Multicenter double-blind placebo-controlled parallel group randomized clinical study of efficacy and safety of Raphamin in the treatment of acute respiratory viral infection in children aged 12-18 years

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-407-003**
Version date:	**November 10, 2020**
ClinicalTrials.gov Id:	**NCT04918771**

Protocol Summary

This document represents the protocol summary for the study on human patients. The study will be carried out in accordance with ICH GCP, Helsinki Declaration of World Medical Association, Rules of good clinical practice, approved by order of the Ministry of Health of the Russian Federation dated April 1, 2016 N 200n, , relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

Multicenter double-blind placebo-controlled parallel group randomized clinical study of efficacy and safety of Raphamin in the treatment of acute respiratory viral infection in children aged 12-18 years.

Phase: III

Sponsor: OOO «NPF "MATERIA MEDICA HOLDING», Moscow, Russia

Protocol No. MMH-407-003

Objective of the study

- To evaluate the efficacy and safety of Raphamin in the treatment of acute respiratory viral infection (ARVI) in children aged 12-18 years.

Endpoints

Primary endpoint

1. Time to resolution of ARVI[1,2] symptoms (PCR-confirmed).

Secondary endpoints

1. ARVI severity (clinically diagnosed and/or PCR-confirmed; based on the area under the curve (AUC) results for the total severity index[3] from days 1 to 6 of observation).
2. Percentage of patients with resolution of ARVI symptoms (clinically diagnosed and/or PCR-confirmed).
3. Time until resolution of ARVI symptoms, (clinically diagnosed and/or PCR-confirmed).
4. Percentage of patients with resolution of ARVI symptoms (PCR-confirmed).

[1]Time from symptom onset at visit 1 until resolution of the disease symptoms.
Resolution of ARVI symptoms will be defined if temperature is ≤37.3^{0}C within 24 hours (without further increase during observation period) + lack/presence of systemic ARVI symptoms ≤2.
[2] Based on a patient diary.
[3]**Total severity index** will be calculated from the rating scores obtained for each of the symptoms of upper respiratory infection (body temperature, general/non-specific flu-like symptoms, and nasal/throat and chest symptoms) with subsequent statistical processing of data by specialists of OOO "NPF "MATERIA MEDICA HOLDING". To determine total score, absolute values of body temperature measured in Celsius degrees will be converted into relative units (or points) based on the following classification: ≤37.3^{0}C=0; 37.4-38.0^{0}C=1; 38.1-39.0^{0}C=2; ≥39.1^{0}C=3.

5. Number of antipyretics taken according to indications on days 1-3 of treatment[4].
6. Percentage of patients with worsening of the disease (development of complications requiring antibiotics or hospitalization) on days 4-14 from the onset of observation.

Safety assessment

1. Adverse events (AEs) during the therapy, AEs severity and relation to the study drug, and AEs outcomes.
2. Changes in vital signs during the treatment.
3. Percentage of patients with clinically relevant laboratory abnormalities.

Study design

Study design: multicenter, double blind, placebo-controlled, parallel group randomized clinical trial.

The study will enroll outpatients of either gender aged 12-18 years with clinical manifestations of ARVI within the first days after onset of the disease. The patients will be recruited during seasonal ARVI morbidity. Collection of history, thermometry, objective examination, laboratory tests, recording concomitant therapy will be made after parent/adoptive parent signing information sheet and informed consent form for the child participation in the clinical study, for children ≥14 years old after signing patient information sheet and informed consent form for children ≥14 years old to participate in the clinical study. The severity of ARVI symptoms will be evaluated acording to 4-point scale “Symptom Severity Score” (0 = no symptom, 1 = mild symptom, 2 = moderate symptom, and 3 = severe symptom).

The nasopharyngeal swabs for PCR diagnosis and verification of respiratory viruses will be performed prior to therapy to confirm the viral etiology of ARVI. To exclude the infection caused by the new coronavirus COVID-19 (Coronavirus disease 2019), a rapid test for SARS-CoV-2 antigen will be made. In case of a positive SARS-CoV-2 test, the physician will act in accordance with the current version of the Ministry of Health of the Russian Federation Temporary methodological recommendations "Prevention, diagnosis, and therapy of new coronavirus infection (COVID-19)".

If a patient meets all inclusion criteria and does not have any exclusion criteria, at Visit 1 (Day 1), he/she will be randomized into one of two groups: patients of group 1 will take Raphamin according to the dosage regimen for 5 days; patients of group 2 will take Placebo using Raphamin 5-day regimen.

