enough data or data are contradictory.

In the event of occurrence of AE, the study physician should take and record their actions in primary and secondary documentation, for example, prescribe additional medications (which, in what dose, for what period), hospitalize the patient (if necessary), etc.

Adverse reaction (AR) - regarding the pre-registration clinical use of a new medicinal product or its use for new indications, especially if the therapeutic doses have not been precisely established, - all the negative reactions associated with the use of any dose of the medicinal product. The term "associated with the use of a medicinal product" means that there is at least a minimal possibility of a causal link between the medicinal product and an undesirable phenomenon, i.e. relationship can not be ruled out.

For registered medicinal products, this term means all the negative reactions associated with the use of the medicinal product in the usual doses used for the prevention, diagnosis or treatment of diseases, as well as for changes in physiological functions.

Unforeseen adverse reaction - an undesirable reaction, the nature or severity of which is inconsistent with known information about the product (for example, with a Investigator's brochure for an unregistered study project)

Investigators must document in the primary documentation and individual registration cards all adverse events that occurred with the patient during the study and / or caused the suspension of the study medication. The patient should be warned that during the break between study visits, he/she should inform the physician about any new symptoms that appear.

All adverse events that occurred during the study (start, duration, ending, description, intensity, outcome), as well as measures for their relief, are recorded in the CRF. In the event of serious adverse events (SAEs), it is necessary to inform representatives of the study sponsor / representatives of the contract study organization within 24 hours.

Any adverse medical event that meets the definition of AE, which, moreover, at any dose, will be considered a serious AE (SAE):

- leads to death;
- poses a threat to life;
- leads to persistent or significant disability or incapacity;
- leads to inpatient hospitalization or extension of current hospitalization;
- represents a congenital anomaly or birth defect;

- any adverse medical event that may not immediately threaten the life and lead to death or hospitalization, but from a medical and scientific point of view may pose a threat to the patient or require the intervention to prevent any of the above outcomes.

These events are usually considered serious.

Attention: the term "life-threatening" refers to an adverse event in which there is a risk of patient's death due to this reaction at the time of adverse event. This does not apply to any event that would hypothetically lead to death, if it would be more serious.

Analysis of safety parameters is based on the following data:

- frequency of occurrence and development of adverse events (AEs) recorded, according to the data of spontaneous patients' reports, clinically significant changes in vital signs (HR, RR) and clinically significant deviations of laboratory test indicators and instrumental methods of examination from baseline values;
- overall assessment of the tolerability of study products by the patient's parent/ adoptive parent and the Investigator.

11.1 Methods and terms of analysis safety parameters recording

The presence of adverse events is assessed according to the patients' complaints, as well as according to the physical examination and the results of laboratory and instrumental examination. Investigators are responsible for identifying, providing necessary medical care, documenting and reporting cases that fall within the definition of AE and SLEEP.

For safety assessment, the following laboratory parameters are determined according to the schedule of Visits (Visit 0 (Screening), Visit 3 (Day 8 ± 1)):

- Clinical blood test;
- Common urine analysis.

Laboratory deviations

Any clinically significant abnormalities in the clinical blood count, clinical urine analysis will be evaluated by the Investigator. In case of significant deviations of laboratory parameters on Visit 3 (day 8 ± 1) in comparison with the initial parameters at Visit 0 (screening), it is necessary to conduct additional laboratory monitoring before normalizing or determining the cause of the deviation.

Any additional laboratory control is carried out by the Investigator's decision. Any clinically significant laboratory deviation shall be documented as AE in the patient's medical record and in the CRF unless the deviation is due to laboratory error; in this case, a corresponding note shall be made in the primary documents.

General medical history and anamnesis morbi

General information about the medical history and anamnesis morbi is collected on the screening visit and includes:

- date of disease onset;
- previous and concurrent diseases, and surgery in the previous 6 months prior to the study inclusion;
- concomitant therapy (drug products, other treatments) and products used for 6 months prior to the study inclusion;
- smoking, alcohol and narcotic drug abuse.

Physical examination

A general physical examination is conducted on Visit 0 (Screening), Visit 1 (Day 1), Visit 2 (Day 3), Visit 3 (Day 8 ± 1). Clinically significant changes on visits - Visit 1 (Day 1), Visit 2 (Day 3), Visit 3 (Day 8 ± 1), absent on Visit 0 (Screening) are regarded and documented as AE in the patient's medical record and in the CRF.

Major vital signs

On Visit 0 (Screening), Visit 1 (Day 1), Visit 2 (Day 3), Visit 3 (Day 8 ± 1), the following basic vital signs are measured: HR, RR, body temperature. Clinically significant changes on visits - Visit 1 (Day 1), Visit 2 (Day 3), Visit 3 (Day 8) absent on Visit 0 (Screening) may be regarded as AE, depending on the clinical situation, at the discretion of the study physician; in this case, they are documented in the patient's medical record and in the CRF.

ECG

12-lead ECG can be performed on Visit 0 (Screening), only if there is a suspicion of cardiovascular pathology.

11.2 Requirements to reports, procedures for recording adverse events and intercurrent diseases and requirements for notification of regulatory authorities

When studying the efficacy of Polyoxidonium®, nasal and sublingual spray, 6 mg / ml (NPO Petrovax Pharm, Russia), a mandatory requirement is the concomitant assessment of the safety and tolerability of the studied doses in patients with a specific disease for whom this drug is being developed (in this case for children aged 1 to 12 years).

The presence and severity of adverse events after taking the investigated drugs will be assessed according to the complaints of patients and / or their parents / adoptive parents, physical examination data and the results of laboratory and instrumental examinations. At the same time, during observation of patients, known AEs related to the use of drugs with the active substance of Azoximer bromide and described in the current instructions for use of the drug Polyoxidonium® (section 5.2) will be especially taken into account.

The Investigator is responsible for notifying the Sponsor of any event that seems unusual, even if this event may be considered as an unexpected benefit to the patient.

All AEs that will occur with the patient after the first dose of the investigational drugs in the indicated dose will be registered.

With the development of any adverse events, the Investigator must record the case in the patient's medical record and fill in the appropriate pages of the CRF, assess the feasibility of continued patient's study participation. Adverse events will be registered from the time of the first use of the drug until the completion of the study.

With the development of SAE, the patient stops taking the drug, but is under the supervision of the Investigator until the resolution or stabilization of the resulting condition. With the development of AE, the patient is under the supervision of the Investigator until the resolution or stabilization of the resulting state.

Adverse events registration

In the occurrence of a serious adverse event (SAE), you must fill in a special notification form (Appendix 4) and report it to ClinPharmInvest LLC and NPO Petrovax Pharm LLC, Russia, namely: send within 24 hours the corresponding completed form by fax or e-mail to the **Qualified Person Responsible for Pharmacovigilance (QPPV) or his/her Deputy**, NPO Petrovax Pharm LLC, Russia.

Qualified Person Responsible for Pharmacovigilance: Anna Viktorovna Tsymbal

Tel.: +7(495) 730-75-45 ext 114

Fax: 8(800)2344480

Mobile: +7(915) 360-02-37

e-mail: TsvmbalAV@petrovax.ru

Deputy QPPV: Mikhail Sergeevich Khmelevskiy

Email: KhmelevskiyMS@petrovax.ru

Tel.: +7(495) 730-75-45 ext. 146

Responsible for the collection of information on SAEs for and on behalf of the organization conducting the study:

Tel.: +7 (901) 385-87-36; +7 (910) 824-19-14

e-mail: pozdneyakov_no@cphinvest.ru

Full name: Nikolay Olegovich Pozdneyakov

All SAEs must be traced until they are resolved or stabilized.

Any subsequent information relating to previously reportable SAEs will be reported according to the same procedures and within the same deadlines. The scope of information for registration of SAE is presented in Appendix 4.

Non-serious adverse events are registered in a working order and provided to the Sponsor at the end of the study (or earlier, if necessary). All non-serious AEs will be reported to the Sponsor at the end of the study in the form of a study report.

The Principal Investigator and the contract study organization, ClinPharmInvest LLC, shall be responsible for the control of reports to the Local Ethics Committee of all cases of AEs/SAEs..

Reporting to the Regulatory Authority about all cases of AE/SAE is in the responsibility of the company - Sponsor NPO Petrovax Pharm LLC, Russia.

Pregnancy

If a female patient is detected as pregnant, she cannot be included in the study. All cases of pregnancy identified during the course of a clinical trial are recorded by the Investigator in the primary documentation of the participants in the clinical trial and the corresponding "Pregnancy Report Form".

A report on the detected case of pregnancy against the background of the use of the study product / placebo is also reported to the Sponsor, LEC/NEC within 24 hours from the moment of receiving information about this event.

Any patient who becomes pregnant during this clinical trial will be excluded from the study.

In the event that a participant of a study / sexual partner of a participant in a study that has occurred during the study or within 3 weeks after it, the participant in the study is obliged to inform the study physician.

Further, with the consent of the pregnant participant/partner of the participant, the study physician will monitor the course of pregnancy until the moment of delivery.

Any complication of pregnancy or a planned termination of pregnancy for medical reasons should be recorded as a SAE. The following cases will meet the severity criteria in such a situation:

- report on the development of congenital anomalies or malformations in a child/fetus;
- report on fetal death;
- spontaneous abortion;
- reports on adverse events in the newborn classified as serious.

Such cases as abortion report without indicating information on the presence or absence of congenital malformations, reports on the drug effect on pregnancy without outcome data, or reports containing information on the normal outcome, are not subject to urgent reporting, since they do not contain an unambiguous indication of the presence of a suspected adverse reaction. However, these reports should be processed in the same way as other reports of adverse reactions to the drug.

12 STATISTICAL PROCEDURES

This section provides an overview of the proposed statistical methodology for the types of data representation that will be used in analyzing the research results. At the same time, the final statistical methods will be documented in terms of statistical analysis, where they will be described in more detail than in this section of the protocol. Statistical data processing (individual maps of all patients from all centers) at the end of the study will be conducted by non-case management staff participating in the study to create conditions for independent evaluation of the results obtained.

