International Multicenter Double-blind Placebo-Controlled Parallel-Group Randomized Clinical Trial of Efficacy and Safety of Ergoferon in the Treatment of Acute Respiratory Viral Infections in Children

Phase IV

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-ER-009**
Version date:	**December 03, 2015**
ClinicalTrials.gov Id:	**NCT03039621**

Protocol Summary

This document represents the protocol summary for the study on human subjects. The study will be carried out in accordance with ICH GCP, National Standard of the Russian Federation GOST 52379-2005 "Good Clinical Practice", Helsinki Declaration of World Medical Association, relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

International Multicenter Double-blind Placebo-Controlled Parallel-Group Randomized Clinical Trial of Efficacy and Safety of Ergoferon in the Treatment of Acute Respiratory Viral Infections in Children.

Phase: IV

Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia

Protocol No. MMH-ER-009

Objective of the study

- To obtain additional data on the efficacy and safety of Ergoferon in therapy of acute respiratory viral infections (ARVI) in children aged 6 months to 6 years old.

Endpoints

Primary endpoint

1. Time to alleviation of all ARVI symptoms[1] (time from enrollment in the study to alleviation of all ARVI symptoms, according to the patient's diary).

Secondary endpoints

1. Time to normalization of body temperature[2].

2. Time to alleviation of flu-like nonspecific symptoms[3].

3. Time to alleviation of respiratory symptoms[4].

4. Flu-like nonspecific and respiratory symptoms total score (TS) for days 2-6 (according to the patient's diary).

5. ARVI severity (based on the area under the curve of TS for days 2-6, according to the patient's diary).

6. Percentage of patients recovered on day 2, 3, 4, 5, and 6 (according to the patient's diary).

---

[1] Criteria of alleviation of all ARVI symptoms: body temperature $\leq 37.5^0$C for 24 hours (without subsequent increase within the observation period) + absence of ARVI symptoms /presence of ARVI symptoms with $\leq$3-point of TS.
[2] Oral temperature $\leq 37.5^0$C for 24 hours (without subsequent increase within the observation period).
[3] Absence of flu-like nonspecific symptoms/presence of one mild flu-like nonspecific symptom.
[4] Absence of respiratory symptoms/presence of one mild respiratory symptom.

7. Rates of antipyretic use per patient during days 1 to 5 of therapy (according to the patient's diary).

8. Percentage of patients with worsening of illness (ARVI complications, including those requiring antibiotics; hospitalization) for 14 days.

Safety assessment

- Presence and type of adverse events during the therapy, their severity, relation to investigational drug, outcomes.

- Dynamics of vital sings.

Study design

Study design: multicenter double-blind placebo-controlled randomized clinical study in parallel groups.

The study will enroll patients of either gender aged from 6 months to 6 years old with clinical manifestations of ARVI within the first day after the onset of the disease. Patients will be included evenly (1:1 ratio) in accordance with the age group: 6 months – 3 years 11 months 29 days; 4 years – 6 years 11 months 29 days. Signed information sheet for parents/adopters (informed consent form) will be obtained from all participants' parents/adopters prior to the screening procedures.

Medical history, thermometry, patient examination by a doctor, assessment of ARVI symptoms severity, and nasopharyngeal swabs will be performed at screening visit (Day 1). If the inclusion criteria are met and exclusion criteria are absent, the patient is included in the study.

Nasopharyngeal swabs will be analyzed by real-time reverse transcription polymerase chain reaction (RT-PCR) to identify the most common respiratory viruses, including (1) Influenza A virus; (2) Influenza B virus; (3) Influenza A (H1N1)pdm; (4) Human metapneumovirus; (5) Human respiratory syncytial virus; (6) Human rhinovirus; (7) Human adenovirus; (8) Human bocavirus; (9) Human parainfluenza virus 1; (10) Human parainfluenza virus 2; (11) Human parainfluenza virus 3; (12) Human parainfluenza virus 4; (13) Human coronavirus OC43; (14) Human coronavirus 229E; (15) Human coronavirus HKU1; (16) Human coronavirus NL63.

Patients are randomized into one of two groups: the 1st group patients will take Ergoferon according to the dosage regimen for 5 days; the 2nd group patients will take Placebo according to the dosage regimen of Ergoferon for 5 days.