The study will use an electronic patient diary (EPD) for recording morning and evening axillary

[4] Based on a patient diary.

body temperature (using a classic mercury-free thermometer) and disease symptoms (Symptom Severity Score). Besides, antipyretic dosing (if applicable) and any worsening in a patient's condition (if applicable, for safety evaluation/AE registration) will also be recorded in a patient diary. The investigator will provide instructions on filling the diary. At Visit 1 the parent/adoptive parent together with an investigator will record ARVI symptom severity and body temperature in the diary.

Patients will be observed for 14 days (screening, randomization - up to 1 day, treatment period − 5 days, follow-up − up to 2 days; deferred "phone visit" − day 14).

During the treatment and follow-up period the patients/physicians will pay 3 visits and the fourth "phone visit" will be scheduled additionally: 1) visits by physician/patient - on Days 1, 5, and 7 (Visits 1, 2, and 3) - in a study center or at home; 2) "phone visit" (Visit 4) - on Day 14.

At Visits 2 and 3, the investigator will perform an physical examination, document changes in the symptoms and concomitant medications, and check patient diaries. At Visit 3 laboratory tests will be performed and compliance will be checked.

"Phone visit" will be performed to interview parents/adoptive parents about the patient's condition, presence/absence of secondary bacterial/viral complications, and use of antibiotics.

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

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of either gender aged 12 to 18 years.
2. Diagnosis of ARVI based on medical examination: axillary temperature ≥ 37.8°C at examination + non-specific flu-like symptoms score ≥4 points, nasal/throat/chest symptom score ≥ 2 points.
3. The first 24 hours after ARVI onset.
4. Contraceptive measures by sexually active adolescents of both genders during the study.
5. Patient information sheet (informed consent form) signed by one parent/adoptive parent of the patient and there is also a signed patient information sheet (informed consent form) for children aged 14 and over.

Exclusion criteria

1. Clinical symptoms of severe influenza/ARVI requiring hospitalization.
2. Positive SARS-CoV-2 (COVID-19/Coronavirusdisease2019) antigen test.

3. Suspected pneumonia, bacterial infection (including otitis media, sinusitis, urinary tract infection, meningitis, sepsis, etc.) requiring administration of antibiotics from the first day of illness.
4. Suspected initial manifestations of diseases with symptoms similar to ARVI at onset (other infectious diseases, flu-like syndrome at the onset of systemic connective tissue diseases, and other pathology).
5. Patients requiring antiviral medication prohibited within the study.
6. Medical history of primary and secondary immunodeficiency.
7. Medical history/suspicion of oncology of any localization (except for benign neoplasms).
8. Exacerbation or decompensation of chronic diseases (diabetes mellitus, children cerebral paralysis, cystic fibrosis, primary ciliary dyskinesia, bronchopulmonary dysplasia, respiratory and ENT congenital defects, etc.) affecting a patient's ability to participate in the clinical trial.
9. Malabsorption syndrome, including congenital or acquired lactase or other disaccharidase deficiency, galactosemia.
10. Allergy/ hypersensitivity to any component of the study drugs used in the treatment.
11. Pregnancy. Breast-feeding.
12. Use of medications specified in the section “Prohibited Concomitant Therapy” within two weeks prior to inclusion in the study.
13. Patients whose parents/adopters, from the investigator's point of view, will not comply with the observation requirements during the study or follow the procedure for taking the study drugs.
14. Medical history of mental diseases of the patient or their parent(s)/adoptive parents.
15. Participation in other clinical trials for 3 months prior to enrollment in this study.
16. Patient’s parents/adopters who are related to any of the on-site research personnel directly involved in the study or are an immediate relative of the investigator. ‘Immediate relative’ means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
17. The patient's parent/adopter who works for OOO “NPF “MATERIA MEDICA HOLDING” (i.e. the company's employees, temporary contract workers, designated officials responsible for carrying out the research or any immediate relatives of the aforementioned).

Criteria for Withdrawal or Termination

1. Screening failure.

2. Failure or refusal of the patient to follow the protocol.
3. The necessity to use medications not permitted in the study.
4. An adverse event requiring discontinuation of the study drug.
5. Patient's or his/her parent's/adopter's decision to withdraw early for lack of efficacy or other reasons.
6. Pregnancy.
7. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.
8. Eligibility error.

Number of patients

It is planned to include 400 patients, 360 of them will be randomized which is expected to yield at least 200 patients (100 per Raphamin and Placebo groups) completing all the protocol procedures.

Interim analysis

The protocol does not schedule unblinded interim analyses. At the sponsor's decision, blinded interim analysis may be carried out to specify population parameters and potential further specification of sample size (increase only).