This study does not provide for intermediate data analysis.

All statistical processing is performed after completion of the clinical part.

Descriptive statistics (averages, scatter, frequency, confidence intervals) will be presented at each visit for all safety and efficiencies collected during the study.

Statistical analysis will be conducted using Statsoft STATISTICA software v.12 or higher, or any other, which will provide the solution of statistical analysis tasks.

12.1 Justification of sample size

The study will include patients with a clinically confirmed diagnosis of ARVI (ICD-10 code: J00, J02, J04, J06), who will be randomized and distributed to one of two groups in a 1:1 ratio: Group 1 - patients who will be prescribed the study product as part of complex therapy; Group 2 - patients who will be prescribed a placebo as part of complex therapy.

A similar study of the efficacy, tolerability and safety of Polyoxidonium® in children with acute respiratory infections [5] involved 98 patients (52 in the group of the study product and symptomatic therapy, 46 in the placebo group and symptomatic therapy). The duration of fever and intoxication in the group of the study product was 2.6 ± 0.2 days, in the placebo group - 3.2 ± 0.2 days. Thus, the superiority of the efficacy of the drug Polyoxidonium® over the efficacy of a placebo in relation to the duration of the period of fever and intoxication was $-0,60 [-0,68; -0.52]$ days; the upper limit of the 95% confidence interval for the difference in efficacy of the study product and placebo was -0.52 days. Data from another study, in general, confirms the indicated efficacy values: in children who received Polyoxidonium® in the complex of therapy, compared with children who received only macrolide drugs, their body temperature decreased by 1-2 days earlier, shortness of breath, coughing, wheezing in the lungs (Kuzmenko L.G. The use of Polyoxidonium® in the treatment of frequently ill children, "EFFECTIVE PHARMACOTHERAPY. Pediatrics, No. 2, 2013).

In this study, the fever duration and intoxication period were selected as the main parameter characterizing the efficacy of the therapy. Value of $\delta = -0.52$ days is considered as the margin of excellence.

Calculation of the sample size is based on the following formula:

$$n = (Z_{\alpha} + Z_{\beta})^2 \cdot \frac{2 \cdot SD^2}{(\mu_o - \mu_p - \delta)^2}$$

where, Z_{α} and Z_{β} are critical values of the normal distribution corresponding to the established error levels α and β (α - and β -errors are 0.05 and 0.2, respectively), SD - a standard deviation [25 - 28].

As a result of calculation based on the above values ($Z\alpha=1.645$, $Z\beta=0.842$, $SD=0.2$ day, $\delta=-0.52$ day, $\mu_o=2.6$ days, and $\mu_p=3.2$ days), the sampling size was obtained that ensures a statistical study power of at least 80%, equal to 78 patients in each group (156 subjects in total). Taking into account the dropout of patients at screening, it is planned to obtain Permission of the Ministry of Health of the Russian Federation to screen 210 patients, of whom 172 will be randomized.

Patients enrolled in the study will be randomized to one of two groups using Polyoxidonium® or placebo.

12.2 Description of the statistical methods to be used, including terms of each interim analysis

Given the main study purposes (efficacy and safety assessment), the main tools for the analysis will be descriptive statistics and graphical representations.

Continuous (quantitative) variables will be tabulated using such parameters of summary statistics as the amount of data, the amount of missing data, mean, standard deviation, median, Q_1 and Q_3 , minimum and maximum values.

The descriptive statistics and tables will be presented for all demographic and baseline data. Baseline demographic characteristics, medical history and examination data are the most recent data recorded before the first product use. A comparative analysis of these data will be carried out in a population of patients who have undergone all the study procedures and completed it according to the Protocol (per-protocol (PP) population). Based on the results of efficacy analysis, the comparative statistics will be presented. Comparison of quantitative indicators satisfying the conditions of normal distribution and equality of variances will be carried out by Student's t-test. Comparison of quantitative indicators not satisfying the conditions of normal distribution and equality of variances will be carried out by Mann-Whitney test. To compare the paired quantitative indicators satisfying the conditions of normal distribution and equality of variances, the paired Student's t-test will be used; for those not satisfying the conditions of normal distribution or equality of variances - the paired Wilcoxon test. A comparative analysis of qualitative variables will be carried out by Chi-square test; if more than 20% of the expected frequencies are less than 5, the exact Fisher's two-tail test will be used.

The efficacy data analysis will be carried out in a population of patients who have undergone all the study procedures and completed it according to the Protocol (PP population). The safety population will consist of all patients who have received at least one dose of the study product, for which further safety surveillance data is provided (ITT population). The safety parameters evaluated during the study include the results of patient's general condition assessment, measurements of vital signs, a general physical examination, patient's examination, a clinical blood test, and urinalysis (compared to baseline values on Visit 0).

Throughout the study the following will be recorded:

- All study product related cases of AEs and SAEs (number, severity).
- All cases of early study termination due to the development of AEs/SAEs associated with the study product administration (number, severity).
- Local adverse reactions (number, severity, connection with the product). Safety parameters will be studied descriptively for each group.

The number of AEs and patients with AEs will be summarized by treatment groups, with a distribution by systems and selected terminology. Additional generalizations will be made on the severity, as well as the connection with the study product.

Early withdrawn patients will be presented in the Patients List and summarized by the main reason for withdrawn, and by each treatment group. Indicators of physiological functions and laboratory analyzes at the baseline (Visit 0), as well as their changes from the baseline (Visit 3), will be summarized by treatment groups. In addition, the tables of changes in laboratory analyzes based on the classification of values as low, normal or high, relative to the norm limits, will be summarized and presented by treatment groups.

Not available or missing data will not be replaced.

In addition to the standard summary analysis, the Sponsor may conduct the additional analyzes, if deemed necessary.

Interim analysis An interim analysis was not planned.

Groups for analysis

Safety population and Per-Protocol Population.

12.3 Efficacy data analysis

A superiority cut-off level $\delta = -0,52$ days was chosen to evaluate the principal efficacy parameter - fever duration. The choice is based on the results of earlier studies, which evaluated fever duration in similar cohorts of patients [4, 5].

Therein, the following statistical hypotheses will be verified:

- **Null-hypothesis (H_0):** efficacy of the study product does not exceed the efficacy of placebo:

$$H_0: \mu_o \geq \mu_p + \delta,$$

where, μ_o and μ_p - average fever and intoxication period in the main group (μ_o) and placebo group (μ_p);

- **Alternative hypothesis (H_A):** therapy with the study product is better than placebo therapy:

$$H_A: \mu_o < \mu_p + \delta$$

A comparison of parameters between two groups of patients can be performed by calculating the 95% confidence interval for the difference between μ_o and μ_p . Efficacy of the study product is considered higher compared with the efficacy of placebo, if the upper limit of 95% confidence interval for the difference between μ_o and μ_p values is less than - (minus) 0.52 days.

12.4 Safety data analysis

Safety population will be evaluated for all types of safety analysis.

Preferred terms of MEDDRA dictionary (Preferred Term) will be used for coding and presenting the Lists of adverse events and associated diseases. All adverse events in the aggregate, as well as serious adverse events, adverse events associated with the therapy, and on other significant adverse events (for example, on adverse events that led to the cancellation of study therapy) will be presented through descriptive statistics.

Comparison of treatment groups by the incidence of AEs will be carried by Fisher's exact test.

Clinical laboratory evaluations together with indication of changes from baseline will be presented through descriptive statistics for each visit.

Laboratory deviations beyond normal values will be marked. Lists and summary descriptions of clinically significant hematological laboratory abnormalities will be presented.

Vital signs together with indication of changes from baseline will also be presented through descriptive statistics for each visit.

For a statistical analysis of quantitative indicators, a preliminary assessment of compliance with the law of normal distribution according to the Shapiro-Wilk criterion will be made. When verifying statistical hypotheses, parametric criteria will be used for indicators with a normal distribution, and non-parametric criteria will be used for indicators which distribution differs from normal. Comparison of groups by quantitative indicators will be carried out by Student's t-test for independent samples in the case of a normal data distribution or the Mann-Whitney test in the case of a distribution other than normal. Comparison of indicators within the group between visits will be performed by T-test for related samples in the case of a normal data distribution, or the Wilcoxon test in the case of a distribution other than normal.

To describe the quantitative variables, the use of the following characteristics is planned: mean, standard deviation, median, quartile, minimum, maximum, coefficient of variation.

Qualitative variables will be analyzed by Pearson χ^2 test or Fisher's exact test (if the absolute frequency of the indicator is 5 or less in at least one of the subgroups). To describe categorical data, the use of percentages or shares is planned.

Differences at $p < 0.05$ will be considered statistically significant.

The selection of statistical analysis method will be determined by the type of source data, kind of distribution. The possibility of using a number of statistical methods will be assessed after the completion of data collection, since the nature of data distribution, sample homogeneity, etc. is unknown. In the course of the analysis, it is possible to expand the list of methods used, if it is necessary for high-quality data processing.

12.5 Applicable level of significance

The statistical hypothesis will be verified at a 5% significance level, indicating the corresponding two-sided 95% level confidence intervals (or one-sided 97.5% confidence intervals).

12.6 Procedures with missing/incorrect data

In this study, absent/missing data will not be completed.

12.7 Procedures for reporting any deviations from the original

Statistical Analysis Plan

If there is a deviation from the planned statistical analysis, all changes should be identified in comparison with the methods described in the protocol. Similarly, if there is a need for any additional changes after the analysis, it will be reflected in the study report.

12.8 Selection of patients for analysis

Planned study population/Safety population

All patients taken the study product will be included in the statistical safety analysis, according to the principle of population of the planned treatment.