Patient's parents/adoptive parents are provided with diaries where daily in the morning and at night they record oral temperature (measured by a digital thermometer provided by Sponsor), symptoms of ARVI (according to the 4-point scale), administered drug and concomitant therapy. Doctors instruct parents/adoptive parents how to fill in diaries; the first scores of ARVI

symptoms severity and oral temperature are made by doctors together with the parents/adoptive parents.

Patients are observed up for 14 days (screening and randomization up to 1 day, therapy for 5 days, follow-up from 6 to 10 day; delayed telephone "visit" on day 14). During the observation period two visits are planned (at home or at the medical center) on day 3 (Visit 2) and day 6 (Visit 3). If patients still have any symptoms of ARVI/complications of ARVI, then an additional (unscheduled) Visit 4 is held on Day 10 of the observation (at the medical center). During Visits 2, 3 (4), doctors carry out an physical examination, record dynamics of ARVI symptoms and concomitant therapy, check patient's diaries, which parents/adoptive parents return back at Visit 3 or 4. At Visit 3 (after 5 days of therapy), compliance with the treatment is additionally assessed. A "telephone visit" (Visit 5, Day 14 ± 1) is carried out to interview parents about the patient's condition, presence/absence of complications, and possible use of antibiotics.

During the study, symptomatic therapy and therapy for underlying chronic conditions are allowed with the exception of the drugs indicated in the section "Prohibited Concomitant Treatment".

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of both genders aged 6 months to 6 years old[5].

2. ARVI based on medical examination: oral temperature of at least 38.0°C at the time of examination + total symptom severity ≥5 points.

3. First 24 hours after ARVI onset[6].

4. Seasonal rise in ARVI incidence.

5. Availability of signed information sheet for parents/adopters (informed consent form) for participation in the clinical trial.

Exclusion criteria

1. Suspected pneumonia, bacterial infection (including meningitis, sepsis, otitis media, urinary tract infection, etc.) requiring a prescription of antibacterial products from the first day of the disease.

2. Suspected initial manifestations of diseases with symptoms similar to ARVI at onset (other infectious diseases, flu-like syndrome at the onset of systemic diseases of connective tissue, oncohaematological and other diseases).

3. Clinical symptoms of severe influenza/ARVI[7] requiring hospitalization.

---

[5] The study participants are aged 6 months to 6 years 11 months 29 days.
[6] Manifestation of fever, or a rise in body temperature to febrile values (≥37.6°C for oral and tympanic temperature, ≥37.4°C for axillary temperature, ≥38.0°C for rectal temperature) is considered the onset of ARVI.

4. Medical history of primary and secondary immunodeficiency; oncologic conditions.

5. Aggravation or decompensation of chronic diseases (diabetes mellitus, cerebral palsy, cystic fibrosis, primary ciliary dyskinesia, bronchopulmonary dysplasia, malformations of the respiratory and ENT organs/ear, throat, mouth, tongue, larynx, trachea, neck and salivary and thyroid glands, etc.), which affect the patient's ability to participate in the clinical study.

6. Malabsorption syndrome, including congenital or acquired lactase or other disaccharidase deficiency, galactosemia.

7. Allergy/hypersensitivity to any component of the drug product used in the therapy.

8. Course administration of the drug products specified in the section "Prohibited Concomitant Therapy" within two weeks prior to inclusion in the study.

9. Patients whose parents/adoptive parents will not fulfill the requirements during the study or follow the order of administration of the studied drug products, from the Investigator's point of view.

10. Participation in other clinical trials for 3 months prior to enrollment in this study.

11. The patient's parent/adoptive parent is a study specialist of the centre and is directly involved in the study, or is an immediate family member of the Investigator. Spouses, parents, children, or siblings, regardless of whether they are siblings or adopted are considered immediate family members.

12. The patient's parent/adoptive parent works at the OOO "NPF "Materia Medica Holding", i.e. they are employees of the Company, temporary employees on a contract basis or appointed officials responsible for conduction of the study or their immediate family members.

Criteria for Withdrawal or Termination

1. Inability or refusal of patient or parents/adoptive parents to comply the Protocol requirements.

2. Necessity in medical products prohibited within the study.

3. Development of adverse event requiring product cancellation.

4. Desire of patient or parent/adoptive patient to complete the study ahead of schedule due to inefficacy of therapy or any other reason.