Treatment

Group 1

Name of the medicinal product: Raphamin

Active ingredient: affinity purified antibodies to human interferon-gamma – 10 000 UMA*,
affinity purified antibodies to CD4 – 10 000 UMA,
affinity purified antibodies to β2-microglobulin major histocompatibility complex class I – 10 000 UMA,
affinity purified antibodies to β1-domain of major histocompatibility complex class II – 10 000 UMA

** UMA – Units of Modifying Activity.*

Excipients: lactose monohydrate, microcrystalline cellulose, magnesium stearate.

Method of administration: Per os without food. The tablet should be held in mouth until completely dissolved. On the first day of treatment, take 8 tablets according to the following scheme: 1 tablet every 30 minutes for the first 2 hours (total 5 tablets in 2 hours), then during the same day take another 1 tablet 3 times at equal intervals. On the 2nd day and beyond, take 1 tablet 3 times a day. The duration of treatment is 5 days.

Dosage form: Tablet for oral use.

Description: Flat, cylinder-shaped, scored beveled edge, white to off-white tablets.

Storage conditions: At temperature below 25ºC. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: N/A

Excipients: lactose monohydrate, microcrystalline cellulose, magnesium stearate.

Method of administration: Per os without food. The tablet should be held in mouth until completely dissolved. On the first day of treatment, take 8 tablets according to the following scheme: 1 tablet every 30 minutes for the first 2 hours (total 5 tablets in 2 hours), then during the same day take another 1 tablet 3 times at equal intervals. On the 2nd day and beyond, take 1 tablet 3 times a day. The duration of treatment is 5 days.

Dosage form: Tablet for oral use.

Description: Flat, cylinder-shaped, scored beveled edge, white to off-white tablets.

Storage conditions: At temperature below 25ºC. Keep out of the reach of children.

Treatment duration

Raphamin/Placebo treatment duration is 5 days.

Observation period

Overall, the patient will be observed for 14 days (screening, randomization for 1 day, treatment for 5 days, follow-up for 2 days; late-scheduled phone visit on day 14).

Symptomatic (Standard) treatment

Throughout the study the patients may receive medications for symptomatic treatment of ARVI:

- antipyretic/non-steroidal anti-inflammatory drug (paracetamol/ibuprofen)
  and/or
- nasal vasoconstrictive agent – oxymetazoline/naphazoline
  and/or
- cough suppressant/expectorant – butamirate/ambroxol, bromhexine, guaifenesine, acetylcysteine.

Indications for antipyretics

Increased body temperature (> 38.5°C) in subjects without complications and comorbidities and > 38.0°C in subjects with concomitant pulmonary, cardiac, nervous system diseases.

If an antipyretic is given to a child by his/her parent/adopter without prescribed indications, the patient is not withdrawn from the trial. The patient's parents/adoptive parent should record body temperature values, the drug name and dose prior to giving the antipyretic.

Antipyretic drugs (Paracetamol 500 mg or Nurofen® 200 mg) will be provided by sponsor for all the study subjects. Selection and prescription of the product will be made by the investigator who will issue the antipyretic product to the parent/adoptive parent at visit 1. According to the patient information leaflet the products are approved for children ≥12 years old.

Prohibited concomitant therapy

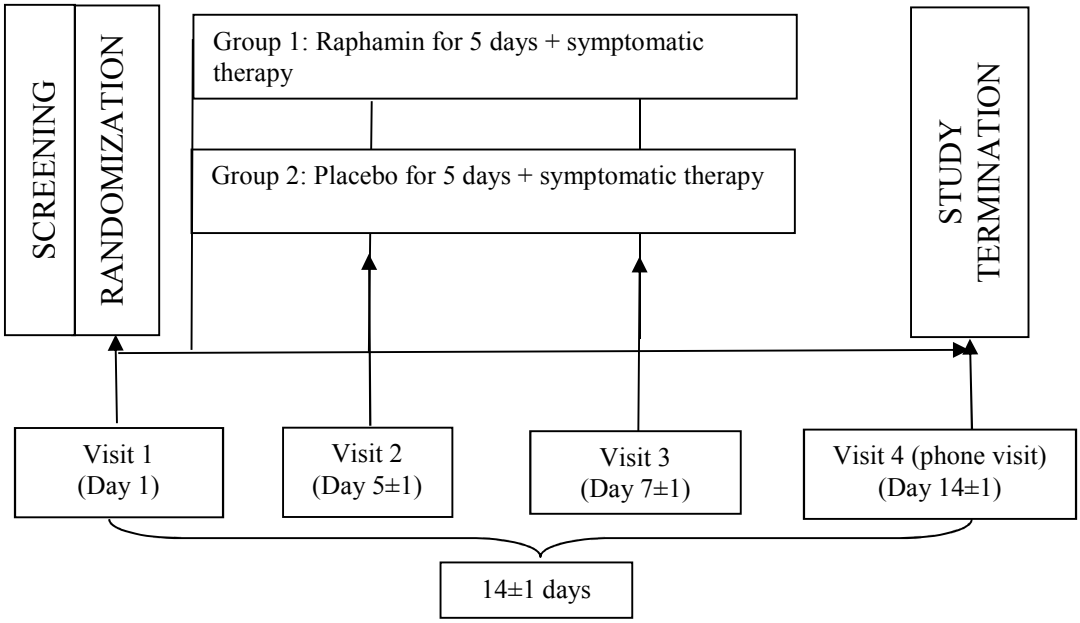
Two weeks prior to the enrollment as well as during the study (from signing of the patient information sheet and initiation of screening) the following medications are not allowed (ATC index is indicated in brackets):