Per-Protocol Study Population

The research results for each patient will be evaluated for compliance with the protocol, with a discussion of any deviations from the protocol in cases where this has occurred. Criteria for inclusion in the per-protocol population are as follows:

- inclusion in the study in compliance with all the inclusion / non-inclusion criteria;
- conducting the study in strict accordance with the protocol.

13 DIRECT ACCESS TO PRIMARY DATA/DOCUMENTS

The sponsor or a person appointed by the sponsor may conduct an audit / inspection of a clinical trial at clinical centers. Regulators can also conduct an inspection at any time during or after the study. An audit / inspection may include checking documentation at a clinical center, including a CRF and primary documentation.

It is the responsibility of the Investigator to provide direct access to the primary data / documentation for the purposes of monitoring, auditing, examination, and inspection by authorized bodies.

The Investigator's file shall contain the complete information on the study, indicating all events and the time at which they occurred.

13.1 Study completion

The clinical center must complete the study and provide all the required documentation, in full compliance with the protocol and current legislation. The study may be suspended until its completion for objective reasons, both by the Sponsor and the study site. Notifications of suspension of the study should be sent to all parties involved in the study as soon as possible. Any extension of the study period must be agreed between the Sponsor and the study site and documented.

13.2 Protocol Compliance

Investigator shall conduct research in accordance with the protocol developed by the Sponsor and approved by the relevant regulatory authorities. If an amendment to the protocol is planned, the Sponsor must submit all changes in the protocol to the regulatory authorities in accordance with the established requirements.

13.3 Deviations from protocol

In general, any deviation from the protocol can be accepted only in an emergency or after receiving a written agreement from the Sponsor and subject to approval by the Ethics Committee. Any deviation from the protocol should be clearly explained in the primary documentation and in the CRF.

All protocol deviations are classified as “Significant” and “Minor”. Significant deviations from the protocol lead to the unsuitability of the data obtained for analysis. A patient with a significant deviation from the protocol should be excluded from the final analysis.

A slight deviation from the protocol may reduce the quality of the data for analysis, but this data can still be used.

Significant deviations from the protocol include, but are limited to:

- Administration of the medicinal products not provided by the protocol
- Significant deviations from visit schedules, including skipping any visit;
- *Deviation from the visit procedures*

- identification of missed use of the prescribed drug (more than 2 skips for patients taking the drug 2 times a day for the entire period of treatment and more than 4 skips for patients taking the drug 3 times a day for the entire period of treatment);
- inclusion in the study of a patient who does not meet the inclusion and non-inclusion criteria of the protocol.
- conducting the study procedures before obtaining the written informed consent of the patient and his/her parent / adoptive parent;
- other significant deviations according to the Investigator or the Sponsor.

If during the study a situation of a direct threat to the patient's life occurred and the additional prescription of any other drugs other than authorized drugs was required, the monitor of the study and the sponsor of the study should be informed within 24 hours about deviations from the protocol.

In this case, the patient who additionally received drugs that are not authorized by the protocol should be excluded from the final analysis.

The investigator will monitor him/her until the state that caused the protocol violation is resolved.

Minor protocol deviations

All other deviations that are not significant, do not affect the patient's safety and do not substantially violate the procedures provided for by the protocol. Classification of protocol deviations for minor deviations and significant deviations will be made by authorized representatives of the Sponsor after the data on deviations from the Protocol are provided (according to monitoring reports and other sources). A complete list of deviations from the protocol will be approved prior to the start of the statistical analysis and the distribution of patients among the populations for analysis. Deviations from the Protocol are always considered individually with an analysis of the reasons that should be reflected in the primary documentation. The decision to exclude a patient with deviations and violations of the Protocol from the study should be made individually in consultation with the Sponsor of the study.

The decision to include these patients in the statistical analysis is made before closing the database of the study.

If significant deviations from the protocol are found, the patient should be excluded from the final data analysis.

14 QUALITY CONTROL AND ASSURANCE

Clinical centers licensed for medical practice, having accreditation and sufficient experience in conducting clinical studies will be selected for this study. Also, the clinical center should have medical personnel with the necessary qualifications and certified equipment necessary to conduct this study. The qualifications of the personnel of the study site participating in the study must be documented. The members of the research team must have the appropriate experience to complete the research tasks, as well as undergo the necessary training on the Protocol and research procedures.

The sponsor and organization conducting the research provides a quality control system that will guarantee the conduct of this study in accordance with the study protocol, ICH GCP rules and current requirements of the legislation of the Russian Federation.

All aspects of the study protocol should be complied with throughout the study. If changes are necessary, they should be discussed without delay by the Investigator, the Study Monitor and the Sponsor. Amendments to the study protocol should be made in writing and contain a detailed justification for the changes. Amendments must be submitted to the Ethics Council at the Ministry of Public Health of the Russian Federation and to the Local Ethical Committees of the centers.

Each deviation from the study protocol must be documented and justified by the Investigator (or the person designated by the Investigator) in the primary documentation, in the CRF and the study file.

14.1 Study monitoring and audit

Throughout the study, monitoring will be conducted to ensure that:

- rights and freedoms of patients are respected;
- the data entered in the CRF correspond to the primary documentation, are reliable, accurate and complete;
- the study is conducted in accordance with the approved latest version of the protocol and the existing amendments to it (when applicable), as well as other study documents.

- The study is conducted in accordance with the principles of ICH GCP and all applicable regulatory requirements of the Russian Federation.

The sponsor and study organizing company are responsible for assigning study monitors for quality monitoring. Monitoring of the study will be carried out regularly in accordance with the plan.

Investigators are required to provide the monitor with direct access to all necessary documents for monitoring, as well as to enable the monitor to:

- visit the study site, have access to the premises where the study is being conducted, the place where the study documentation is stored, the location of the study product;
- meet with members of the study team;
- check the correctness of filling out the CRF and reconcile the CRF with the primary medical documentation;
- reconcile drug registration; monitor compliance with the course of the study protocol.

The purpose of the audit, conducted separately and independently of routine monitoring and quality control functions, is to assess the compliance of the study with the Protocol, SOP, ICH GCP and regulatory requirements.

14.2 Sponsor's actions for non-compliance with applicable requirements.

Failure to comply with the Protocol, SOP and / or relevant regulatory requirements by the Investigator / study site, the IOC or the Sponsor's staff should lead to immediate action by the Sponsor to ensure their compliance. If serious and / or repeated incidents of non-compliance with the applicable requirements by the investigator / medical institution are found during the monitoring or audit, the CRO, the Sponsor must terminate the participation of the offending party in the study. If the participation of the Investigator / study site is terminated as a result of serious or repeated cases of non-compliance with applicable requirements, the Sponsor must notify the regulatory authorities hereof.

14.3 Study-related documents

The study organizing company shall provide the following basic documents and materials to the study center:

- Study Protocol (and amendments thereto, if any);
- Investigator's brochure;
- CRF (or access to an eCRF);
- Patient information sheet with Informed Consent Form;
- scales, questionnaires, surveys, diaries used in the study;
- Investigator file with the necessary set of forms and logs according to the requirements of ICH GCP;
- Study product and Comparator;
- Study contract;
- approval of the Ministry of Health of the Russian Federation for conducting a study and approval of the Ethics Board of the Ministry of Health of the Russian Federation;
- documents required for submission to the local Ethics Committee;

Investigators shall provide to the study organization with the following basic documents before the study begins:

- forwarding letter to the local Ethics Committee;
- signed confidentiality agreement;
- signed study protocol;
- approval by the local Ethics Committee for conducting this study;
- constituent documents of LEC: order on formation, composition of LEC, LEC's SOPs;
- current CVs of all Investigators and co-Investigators (signed and dated);
- laboratory standards of the local clinical laboratory, signed and dated by the head of the laboratory;
- certificates for medical and laboratory equipment that will be used in a clinical trial;
- the order of the head of the medical organization about the beginning of the study and the appointment of the principal investigator and co-investigators to conduct this research.

By signing this Protocol, the Investigator agrees to follow the procedures for storing and archiving research documentation. Primary documentation and the local file of the Investigator are subject to storage, including the identification sheet of participants and the correspondence connected with research.

The main documents of the clinical trial must be kept at the study site for at least 15 years after the final version of the clinical trial report has been submitted to the regulatory authorities.

The sponsor is responsible for archiving the Master Study File. If the Sponsor discontinues the clinical development of the investigational product, the Investigator and the regulatory authorities should be notified. The sponsor must inform the Investigator in writing of the need to keep records related to the research.

14.4 Amendments to the Protocol and/or Protocol revision

Changes to the study protocol are not allowed unless they are urgently needed (for example, changes in the inclusion or non-inclusion criteria, if the number of patients is too low for a certain period of time, or if the agreed criteria are too often violated). Any significant protocol changes require the publication of amendments to the Protocol.

Amendments are considered significant, if they can affect:

- patients safety or physical or mental integrity;
- scientific value of the study;
- study procedures;
- quality or safety of any study product used during the study.

Amendments to the study protocol should be submitted for consideration to the Ministry of Health of the Russian Federation and Local Ethics Committees and cannot be applied until written authorization / approval of these organizations is received.

After obtaining permission / approval of the amendment, all patients included in the study must comply with the requirements of the amended protocol, or may withdraw their consent to participate in this study.

14.5 Reporting

The final report on the study shall be prepared by the organization involved by the Sponsor to conduct this study in accordance with the SOP, GOST R 52379-2005 and Federal Law FZ-61 "On Medicine Circulation" of 12/04/2010. The original report shall be kept in the Sponsor's office, and copies are included in the main study file and files are kept in the centers.

15 REGULATORY AND ETHICAL ASPECTS, INCLUDING THE SIGNATURE OF INFORMED CONSENT AND PROTECTION OF PATIENT'S CONFIDENTIAL DATA

15.1. Regulatory authorities

In accordance with the current legislation, a study protocol and other necessary documents will be submitted to the regulatory authorities to obtain permission to conduct a study to begin research.