---

[7] Criteria of severe influenza/ARVI (RF MH, 2009, 2014; Union of Pediatricians of Russia, 2014; WHO 2011; CDC 20013-2014): extreme severity of disorder (toxic shock syndrome III, critical general condition disorder, decreased activity or weakness up to complete adynamia, irritability/cry when touched, lethargy, drowsiness/longer sleep, lack of eye contact during examination, refusal to eat or drink, severe tachycardia/bradycardia, tachypnea, hypo- or hyperventilation, microcirculation disorder, peripheral cyanosis, slower capillary filling of the nailfold, continuous vomiting, signs of dehydration, decreased diuresis/anuria, convulsions, symptoms of meningism), hemorrhagic syndrome (nosebleeds, petechiae on the skin and mucous membranes), hemodynamic instability, severe obstructive disorders (stenosing laryngotracheitis, bronchial obstruction syndrome), acute respiratory failure, primary and secondary pneumonia. Risk factors for severe influenza/ARVI and development of complications are chronic diseases of the cardiovascular system, respiratory system, diabetes mellitus, immunodeficiency conditions, and cancers.

5. Cases not specified by the protocol when, according to the investigator's opinion, further participation in the study harms the patient.

6. Incorrect inclusion of ineligible patient.

Number of subjects

It is planned to include 288 patients, which is expected to allow completion of all protocol procedures by at least 216 patients (108 patients in the Ergoferon and Placebo groups, exclusion rate is 25%).

Interim analysis

An interim statistical analysis is not scheduled within the study.

Treatment

Group 1

Name of the medicinal product: Ergoferon

Active ingredient: affinity purified antibodies to human gamma interferon – 0.006 g*, affinity purified antibodies to histamine – 0.006 g*, affinity purified antibodies to CD4 – 0.006 g*

* Mixture of water-ethanol dilutions 100^{12}, 100^{30}, 100^{50} of active substance used for saturation of lactose monohydrate.

Excipients: Lactose monohydrate – 0.267 g, microcrystalline cellulose – 0.03 g, magnesium stearate – 0.003 g.

Method of administration: Tablet for oral use, 1 tablet per intake (outside a meal/feeding). On day 1, five tablets are taken in the first 2 hours (one tablet every 30 min), followed by three more tablets regularly spaced during the rest of the day (total 8 tablets). From day 2, one tablet is taken every 8 hours. The drug is administered outside a meal (in the interval between meals or 15 minutes before meal or fluid intake). Keep the tablet in the mouth, without swallowing, until completely dissolved. For young children (aged 6 months to 3 years old), the tablet is recommended to be dissolved in a small amount (1 tablespoon) of drinking water of room temperature.

The therapy lasts for 5 days.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store in a dry place protected from light, at the temperature not exceeding 25°C. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: Lactose monohydrate – 0.267 g, microcrystalline cellulose – 0.03 g, magnesium stearate – 0.003 g.

Method of administration: Placebo using Ergoferon scheme.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store in a dry place protected from light, at the temperature not exceeding 25°C. Keep out of the reach of children.

Treatment duration

Ergoferon/Placebo treatment duration is 5 days.

Observation period

In total, the patient is observed up for 14 days (screening and randomization up to 1 day, therapy for 5 days, follow-up from 6 to 10 day; delayed telephone "visit" on day 14).

Symptomatic (Standard) treatment

Throughout the study, patients can receive symptomatic flu/ARVI therapy based on the approved standards of care.

Indications for prescription of antipyretics:

- body temperature over 38.5°C;
- body temperature ≥38.0°C in case of concomitant chronic diseases of the lungs, heart, nervous system.

If an antipyretics was received by the child from parent/adoptive parent independently (without any recommendation by the doctor) and in the absence of indications for use, the patient will not be excluded from the study. The patient's parent/adoptive parent is recommended to record the thermometry values prior to drug intake, its name and dose in the patient's diary.

Drug products allowed for use as antipyretics (the ATC group is indicated in brackets):

1. Paracetamol (N02BE01).
2. Ibuprofen (M01AE01).
3. Metamizole sodium (N02BB02) only under prescription (for emergency care at hyperthermia resistant to paracetamol/ibuprofen, parenteral).

   The antipyretic drugs (Panadol for children, 120 mg/5 mL or Nurofen® for children, 100 mg/5 mL, suspension for oral administration) will be provided by the Sponsor for all the participants of the study. The doctor prescribes antipyretics which issues to the patient's

parent/adoptive parent at Visit 1. In accordance with the Instruction for Medical Use, the drug products are allowed for administration in children aged at least 3 months.