No patient can be enrolled until the regulatory authorities' approval is obtained.

15.2 Independent Ethics Committee

This study starts only after the written authorization of Ethics committees is received.

The Investigator, the head of the medical institution or another responsible person must submit the required documentation in time for consideration to the local ethics committee. Documents submitted to the local ethics committee may vary in different institutions, but must necessarily include the final version of the clinical trial protocol, information for the patient, patient information leaflet with the informed consent form, the Investigator's brochure with information about the test drug, documents confirming the quality of the test drug / placebo, the insurance contract for patients participating in this study, the summary of the principal investigator used in the study scale s diaries.

15.3 Ethical study procedures.

Investigators, as well as all parties involved in study, must conduct it in accordance with the ethical principles of the Declaration of Helsinki, the rules of good clinical practice (ICH GCP), and the current legislation of the Russian Federation. Investigator and Sponsor shall sign a protocol and contract for conducting a study. The Investigator should not make any changes to the study protocol without the consent of the sponsor and the authorization of the ethics committee, unless it is necessary to immediately eliminate the immediate danger to the patient or when the changes concern only matters of supply or administrative aspects.

15.4 Patient Information and Informed Consent

Information about the study should be presented both in writing and orally in simple and accessible language. Written informed consent of the patient shall be approved by an independent Ethics Committee.

The decision on the patient's participation in the study shall be made by patients and their parents/adoptive parents on a voluntary basis, no patient can be enrolled in a compulsory manner.

The Investigator is responsible for explaining to the patients and their parents/adoptive parents the study objectives, as well as all aspects related to its conduct. Prior to the study, all Investigators responsible for obtaining informed consent will be additionally instructed on the specifics of signing this document in children and their parents / adoptive parents. In this case, the Investigator should try to explain to the child in the most accessible way the meaning of participation in a study and describe the procedures provided for by the protocol. The Investigator is responsible for obtaining a written confirmation of consent to participate in the patient's study and compliance with the requirements of the protocol procedures by signing the informed consent form by the patient's parent / adoptive parent and the patient himself (if the patient is ≥ 10 years old), and children under 10 will be offered information in the form of pictures and printed text in understandable format.

Conversation with the patient and his/her parent/adoptive parent shall take place without the presence of unauthorized persons.

In an interview with the patient and the child's parent/adoptive parent at an easy to understand level, the following provisions should be discussed:

- experimental nature of the study;
- study objective;
- details (pharmacological group, mechanism of action, indications and contraindications for use, possible adverse events, route of the drug administration and dose) of the study medicinal product;
- existence of permission to conduct the study;
- study procedures, including the conditions for sampling blood, urine, ECG (if necessary), the patient's arrival time at the clinical center for visits, the need to keep a patient's diary, to measure body temperature;

- patient's rights and obligations;
- benefits of participating in the study from a medical point of view, in addition to examination and obtaining information (within the scope of the Protocol) on the state of their health;
- possibility of adverse reactions and their manifestations when taking the study product/comparator, drug adjuvant therapy;
- possibility of medical care during the study;
- insurance conditions;
- possibility of voluntary refusal of the study at any of its stages;
- ensuring the confidentiality of patient information: the family name and other personal information will be kept confidential and may be disclosed only to the extent permitted by law, and will not be disclosed in publications;
- granting permission to the patient and/or child's parent/adoptive parent when signing the Patient Information Sheet with Informed Consent Form for direct access to the original medical records to verify the study procedures and data to the monitor, auditor, representatives of the LEC and the regulatory authorities, without violating confidentiality his/her personal data;
- timely provision of new information that could affect the patient's desire to continue to participate in the study, as well as any additional information about the study and the rights of participants, as well as contact information about individuals and organizations that can be consulted for additional information in the event of a change in well-being;
- possible circumstances and/or reasons why the patient's participation in the study may be terminated;
- estimated study duration and the number of patients to be enrolled.

The patient and/or parent / adopter of the child should have enough time to think about participation in the study. The patient and the parent / adopter of the child should be given the opportunity to ask additional questions and get comprehensive answers to them. The consent of the patient and / or child's parent/adoptive parent to participate in the study must be confirmed by signing the "Patient information sheet with the informed consent form" by the child's parent/adoptive parent, as well as by the child (if the child is ≥ 10 years old).

“Patient information sheet with an informed consent form” in duplicate must be signed and dated by both the patient (if aged ≥ 10 years) and the child’s parent/adoptive parent, and the research doctor. One copy of the signed document must be provided to the patient and the child’s parent/adoptive parent, and the other copy must be stored together with the primary documentation at the study site. After that, the patient will be assigned a four-digit screening number (described in detail in “Screening and Randomization” section of Protocol).

The signed informed consent form must be kept at the study site and available for review by the study monitor or by auditors upon request. All information on the process of obtaining informed consent should be reflected in the primary documentation.

If changes are made to the protocol and documents intended for patients and/or parents/adoptive parents to read, updated versions of the documents must be reviewed and approved by the regulatory authorities and LEC, and signed by the Investigators and all study participants (parents/adoptive parents and patients, if applicable), who did not complete the study.

The procedure for issuing and signing Informed Consent can take place both at the clinical center and at home.

15.5 Confidentiality of patient information

The patient’s personal medical information obtained during the course of the study is considered confidential and cannot be disclosed to third parties. This information may be communicated to the patient's attending doctor or other medical professional responsible for the patient's health after patient consent.

Each patient will be assigned an identification number that will be used instead of the patient's last name to maintain patient confidentiality when transmitting information about adverse events or other data related to the study.

Full identification information about each patient will be kept only by the Investigator, who must provide it at the request of the auditor, the insurance company or the official authorities. This information should be kept in view of its confidential nature.

All persons involved in the study process must ensure patient confidentiality, for example, by prohibiting the use of any information that can identify the patient (for example, his/her name or address).

16 DATA COLLECTION, HANDLING AND RECORDING

16.1 Data collection

All data obtained, including the results of examinations, for each patient will be recorded in the KFM. For patients who leave the study for any reason ahead of time, all the necessary documentation is completed, indicating the reason for the early termination of the study.

The monitor should check the information entered in the CRF for compliance with the primary documentation, which will confirm the absence of discrepancies in various documents during data registration. If the monitor detects inconsistencies, the necessary changes will be entered to the CRF. In case of discrepancies, the monitor should discuss this issue with the Investigator in order to ensure timely introduction of appropriate changes in the CRF.

The Investigator is responsible for ensuring that all the data entered in the CRF are accurate and complete, written legibly (in the case of paper-based CRFa) and always have the appropriate confirmation in the primary documentation. The Investigator is obliged to provide primary documentation to the monitor for data verification.

Laboratory tests will be carried out in local laboratories of study sites.

All corrections and changes of data in the CRF should be made only in accordance with the instructions. The monitor should monitor the completeness and correctness of filling the CRF. The monitor has no right to make corrections in the CRF. A Investigator or other person authorized to complete a CRF must complete a CRF during or immediately after each survey in accordance with the original documents.

16.2 Primary documents

Primary documents include: original documents related to the examination, treatment, history and description of the patient's condition. For example, such documents include outpatient cards, diaries, admission journals, prescription and issue registers, forms of the local laboratory of the study site with the results of laboratory tests and other documents.

The following information should be reflected in the primary medical records:

- Demographic data,
 - Information regarding inclusion and non-inclusion criteria,
 - Fact of participation in the study with the study number and patient ID,
 - Date and time of all examinations,
 - Anamnesis and physical examination data,
 - Adverse events,
 - Prior and concomitant therapy,
 - Findings,
 - Lab results,
 - Information on the use of study products and antipyretic drugs.
- Reason for the early termination of the study (when applicable).

16.3 Data processing

Data processing will be coordinated by the organization conducting the study. All information for each patient, which is registered in accordance with the protocol, should be promptly entered into the CRF, the design of which was developed in accordance with this protocol.

In order to ensure the most efficient data collection and transmission process, the Investigator or authorized employee of the study site should enter information into the CRF as soon as possible immediately after examining the patient. The CRF and other documents (for example, primary documentation) should be available for inspection by the monitor.

No primary information will be entered in the CRF. All data entered in the CRF should be contained in the primary documentation of the subject.

The employee responsible for the electronic database maintenance, after entering all the data, checks the base for the presence of inconsistencies, erroneously entered data, and missing data. If you have any questions, the “Data Update Form” will be sent to the clinical center to the principal investigator. When receiving answers from the Investigators to the questions posed, the officer responsible for maintaining the research database checks for inconsistencies, erroneously entered data, and missing data. After the final completion of the collection and application of data, the database is closed, after which statistical processing can begin.

16.4 Statistical Report

The statistical report shall be prepared by the organization involved by the Sponsor to conduct this study, in accordance with its standard procedures and study design, as well as regulatory requirements.

17 FINANCING AND INSURANCE

The sponsor provides insurance for patients and Investigators during this study in accordance with current Russian legislation.

In accordance with the Rules of compulsory life and health insurance of a patient participating in clinical trials of a medicinal product, approved by the Decree of the Government of the Russian Federation dated 13/09/2010. No. 714 (including amendments of May 18, 2011), the sponsor of the study concludes a contract of compulsory life insurance and health of patients participating in a study with the IPJSC Ingosstrakh.

For the conclusion of the contract, the insurer sends to the insurer a written statement about the conclusion of the contract indicating the maximum number of patients participating in the study, the name of the medicinal product undergoing clinical research, the objectives of the study, the title of the study protocol.

The contract is concluded from the day it is signed and enters into force from the day the insurer receives information on the inclusion of the first patient in the study, provided that the insurance premium has been paid before the day the contract entered into force.

The registry (registries) of individual patient identification codes is an integral part of the contract and attached to it will be provided to the insurance company as patients are included in the study.

The establishment of an individual patient identification code is carried out by the sponsor after he receives permission from the Russian Ministry of Health to conduct a study.