Prohibited concomitant therapy

Two weeks before inclusion in the study[8], as well as during the study (from signing of the information sheet for parents/adopters /informed consent form) it is prohibited to administer the following drug products (their ATC group is indicated in brackets):

1. Antivirals (J05), except for Ergoferon prescribed within this study.

2. Immunostimulants (L03), including:

   - interferon inducers (acridonoacetic acid, meglumine acridone acetate/cycloferon®, umifenovir/arbidol®, kagocel®, tiloron/amixin®, polyadenyl acid + polyuridylic acid/poludan®, sodium oxodihydroacridinyl acetate/neovir®, lavomax®, tilaxin®, etc.)

   - interferons;

   - bacterial immunomodulators (including ribomunyl®, sodium ribonucleate/ridostin, etc., sodium deoxyribonucleate/derinat®, etc., IRS-19, imudon®, broncho-munal®, etc.).

   - pidotimod/immunorix;

   - interleukins;

   - synthetic immunostimulants (levamisole, alpha-glutamyl-tryptophan/thymogen, etc.);

   - drug products with thymus hormones;

3. Antihistamines (R06).

4. Fenspiride (R03DX03), omalizumab (R03DX05).

5. Steroidal and non-steroidal anti-inflammatory drugs (except for ibuprofen).

6. Analgesics and antipyretics (except for paracetamol, metamizole sodium).

7. Analgesics/antipyretics combinations for symptomatic therapy of acute respiratory infections.

8. Drug products based on ultra-low doses of antibodies (anaferon (L03AX), epigam, etc).

9. Homeopathic drug products.

10. Immunosuppressants (L04).

11. Antineoplastic agents (L01) and combined (with hormones) antineoplastic endocrine therapy (L02).

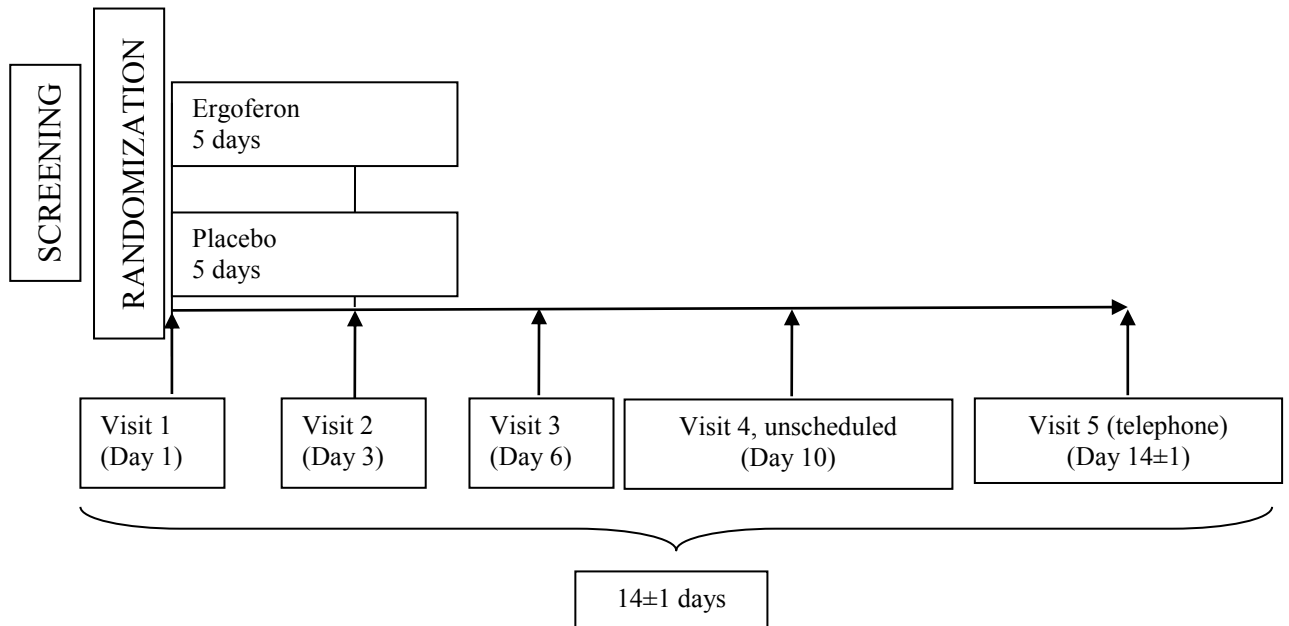12. Immune sera and immunoglobulins (J06).