The Investigator must inform the patient about the conclusion of the contract of compulsory insurance, and also explain to him that other types of treatment and concomitant therapy during the study (except for emergency medical care) can only be carried out with the permission of the Investigator.

The insurance covers damage to the life and health of patients as a result of the following events:

- deficiencies and / or defects in medical equipment used during the study;
- errors and omissions in the provision of medical care and patient care;
- non-compliance with the study protocol;
- other errors and omissions made during the study of the medicinal product;
- deficiencies of the study medicinal product;
- insufficient information about the medicinal product that led to adverse events, as well as an unexpected side effect of the product.

The beneficiaries (persons in whose favor the insurance contract was concluded) are as follows:

- in the case of harm to health - patients participating in a study, according to the approved Protocol of clinical studies;
- in the event of the patient's death - a person who has suffered property and (or) moral damage as a result of the death of the patient.

When an insured event occurs, the insurance company makes an insurance payment in the following amount:

- a) in the event of the insured person's death - 2 million rubles. The insurance payment in the specified amount is distributed between the Beneficiaries in proportion to their number in equal shares;
- b) when the health of the insured person deteriorates, resulting in:
 - establishment of disability group I - 1.5 million rubles;
 - establishment of disability group II - 1 million rubles;
 - establishment of disability group III - 500 thousand rubles;
- c) when the health of the insured person deteriorates, which does not entail the establishment of a disability - not more than 300 thousand rubles.

The study will be funded by the study Sponsor - NPO Petrovax Pharm LLC, Russia.

18 PUBLICATION POLICY

Information relating to the study product and/or this study conditions or results, as well as unpublished scientific data about the study product is considered confidential and the property of the Sponsor of the study.

This information may be transferred only to those who authorize to conduct the study, or to those who participate in the study on a confidential basis. The Investigator should use this information only for the purpose of conducting this study, unless otherwise authorized by separate written Sponsor's permission.

The Investigator agrees that the Sponsor may use the information obtained during the study for publication and, thus, make it available to other Investigators or regulatory authorities.

Publication of study results by the Investigator is possible only after agreement with the Sponsor. The Investigator shall submit the planned publication manuscript to the Sponsor for approval.

The Investigator understands that the data obtained in the study can be used by the Sponsor or its agent to provide it to other Investigators or state institutions. It is necessary to realize that all the data obtained in the study shall be provided upon the first company's request. Company representatives, as well as representatives of state institutions should have access to any primary sources of documents, however, the anonymity of the study subjects should be respected as a professional standard.

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Appendix 1. Symptom Assessment Scale

Patient's screening No.: □□□

Randomization patient's ID: □□□

To be completed by a physician/patient (on Day 5 of treatment)

Completed on (dd.mm.yyyy): _____ Time of filling out:
_____ h _____ min

Common symptoms of intoxication	Assessment			
Modified/reduced activity (or impaired behavior)	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Impaired appetite or refusal of feeding	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Sickly (or different from usual) look	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Disturbed or altered sleep	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Nasal Symptoms				
Nasal discharge	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Nasal congestion/impaired nasal airflow	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Sneezing	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Throat and chest symptoms				
Hoarseness	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Sore throat	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Cough	No (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Total points				

Investigator's Signature: _____

Appendix 2. IMOS (Integrative Medicine Outcome Scale)

Patient's screening No.: □□□
Randomization patient's ID: □□□
To be completed by a physician

Completed on (*dd.mm.yyyy*): _____ **Time of completion:**
_____ **h** _____ **min**

To assess the therapy efficacy by a physician at the end of treatment course

- 0 points - Complete resolution
- 1 point - Significant improvement
- 2 points - Mild to moderate improvement
- 3 points - Same
- 4 points - Worsening

Investigator's Signature: _____

Appendix 3. IMOS (Integrative Medicine Outcome Scale)

Patient's screening No.: □□□
Randomization patient's ID: □□□
To be completed by the patient

Completed on (*dd.mm.yyyy*): _____ **Time of completion:**
_____ **h** _____ **min**

To assess the therapy efficacy by the patient at the end of treatment course

0 points - Excellent

1 point - Good

2 points - Satisfactory

3 points - inefficiently

Patient's signature:

Investigator's Signature: _____

	_ _ _ _ (dd/mm/yyyy)		_ _ _ _ (dd/mm/yyyy)		_ _ _ _ (dd/mm/yyyy)
	_ _ _ _ (dd/mm/yyyy)		_ _ _ _ (dd/mm/yyyy)		_ _ _ _ (dd/mm/yyyy)
	_ _ _ _ (dd/mm/yyyy)		_ _ _ _ (dd/mm/yyyy)		_ _ _ _ (dd/mm/yyyy)
PREGNANCY					
Who is pregnant? <input type="checkbox"/> Subject <input type="checkbox"/> Partner		Estimated Conception Date _ _ _ _ (dd/mm/yyyy) <input type="checkbox"/> Unknown		Start date of the last menstruation _ _ _ _ (dd/mm/yyyy) <input type="checkbox"/> Unknown	
				Estimated delivery date _ _ _ _ (dd/mm/yyyy) <input type="checkbox"/> Unknown	
PREGNANCY OUTCOME (choose one of the options)		RISK FACTORS (select all applicable)		CHILD INFORMATION Gestational age before birth	
<input type="checkbox"/> Ongoing <input type="checkbox"/> Live birth <input type="checkbox"/> Still birth <input type="checkbox"/> Unknown <input type="checkbox"/> Fetal death <input type="checkbox"/> Spontaneous abortion <input type="checkbox"/> Planned abortion <input type="checkbox"/> Case is not tracked		<input type="checkbox"/> Absent <input type="checkbox"/> Unknown <input type="checkbox"/> Alcohol consumption <input type="checkbox"/> Smoking <input type="checkbox"/> Drug abuse <input type="checkbox"/> Diabetes mellitus <input type="checkbox"/> Infection <input type="checkbox"/> Other		Multiple pregnancy Apgar score Gender <input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Unknown Birth outcome <input type="checkbox"/> Birth of a healthy child <input type="checkbox"/> Unknown <input type="checkbox"/> Birth of a child with pathology (diagnosis)	
Date of <u>delivery / miscarriage / abortion / fetal death</u> _ _ _ _ (dd/mm/yyyy)					
REPORT COMPLETED BY: Signature		Date _ _ _ _		Telephone	
(Full name)		(dd/mm/yyyy)			

INVESTIGATOR: (Full name)	Signature	Date (dd/mm/yyyy)	Telephone _____
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Appendix 5. Summary schedule of visits and study procedures

Visits*****	Screening* (Day - 1... Day 0)	Therapy period			Follow-up period
	Visit 0	Visit 1 (Randomization, Day 1)	Visit 2 (Day 3)	Visit 3 (Day 8 ± 1)	Visit 4** (Study completion, Day 12 ± 1)
Signing of informed consent	X				
Demographic and anthropometric data collection	X				
Anamnestic data collection	X				
Assessment of concomitant therapy	X	X	X	X	X
Measurement of major vital signs***	X	X	X	X	
Collection of patient's complaints	X	X	X	X	X
Physical examination	X	X	X	X	
Clinical blood test	X			X	
Common urine analysis	X			X	
Pregnancy test****	X				
12-lead ECG*****	X				
Symptom Assessment Scale completion	X	X	X	X	
Assessment of the ongoing therapy efficacy by a physician (IMOS scale)				X	
Assessment of the ongoing therapy efficacy by the patient's parent/adoptive patient (IMOS scale)				X	
Assessment of inclusion/non-inclusion criteria	X	X			
Randomization		X			
Prescription and administration of the first dose of SMP/placebo		X			
Issuance of the SMP/placebo and a frequency and technique to perform the product administration		X			
Issuance and training of parents/adoptive parents how to take the antipyretic drugs		X			
Return of the product				X	
Issuance and training how to complete the Patient's diary		X			
Checking the Patient's diary completion			X	X	
Assessment of exclusion criteria			X	X	
Assessment of compliance with prescribed therapy			X	X	
Adverse events registration		X	X	X	X
Express test for influenza using test strips	X				
Express test for streptococcal infection using test strips	X				

* - Visits of 0 and 1 may coincide

** - Visit is a telephone contact.

*** - HR, RR, body temperature.

**** - for female patients with a history of menarche

***** - only if there is a suspicion of cardiovascular pathology

***** - Visits 0, 1 and 2 can be carried out by the physician's home visit to the patient.

Appendix 6. Patient Information Sheet with Informed Consent Form

Sponsor:
NPO Petrovax Pharm LLC, Russia

Protocol No.: PoArvi/PhIII_2017
Version: 2.0 of 30/05/2018

PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM FOR PARTICIPATION IN A STUDY

**“A multicenter, prospective, randomized, double-blind, placebo-controlled parallel-group study of the efficacy and safety of Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) in children aged 1 to 12 years with a diagnosis of acute respiratory viral infections (ARVI)
Study Protocol No.: PoArvi/PhIII_2017**

Study Sponsor: NPO Petrovax Pharm LLC, Russia

Signature of the study Sponsor: 1, Sosnovaya st., Pokrov village, Podolsky, Moscow Oblast, Russia, 142143 Tel./Fax:+7 (495) 926-21-07.

Company authorized by the Sponsor to conduct the study: ClinPharmInvest LLC

Address of ClinPharmInvest LLC: 68, Uglichsкая st., Yaroslavl

Telephone of ClinPharmInvest LLC: 8 (4852) 59-47-71

Principal investigator:	_____
Site name:	_____
Site Address:	_____
Site telephone:	_____
Full name of a physician:	_____
Telephone of a physician for round-the-clock communication:	_____

Patient's ID

Permission of the Ministry of Health of Russia No.	Permission's date of issue DD.MM.YYYY	Serial number of the medical organization specified in the Permission	Patient's initials, full name in Russian	Patient's date of birth DD.MM.YYYY	The code is assigned by the Clinical Center	Patient's screening No.

This consent form contains important facts that will help you decide whether you want to participate in this study or not. Please, take the time to carefully review this form of informed consent. You can discuss it with friends and/or relatives. You can ask any questions about the read information to the study physician or the medical personnel of the study center. If you agree to participate in this study, you will be asked to sign this consent form, and will be given the original of this form on hands.

Moscow, 2018

Page 1 of 22

Patient information sheet with Informed Consent Form
Version 2.0 dated 30/05/2018

Sponsor:
NPO Petrovax Pharm LLC, Russia

Protocol No.: PoArvi/PhIII_2017
Version: 2.0 of 30/05/2018

1. Invitation to participate

Dear parent/adoptive parent of the patient,

Your child is invited to participate in a study. Before agreeing to participate in this study, please read the information provided in this document carefully. This study is planned to include 172 patients. In this Information Sheet with Informed Consent Form, you will find information about the study product, the study objectives, its procedures, and the rights and obligations of your child as a study subject and you as a parent. You can also discuss this information with your friends, relatives or other physicians. Your study physician will explain to you what may not be clear and answer all your questions. Please, feel free to ask if you want to discuss any aspect of the study in more detail, or if you want to get more information.

If you want your child to participate in this study, you should sign two copies of the Patient Information Sheet and the Informed Consent Form. You will be issued and handed a copy of the Patient Information Sheet and the Informed Consent Form for participation in the study, also signed and dated by your study physician. Your study physician will keep a second copy of the Consent you signed in your medical record. If your child is > 10 years old, he/she will also need to sign two copies of the Patient Information Sheet and the Informed Consent Form along with you.

Your child's participation in this study is voluntary. You can opt out of your child's participation; your child can also terminate the study at any time without any negative consequences for you and for him/her.

This study is approved by the Ministry of Health of the Russian Federation, the Ethics Board of the Ministry of Health of the Russian Federation, and the Ethics Committees of study sites.

The study is sponsored by NPO Petrovax Pharm LLC, Russia.

This document was reviewed and approved by the Ethics Board of the Ministry of Health of the Russian Federation, which examines the study documents in order to protect the rights and protect the well-being of their participants.

Sponsor:
NPO Petrovax Pharm LLC, Russia

Protocol No.: PoArvi/PhIII_2017
Version: 2.0 of 30/05/2018

Contacts of the Ethics Board: 3, Rakhmanovsky lane, Moscow 127994, Telephone: +7 (495) 625-44-21.

2. Study objective

This study objective is to demonstrate the superiority of Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) therapeutic benefits over placebo, when used as part of complex therapy in children aged 1 to 12 years with a diagnosis of ARVI.

The obtained data will be used to register the study product Polyoxidonium[®], nasal and sublingual spray, 6 mg / ml (NPO Petrovax Pharm, Russia) in the Russian Federation.

3. Study product and Comparator, Concomitant therapy

Study product - Polyoxidonium[®], nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia). This drug is registered in the Russian Federation in the form of tablets for oral administration, vaginal and rectal suppositories, a lyophilisate for preparing a solution for injection and topical use, and for more than 15 years it has been used in adults and children intravenously, intramuscularly, orally, sublingual and intranasal, including the same dosage as the study product. However, in this case, the drug is called investigative, because its use in the form of a nasal and sublingual spray has not yet been approved for use in the Russian Federation. This study is required to obtain permission for its use. Previously, a study was conducted with the participation of adult healthy male and female volunteers, during which it was shown that Polyoxidonium[®], nasal and sublingual spray, 6 mg / ml (NPO Petrovax Pharm, Russia) is safe.

The comparison drug will be Placebo, nasal spray and sublingual (NPO Petrovax Pharm, Russia).

The active ingredient of the study product Polyoxidonium[®] is Azoximer bromide - a substance that has a complex effect: immunomodulating, detoxification, antioxidant, moderate anti-inflammatory.

The comparator Ppacebo does not contain the active ingredient.

Concomitant medications

To reduce body temperature in children, according to the existing standards of ARVI treatment, the use of Paracetamol up to 60 mg/kg/day is recommended.

Sponsor:
NPO Petrovax Pharm LLC, Russia

Protocol No.: PoArvi/PhIII_2017
Version: 2.0 of 30/05/2018

Effergal (INN: Paracetamol), syrup for children 30 mg/5 ml (UPSA SAS, France), will be used as an antipyretic agent in this study. The selection of this product is justified by the fact that it is the original product of paracetamol in this dosage form and can be used as an antipyretic for ARVI in children aged 1 month to 12 years, weight from 4 to 32 kg, as indicated in the patient information leaflet. This product will be purchased within a study and provided to patients free of charge for the entire period of treatment. For you

The product is prescribed only with febrile temperature ($\geq 38.5^{\circ}\text{C}$) once per set dose. The next intake of the product is possible not earlier than in 4-6 hours, provided the patient still has febrile temperature. It is necessary to prevent the unjustified prescription of any antipyretic drug, and use it strictly according to the indication.

Permitted concomitant therapy

Combined with the intake of a study product, by decision of a study physician; the following products for the acute respiratory infection symptom relief may be prescribed to patients who participate in this study:

- Ascorbic Acid (Vitamin C)
- Adrenomimetics, e.g. xylometazoline (intranasal)
- Expectorant drugs (Codelac Broncho)
- Mucolytic drugs (Acetylcysteine)
- Fenspirid

Each intake of the above and any other drugs in this study shall be justified and documented in the Patient's diary.

4. Study procedures

The study is conducted on an outpatient basis and consists of three periods: the screening period (assessment of your child's participation in this study, Visit 0) for a period of not more than 24 hours, the treatment period (Visit 1, Visit 2 and Visit 3) for 7 days and follow-up (Visit 4) for 12 ± 1 day. It is expected that your child's participation in the study will not exceed 13 days.

During the study, you and your child will have to visit the clinic, or the physician will come to your home by himself at the appointed time.

Altogether, 4 or 5 visits are provided for the study period (Visit 0 and Visit 1 can be combined), of which Visit 4 will be held through telephone contact with your study physician.

Sponsor:
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Protocol No.: PoArvi/PhIII_2017
Version: 2.0 of 30/05/2018

For the rest of the Study Visits, you will need to come to the clinical center with your child, or you may have home visits (Visit 0, 1, 2), Visit 0 and Visit 1, at your physician's discretion, can be done in 1 day.

During the screening period (Visit 0), before the start of all procedures related to this study. You and your child will be asked to voluntarily participate in it and, if you agree, sign this Patient Information Sheet with an informed consent form for participation in the study yourself. In addition, your child must also sign this document if his age \geq is 10 years old. If your child is <10 years old, he will receive a document with pictures and text describing the study in a format more accessible to children. After signing this document, your child will be issued an insurance policy.

Before your child is included in this study. Your study physician will conduct the necessary physical examinations and tests to ensure that your child meets all inclusion criteria, and your child does not have any non-inclusion criteria for this study.

You and your child (if possible) will be asked to answer questions regarding the course of your child's illness, previous and current treatment for this pathology, as well as other diseases that your child has and other medications. Complaints will be collected from your child on anamnestic data (duration of history, effect of previously received therapy, and data on concomitant therapy), general medical (physical) examination, assessment of anthropometric and demographic data, examination of the oral cavity, and measurement of heart rate (HR), respiratory rate, body temperature, oropharyngeal and nasal smear sampling for the diagnosis of influenza and streptococcal infections, ECG (electrocardiography) at the discretion of the study physician. The study physician will offer you to jointly fill out a questionnaire describing the severity of ARVI symptoms in your child.

At this stage, your child will have blood taken from a finger for a clinical blood test, and your child will take urine for a general urine test, a pregnancy test (for female patients who have at least 1 menstruation).

Visit 1, at the discretion of the study physician, in case of readiness of the results of all the procedures of the Visit 0, can take place on the same day as Visit 0. If this is not possible, you and your child will be invited to the clinical center on the next day at the appointed time, or the physician will come to your home at the appointed time (but no later than within 24 hours from the onset of symptoms).

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On Visit 1, you will be asked to answer questions about medicinal products taken by your child, including antipyretic ones. The study physician will conduct a general medical examination of your child, an oral cavity examination, and will actively ask you about any changes in the health of your child from a previous visit. Heart rate (HR), respiratory rate (RR), and body temperature will be measured. The study physician will offer you to jointly fill out a questionnaire describing the severity of ARVI symptoms in your child.

If your child meets all the inclusion criteria and does not have any non-inclusion criteria, then he/she will receive the study product, and all the procedures provided in the study protocol will be performed.

Your child will be (as when tossing a coin) randomized into one of two possible treatment groups: study product Polyoxidonium or a placebo (a drug without an active ingredient).

Before your child first uses the prescribed product, the study physician will give you a Patient's diary and provide you the detailed instructions on how to complete it at home. The study product and the comparator are a nasal and sublingual spray. The route of SP/placebo administration (intranasal or sublingual) shall be selected based on the age: children aged 1 to 2 years - sublingual, children aged 2 to 12 years - intranasal. The selected route of administration should be maintained throughout the study.

The study physician will give you detailed instructions on how to use the product at home.

Polyoxidonium® contains 6 mg of active ingredient - Azoximer bromide, the placebo does not contain the active ingredient. The probability that your child will be given Polyoxidonium® or the placebo is 50% to 50%. The course of product administration is designed for 7 days of therapy. Depending on your child's age and the route of product administration, the frequency of administration will be as follows:

Age/Weight	Intranasal	In the sublingual region
Aged 1 to 2 years With a weight of 9 to 12 kg	-	1 spray - 2 times a day
Aged 2 to 5 years	1 spray in every	-

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With a weight of 12 to 18 kg	nostril - 2 times a day	
Aged 5 to 8 years	1 spray into each nostril - 3	-
With a weight of 18 to 27 kg	times a day	
Aged 8 to 12 years	2 sprays into each nostril - 2	-
With a weight of 27 to 39 kg	times a day	

The first use of the product will be made on Visit 1 at the clinical center/at home, under the [physician's supervision, and you will conduct all other administrations to your child at home.