13. Vaccines (J07).

---

[8] If the patient has taken any drug product listed in "Prohibited Concomitant Therapy" (except for the drugs specified in par. 10-14) once prior to the study, it is not considered an exclusion criterion.

14. Drugs that previously caused hypersensitivity/ allergic reactions in patient.

Study design scheme

Schedule of study procedures

Procedure/ Visit	Visit 1 (Day 1)	Visit 2 (Day 3)	Visit 3 (Day 6)	Visit 4[*] (Day 10)	Visit 5 (Day 14±1)
Informed consent	+				
Collection of complaints	+	+	+	+	
Medical history	+				
Physical examination	+	+	+	+	
ARVI symptoms registration	+				
Inclusion/exclusion criteria	+				
Concomitant therapy	+	+	+	+	+
Nasopharyngeal swabs for RT-PCR	+				
Randomization and prescription of study drug	+				
Study drug supply	+				
Antipyretics	+				
Study drug accountability, compliance assessment			+		
Diary supply	+				
Checking the correctness of filling the diary		+	+	+	
Diary return			+	+	
Evaluation of treatment safety	+	+	+	+	
Telephone survey					+

[*] Visit 4 – unscheduled (additional), provided if the patient still experiences the ARVI symptoms/ complications

Statistical Analyses

Samples

Total set: all patients included in the study whose parents/adoptive parents signed the Informed Consent Form for the patient's participation in the study. All AEs will be considered throughout the study for this sample.

Safety population: all patients who received at least one dose of the test drug. This sample will be used to **analyze the study therapy safety**, since all the AEs detected in the patient after administration of the drug product will be recorded. The AEs registered in patients of the *Total set* sample from the moment of signing the Informed Consent Form, but before the test drug administration will not be taken into account when analyzing the study therapy safety.

Full Analysis Set. This sample includes all the enrolled patients, except for those who have experienced at least one of the following events:

1) non-compliance with inclusion / exclusion criteria ;

2) the patient has not taken a single dose of the study drug;

3) lack of any data of the patient following randomization.

This sample, the most consistent with the "Intention-to-treat" principle**,** will be used for the **Intention-to-treat analysis (ITT analysis)** *of the* **the study therapy efficacy**.

To fill in the missing data (indicators/options), the method "LOCF" (Last Observation Carried Forward)" will be applied.

Per protocol set. This sample includes all the patients who have received the complex therapy under the Protocol, completed all the scheduled visits and had no significant deviations from the Protocol. This sample will be used for the **Per Protocol analysis (PP- analysis)** *of the* **the study therapy efficacy**.

Evaluation of sample size

The sample size has been assessed on the basis of the following rules and assumptions:

1. Statistical provisions.

    1.1 the power of the statistical tests "P = (1 - β)" is assumed to be 80% (the probability of correct rejection of the null hypothesis is 0.8);

    1.2 the probability of a type I error "α" is allowed to be less than 5% (the probability of the erroneous acceptance of an alternative hypothesis is less than 0.05);

    1.3 the statistical criteria used are 2-sided;

    1.4 the calculation of the sample size is based on the assumptions about the expected effects, mainly declared in the primary efficacy criterion of the Protocol;

    1.5 statistical null and alternative hypotheses are formulated as follows:

$$H_0: m_2-m_1 \leq 0$$

$$H_1: m_2-m_1 > 0,$$

where m_1 – time to resolution of all the disease symptoms in the Ergoferon group, m_2 – time to resolution of all the disease symptoms in the Placebo group;

1.6 the sample size of the first and second groups for the two-sided criterion is calculated with the formula:

$$N_1=N_2=\sigma^2(z_\alpha + z_\beta)^2/(m_2-m_1)^2,$$

where N_1 and N_2 – sample sizes of the Ergoferon and Placebo groups; σ– expected standard deviation of the first and second groups; z_α and z_β – z-criterion values for α and β; m_1 – time to resolution of all the disease symptoms in the Ergoferon group; m_2 – time to resolution of all the disease symptoms in the Placebo group;

1.7 the final sample size is calculated with the following formula:

$$N_F=N_{PP}/(1-К_В),$$

where N_F – final sample size; N_{PP} – result of calculations in par. 1.6, i.e. the planned number of patients completing the study in accordance with the Protocol; $К_В$ – exclusion rate.