You will also be given a sufficient amount of the antipyretic drug Efferalgan®. The study physician will inform you about the dose, frequency and duration of product administration by your child.

You will be given the Patient's Diary and instructed on how to complete it.

During the study, if your child will need to take other medications, please contact your study physician and consult with him/her on this issue.

In the future, during the treatment period, you and your child will need to visit the clinic, or wait for the physician at home.

On Visit 2, which is carried out on Day 3 after the start of treatment, your child will undergo the following tests and procedures:

- Collection of complaints
- Physical examination
- Oral examination
- Measurement of major vital signs (HR, RR, body temperature);
- Symptom Assessment Scale completion
- Checking the patient's diaries completion at home;
- Adverse events registration (any adverse medical event occurred after taking the study product)
- Survey on the use of other products in addition to the study one
- Evaluation of the implementation of physician's recommendations regarding the prescribed therapy
- Assessment of exclusion criteria.

On this visit, the Investigator shall assess the course of disease and decide whether to prescribe the antibacterial drugs (in this case, your child will be withdrawal), or your child will continue the previously prescribed therapy.

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On Day 5 of the therapy onset, you will need to complete the Symptom Assessment Scale on your own at home.

On Day 8 of the therapy onset (Visit 3), you and your child will need to make another visit to the clinic.

On Visit 3, your child will undergo the following tests and procedures:

- Collection of complaints
- Physical examination
- Oral examination
- Measurement of major vital signs (HR, RR, body temperature);
- Symptom Assessment Scale , IMOS completion
- Checking the patient's diaries completion at home;
- Adverse events registration
- Survey on the use of other products in addition to the study one
- Assessment of the patient following the prescribed therapy
- Assessment of exclusion criteria

To control the safety of treatment conducted, the blood will be taken from the finger for a common blood count, and your child's urine will also be taken for a common urine analysis. On this visit, you will be asked to return the unused and used medicinal product to the clinical center.

On Day 12 of the therapy onset (Visit 4), the study physician will call you at a time convenient for you and your child.

Clinical investigator will perform the following procedures:

- Survey on the presence of any complaints or adverse events in your child;
- Survey on the use of products other than the study one.

If your child does not have any clinically significant abnormalities in health state, participation in the study for your child will be completed.

In the case of your child's early study termination (dropout), the Visit of study termination shall be conducted as early as possible where your child will need to undergo examinations and procedures corresponding to Visit 3 (described above).

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In case of early withdrawal of your child due to any undesirable event development, further monitoring of your child's health state will be carried out by the study physician in accordance with the treatment standards adopted by the study center for the undesirable event (until its resolve or stabilization).

5. Possible inconveniences and risks

In this study, the well-known side effects of Polyoxidonium® may be observed, as well as the previously adverse effects that have not been reported can be revealed. Side effects:

- An allergic reaction may develop in case of increased individual sensitivity to the product components.
- Possible body temperature elevation.

Administration of antipyretic drug (Efferalgan®) can also result in the development of side effects, namely: possible diarrhea (loose stools), abdominal pain, nausea, vomiting, tenesmus (false urge to defecation), decreased or increased prothrombin index and the international normalized ratio (laboratory parameters, which characterize the blood-clotting system), blood pressure reduction, thrombocytopenia (reduced platelet count), leukopenia (reduced WBC count), neutropenia (reduced neutrophil count), allergic skin and subcutaneous tissue reactions (skin rash, pruritus, urticaria, angioedema, anaphylactic shock, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis).

Procedures that are performed at each study stage are common medical procedures:

A child's finger puncture for blood sampling for a common blood count may be accompanied by pain and/or possible bruising in the needle insertion site. Dizziness and/or asthenia may occur during or shortly after blood drawing.

The use of study product may cause any of the side effects listed above. The occurrence of the unknown and unexpected adverse events while taking a new drug is also possible. Therefore, all the above procedures will be carried out under the supervision of a physician.

6. Who cannot participate in this study.

Your child will not be able to participate in this study if he or she is currently participating in another study, study project or has participated in such studies in the past 3 months.

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If your child participated in another study, you should discuss with your study physician the possibility of your child's participation in this study, since there must be a certain period of time between studies, depending on the type of study product. If you or your child has any other restrictions that prevent his/her participation in the study, please inform your physician.

Please contact your study physician, if you have any questions about this section, or if you need the additional information.

7. New information

If during the study any new information about the study product is obtained that may affect your desire or your child's desire to continue the study participation, your study physician will immediately inform you of the occurrence of such facts.

If, after reviewing the new data, you decide to discontinue your child's participation in the study, the study physician will remove your child from the study and discuss his/her further treatment

8. Alternative treatment

Your child's participation in this study is not mandatory. There are other approved treatment methods available for your child. Participation in this study is not a substitute for the usual medical care of your child, conducted by your physician. Section 3 also lists those drugs that can be used in this study.

9. Benefits of study participation

Participation in this study does not allow you and your child to receive any payments, however, your child will be able to receive a free examination and treatment provided by the study protocol and current treatment standards for children with ARVI.

The information obtained as a result of this study may allow to register the study product Podioxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm, LLC, Russia) and to use it in patients with ARVI.

10. Pregnancy

If your child is female and has already had the first menstruation, then she will need to pass the urine test for pregnancy on the Screening visit, since the effect of study therapy on pregnancy and the unborn child is not fully studied.

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Therefore, in the case of pregnancy detection, your child will not be able to participate in this study.

11. Voluntary participation in the study and its termination

Your child's participation in this study is absolutely voluntary. If you or your child decides to terminate this study, it will not affect your child's current or future health care service, you will not lose any benefits that you and your child are rightfully entitled to.

If you or your child decides to refuse further participation in this study, the following steps should be taken:

1. You shall notify the study physician of your decision;
2. You and the child shall come to the physician's office for a final examination (in accordance with Visit 3 plan).
3. You have to return all the unused and used drug along with all other materials used in this study (Patient's Diary, Questionnaires) and given to you on Visit 1.

If your child's participation in this study is discontinued (for any reason), information related to your child's participation, which was collected prior to his/her discontinuation, can be further used for the purposes described in this consent form. The study physician, a Sponsor company, or an authorized state or federal authorities may, at any time, without your consent, terminate your child's participation in the study for any of the following reasons:

- if you or your child does not follow instructions of the study physician;
- if it is found that your child cannot participate in the study due to violations of eligibility criteria;
- if the study is terminated by decision of the Sponsor and/or authorized state or federal authorities;
- if further participation in the study may harm your child's health.

12. Costs

All costs associated with study conduction (study products, examinations, including laboratory tests) will be covered by the Sponsor. Participation in the study should not be associated with any of your direct costs.

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13. Payments and compensation

No payments and/or compensation are provided for you and your child for participation in this study.

The study product Polyoxidonium®, nasal and sublingual spray, 6 mg/ml (NPO Petrovax Pharm LLC, Russia) or Placebo, as well as the antipyretic drug Efferalgan® will be provided to you free of charge. You will not incur any costs associated with conducting tests, procedures and surveys in this study.

14. Confidentiality of medical information and personal data

Information obtained in this study will be provided to the Sponsor - NPO Petrovax Pharm LLC, Russia, and health authorities. In accordance with the regulations on information protection, anonymous data will be transferred to the Sponsor regarding only this study without the possibility of identifying the study subjects.

You can be sure that your child's medical records will remain strictly confidential and your child's identity will remain anonymous (for example, when publishing the study results). Authorized representatives of the Sponsor - NPO Petrovax Pharm LLC, the Ethics Committee, or representatives of the relevant regulatory authorities of our country, as well as other countries will or may, for the purpose of testing, have direct access to your child's original medical records, which may contain information allowing to directly determine the patient identity. These people are required to maintain the strict confidentiality regarding your child's data.

Your child's personal data will remain confidential, when any results of this study are published. If your child participates in this study, you will be provided with the results of all laboratory and clinical examinations.

If your child participates in this study, you will not have the ownership rights to any information collected or created for the purposes of this study, and you will not be able to demand that your child's information be removed from the study data. Your child's medical records will be collected and analyzed as part of this study. These medical records may include a medical history of your child and the results of examinations conducted as part of the study described herein.

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If you or your child have any questions about specific medical records transmitted to the Sponsor of the study for data analysis, your study physician will answer them.

By signing this document, you give permission to the study physician and members of the study team to use this information in the study and to provide direct access to this information to the Sponsor and other persons, including third parties working with the Sponsor, to monitor the study course or analyze the study data. Access to this information is necessary for the Sponsor to verify that the study is being conducted correctly, and to collect and analyze safety and efficacy data of the study product.

The Sponsor will not disclose information about the your child's state of health to insurance companies, except when required by law or if you will not provide a separate written consent for that.

If you do not agree to use the information collected or created for the purposes of this study, you should not give consent for your child's participation in this study. In no case, this will not affect the quality of care provided to your child within the current standards of medical care, or the relationship with your physician.

It is advisable that you inform your physician that your child participates in the study of Polyoxidonium, since due to the lack of information, your physician may prescribe the additional treatment, which, in turn, may lead to incorrect interpretation of the study results (efficacy and safety assessment), as well as early termination.

The results of this study may be presented at Conferences or in publications, but your child's personal data will not be provided in such presentations. In no case the name of your child will be used in publications indicating this study results.

In the case of new information on the study product efficacy and safety, you will be informed as soon as possible.

15. Insurance

Being a subject of this study, your child, will be insured with IPJSC Ingosstrakh in accordance with Art. 44 of the Federal Law No. 61-FZ "On Medicine Circulation" of 12/04/2010" and Government Regulation No. 714 of 13/09/2010.

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The sum insured covers harm to life or health caused as a result of participation in the study.

Insurance of subjects is required by law and not associated with the expected harm to health. In this case, the insurance payment will be made only if a causal cause-and-effect is established between the harm to your child's health and participation in a study of the product.

The Principal Investigator and/or the study center employees will provide you with additional information about insurance, and also issue you with a Policy of Compulsory Life and Health Insurance for a subject of clinical studies of the product. Individual identification code of patient will be indicated in the Policy.

You and your child shall observe the following rules:

- a) Strictly follow the recommendations of the physician conducting the study. Inform the study physician of any deterioration in the health state of your child.
- b) During the study, any other therapeutic measures are allowed only after discussion with the physician conducting the study. Naturally, in urgent cases of this para, an exception is made, but in this case you should as soon as possible inform the physician conducting the study on the fact of another therapeutic measure.
- c) Any harm to health that may be due to participation in the study shall be immediately provided by you to the study Sponsor - NPO Petrovax Pharm LLC, Russia, at: 1 Sosnovaya st., Pokrov village, Podolsk, Moscow Oblast, Russia, 142143 Tel./Fax: +7 (495) 926-21-07.

Application for the payment of insurance compensation shall be made in writing to the insurance company INGOSSTRAKH (Russia) at 12 Pyatnitskaya St., bldg. 2, Moscow, 117997, contact phone: +7 495 956-55-55

Failure to comply with the above rules may lead to loss of insurance protection. Any additional voluntary insurance of the patient participating in this study is not provided.

In the event of health deterioration due to participation in the study, it is necessary, first of all, to contact the attending physician of your child by telephone, the number of which is specified herein.

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The cost of treatment will not be reimbursed if the damage to health or the disease is caused by a violation of study physician's instructions regarding the study conduction, including those listed in this Information Sheet.

Participation in the study may violate the terms of your child's voluntary health insurance policy (VHI) and deprive your child of the right to receive medical care within the VHI. In this regard, if your child has a valid VHI policy, you need to review the insurance terms and conditions and familiarize yourself with existing restrictions in them.

16. CONTACTS

If you have any questions or concerns regarding this study, or if you need to report on your health deterioration, use the contact information listed on the first page hereof:

If you have any questions regarding the rights of your child as a subject of study, you may contact the Ethics Committee's representative, who controls the study procedures at this clinic.

Full name of the Chairman of Ethics Committee _____

Tel. _____

You may also contact the company conducting the study to get answers to questions: ClinPharmInvest LLC, Tel.: 8 (4852) 59-47-71

If you have any questions about the rights of a study subject, please contact the Ethics Board at: 3, Rakhmaninovsky Lane, Moscow 127994 Telephone: +7 (495) 625-44-21.

Do not sign this information sheet if you have not had the opportunity to ask questions and get satisfactory answers to all your questions.

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Information for children participating in the study

Applicable (age ≥ 10 years old)

Not applicable (age < 10 years old)

Now you have an acute viral infection, so you may have a sore throat, a runny nose, fever, and cough. To get better quickly, you take medicines.

Now we will talk about a new medicinal product - Polyoxidonium® spray, which is administered in the nose or under the tongue.

This medicinal product (Polyoxidonium) has already been taken by both adults and children in the form of drops. But now, this product is being studied in a new dosage form - nasal and sublingual spray for children aged 1 to 12 years.

We want the pediatric patients (children aged 1 to 12 years) to also take this medicinal product.

Before any new medicinal product can be used for curative purposes, its efficacy and safety shall be carefully studied.

Human studies reviewing the product efficacy and safety are called the “clinical studies”.

A medicinal product used in the study is called the “study product”. This study product is Polyoxidonium®. In this study, you will be prescribed either Polyoxidonium® or placebo.

Placebo looks exactly the same as the study product, but does not contain a drug substance. During this study, you will take either Polyoxidonium® or placebo, and we will call your treatment “Treatment with the study product”. Neither you nor your study physician will know what exactly you take - Polyoxidonium® or placebo.

We ask children who, like you, have a cold, take the study medicinal product to determine its effect, to get more information about the product safety and efficacy in treating the common cold. This way, the physicians can learn more about the product to help other children, like you. About 172 children from all over the country with a cold infection will participate in this study.

Listen carefully and think about whether you want to take the study product.

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Please, ask questions if something is not clear to you.

During the study, you will administer the study product either in the nose, 2 sprays 2 times a day in each nasal passage, or in the sublingual area 4 sprays 2 times a day.

Parents or adoptive parents will help you with each spray intake.

What will happen at the study center?

When you decide to take a study product, your study physician will take care of you and perform various procedures, such as:

- determination of your height and weight;
- determination of your heart rate, respiratory rate, body temperature;
- medical examination;
- a swab from the oropharynx and nasal passages to determine the possible presence of influenza virus and streptococcal infection;
- blood sampling from finger and urine

On the first visit, you will be told about the study and you will tell us what you decided. If you would like to participate in a study, on the same day you will start taking the study product.

What will you need to do every day?

During the study, you will administer the study product either in the nose, 2 sprays 2 times a day in each nasal passage for 7 days.

Also during the first 3 days, you may need to take a product that lowers the temperature. The physician will give this product to your parent or adoptive parent.

Your relatives will keep a diary, in which every day you need to describe the temperature (morning and evening), administration of the study product, a febrifugal drug and other drugs, and complaints.

Pros and Cons of the new medicinal product Polyoxidonium

Pros

- The study medicinal product can help to quickly recover from a cold and relieve symptoms.

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Cons

- You may be allergic to the drug or your body temperature may rise while you are taking a study product.

Taking a blood sample can lead to unpleasant pain and, in some cases, bruising.

If you feel something unusual, immediately tell your relatives and your study physician about it. Your study physician will review the treatment or perform an examination. Ask about everything that bothers you.

You have now been told about the study product. Do you want to take it? Please ask us any questions if something is not clear to you or if you have other concerns. Even if you do not take the study product, you will be prescribed another treatment that will also help you to get better.

Your parent will receive your Individual Insurance Policy, which will contain your individual identification code.

If you try to take a study product, but you don't like it, you can change your mind. If something is bothering you, you can tell any lies to us about it. You can talk to your study physician and your family to stop taking the drug at any time.

You will be given home with you a signed and dated copy of this consent form.

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- I confirm that I or my parent/adoptive parent have received a copy of a completed insurance policy for a patient participating in a study and a reminder for the insured patient from Ingosstrakh insurance company.
- I voluntarily agree to participate in this study. My parent/adoptive parent have received a signed and dated copy of the Information for the study participant with the Informed Consent Form on 22 pages.

I, (full name of the patient, by patient's hand, legible), if aged 10 to 12 years _____

have familiarized with the information on the upcoming study objectives and methods and received a signed and dated copy of this document. I have had the opportunity to discuss with the physician all the questions that interest me, and received the satisfying answers.

Not applicable (age <10 years old)

Patient's signature: _____ Date: _____ Time _____ : _____

Full name of the study physician (by hand of the study physician, fully legible and in block letters):

Physician's signature: _____ **Date:** _____ **Time** _____ : _____

Not applicable (Patient's age < 10 years old)

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I, a parent/an adoptive parent, confirm that:

- I have received information on the purpose and course of this study, information about Polyoxidonium® (manufactured by NPO Petrovax Pharm, Russia), about the possible benefits, probable and potential risks of participating in the study, my child's rights and obligations as a study subject.
- I am warned about possible adverse events and the necessary actions in such cases when using Polyoxidonium®/Placebo.
- I have had the opportunity to discuss with the physician all the questions that interest me, and received the satisfying answers.
- I voluntarily and deliberately agree to my child's participation in this study and I understand that I and my child have the right to refuse to participate in the study or to terminate it at any time without explanation.
- I am aware that if I/my child decide to terminate the study, I shall inform the study physician of that in order to give him/her the opportunity to assess my state and give necessary recommendations.
- I agree to correctly follow the instructions, cooperate voluntarily with the study physician, and immediately inform him/her of any changes in my child's state of health.
- I understand that participating in the study, my child shall observe the restrictions described herein.
- I have received information that if the health of my child is damaged due to the direct intake of study products or a medical procedure during the study, my child will receive the necessary medical care, the costs of which will be reimbursed by the insurance company - Ingosstrakh Joint Stock Company. The amount of compensation may be revised if the deterioration of health occurred due to non-compliance with the instructions of the study physician.
- I have received information that my child's medical and personal data are confidential and can be disclosed only to official representatives, subject to anonymity.
- I agree to the collection, processing and use of my child's personal data obtained in the course of this study.
- I have received information that I have the right to access to my child's health data and the results of all tests.
- I voluntarily consent to the collection of my child's blood and urine samples, oral scraping for analysis, as described herein.

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- I have received the contact information for any additional questions.
- I give permission for access to my child's medical data obtained during the study to the developer of product Polyoxidonium (NPO Petrovax Pharm LLC), an organization involved by the developer for the purpose of study (ClinPharmInvest LLC), members of the study team of the study physician, representatives of the Ethics Council of the Ministry of Health of the Russian Federation, and the local Ethics Committee of the study center, and other authorized representatives of the Russian regulatory authorities.
- By signing this document, I do not waive the legal rights of my child as a study subject.
- I confirm that I have received in hands a copy of a completed insurance policy for a patient participating in a study and a reminder for the insured patient from Ingosstrakh insurance company.
- I voluntarily consent to my child's participation in this study. I have received a signed and dated copy of the Information for the study subject with the Informed Consent Form on 22 pages.

Full name of the child's parent/adoptive parent (by hand of the child's parent/adoptive parent, fully legible and in block letters):

Signature of parent/adoptive parent: _____ Date: _____ Time _____ : _____

Full name of the study physician (by hand of the study physician, fully legible and in block letters):

Physician's signature: _____ Date: _____ Time _____ : _____

This form is signed in 2 copies, stating the date: 1 copy for the study physician, 1 copy for the patient's patient/adoptive parent.