2. Assumptions about the expected effects of the clinical study.

It is assumed that the difference between the average duration of the disease (before recovery / resolution of the disease) in the Ergoferon group and in the Placebo group will be at least 0.5 days, and the standard deviation in both groups will not exceed 1.3 days.

Based on the above statistical rules and assumptions, the size [9] of each group will account for 108 people (sample for the PP analysis).

Given the possible exclusion of the patients during the screening process, as well as in the study for various reasons, it was decided to increase the sample by 25% ($К_В$=25%) and include at least 288 patients (144 patients in each group).

Statistical criteria

All the statistical calculations will be performed using two groups of statistical criteria:

- parametric – to assess continuous and interval random variables;
- non-parametric – for:

---

[9] The formula has been taken from: O'Brien, R. G. and Muller, K. E. (1993), "Unified Power Analysis for t-Tests through Multivariate Hypotheses," in L. K. Edwards, ed., Applied Analysis of Variance in Behavioral Science, 297–344, Section 8.2.1. New York: Marcel Dekker.

- assessments of equality / inequality in the proportion of patients when compared for different visits,

- analysis of frequencies of the compared features,

- assessment of continuous and interval random variables in case of violation of the normality assumption.

Parametric criteria

The application of parametric criteria will be accompanied by a check for normality of the compared samples (Kolmogorov-Smirnov test).

The following parametric methods and approaches are supposed to be used:

1. To assess the differences of continuous variables obtained in two different (independent) groups –Student t-test for independent samples.

2. To assess the differences of continuous variables obtained in one group at two different visits – Student t-test for for paired samples.

3. To assess the temporal dynamics of the compared indicators – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.

4. In case of multiple comparisons between the groups will apply a variety of corrections for multiplicity (Dunnett), (Tukey), (Scheffe), Holm adaptive test, etc.

5. In case of abnormal data distribution, approaches with the Generalized Linear Models and / or Mixed Linear Models will be used.

6. Selection of the type of distribution, clarification of the factor and covariance structures of the model is carried out with fit statistics such as AIC (Akaike information criterion).

To perform the above-mentioned statistical tests and techniques, it is assumed that the following SAS procedures are used:

- UNIVARIATE – check for normality of the compared distributions;

- CORR, MEANS – calculation of descriptive statistics;

- TTEST – Student t-test with all the modifications;

- GLM – analysis of Generalized Linear Models for studying temporal dynamics (ANOVA, ANCOVA);

- GENMOD – analysis of Generalized Linear Models.

    MIXED – analysis of Generalized Linear Models.

Non-parametric criteria

Below, there are the main types of possible comparisons with the respective criteria:

1. To assess the differences of continuous variables obtained in two different (independent) groups – Mann-Whitney U-test.

2. To assess the temporal dynamics of the compared indicators – Friedman test, non-parametric analogue of analysis of variance with repeated measures.

3. For the frequency analysis of 2×2 cross tables – χ^2-test (if the compared frequencies are greater than 5) or Fisher exact test (if one of the compared frequencies is less than 5).

4. For the frequency analysis of cross tables with independent strata – Cochran–Mantel–Haenszel test (modification of the χ^2-test for multiple comparisons).

5. For the frequency analysis of data on the presence / absence of an event or outcome during repeated measures (cross tables with dependent strata) – survival analysis.

To perform the above-mentioned non-parametric statistical analysis options, it is assumed that the following SAS procedures are used:

- FREQ – Friedman test, χ^2-test and / or Fisher exact test; Cochran–Mantel–Haenszel test.
- LIFETEST – survival analysis .
- NPAR1WAY – Mann-Whitney U-test.

Safety parameters

Adverse events recorded during the study will be grouped into frequency tables by severity, seriousness and relationship with the study drug.

Data presentation

Descriptive statistics will be provided for each study continuous / interval variable. Numerical data will be presented by mean, standard deviation, min and max values. Comparisons suggesting statistical conclusion will have the relevant confidence intervals. Outliers will be analyzed individually. The data will be grouped by visits. The categorical variables will be presented as frequency tables by visits.