1. Antiviral drugs (J05).
2. Anti-infectives and antiseptics for local oral treatment (A01AB).
3. Throat preparations (R02A).
4. Immunostimulants, 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.);
    - medications containing thymus hormones.
5. Non-steroidal anti-inflammatory drugs (M01, except for ibuprofen).
6. Analgesics and antipyretics (N02A, N02B, except for paracetamol).
7. Combination products for symptomatic therapy of acute respiratory infections.
8. Homeopathic medicines for the treatment of upper respiratory tract infections.
9. Systemic (oral or parenteral) corticosteroids.
10. Immunosuppressants (L04).
11. Antineoplastic agents (L01) and antineoplastic hormonal agents (L02).
12. Immune sera and immunoglobulins (J06).
13. Vaccines (J07).

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

[*] *Patients will be allowed to take a single dose of prohibited medications (except for 9-14) prior to inclusion, if the interval between the medication intake and randomization was more than 12 hours.*

Study design scheme



Schedule of study procedures

Procedure/Visit	Visit 1 (Day 1)	Visit 2 (Day 5±1)	Visit 3 (Day 7±1)	Visit 4 (Day 14±1)
Informed consent	+			
Registration of a study patient in the IVRS* and assignment of patient ID	+			
Complaints collection	+	+	+	
Medical history	+			
Concomitant diseases and conditions	+	+	+	+
Physical examination	+	+	+	
ARVI symptoms	+	+	+	
Concomitant therapy	+	+	+	+
SARS-CoV-2 rapid test	+			
Pregnancy test	+			
Inclusion/exclusion criteria	+			
Randomization	+			
Nasopharyngeal swabs for PCR	+			
Safety laboratory tests**	+		+	

Procedure/Visit	Visit 1 (Day 1)	Visit 2 (Day 5±1)	Visit 3 (Day 7±1)	Visit 4 (Day 14±1)
Study drug supply	+			
Antipyretic drug supply	+			
Evaluation of the study drug safety	+	+	+	+
Patient diary	+	+	+	+
Study drug accountability and return			+	
Treatment compliance			+	
Visit completion	+	+	+	+
Telephone survey				+
Study completion***				+
** Interactive voice/web response randomization system* *** Laboratory tests include hematology, urinalysis, serum chemistry (total protein, C-reactive protein, glucose, total bilirubin, creatinine, ALT, AST, cholesterol). Performed with availability of signed PIS and ICF including the patient's consent for blood and urine sampling.* **** In case of early withdrawal the procedure may be carried out at Visits 1, 2 or 3.*				

Statistical Analyses

SAS-[9.4].[5] will be used for data processing and statistical calculations.

Samples

Total set: all enrolled patients who have signed ICF. This sample will consider all the recorded AEs, including those occurred prior to the study therapy.

Safety population: all included and randomized patients who received at least one dose of the study drug. This sample will be used for ***analysis of the study treatment safety and tolerability***, as all adverse events identified after the study drug administration will be recorded.

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

1) non-compliance with inclusion / exclusion criteria;
2) patient did not take a single dose of the study drug;
3) lack of any data about the patient after administration of the study drug.

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

Per protocol set. This sample includes all patients who completed the therapy as per the study protocol and completed all the scheduled visits. This set will be used for the ***Per Protocol analysis (PP analysis)*** of the study therapy efficacy. *PP set* will not include the patients with their data completely or partially invalid for analysis due to a protocol deviation.

[5] Holder of license: OOO "NPF "MATERIA MEDICA HOLDING", No. 70100045.

The list of deviations that may result in complete or partial invalidity of data is developed by a medical expert jointly with a biostatistician according to the study design.

The deviations that may result in partial or complete invalidation of the study subject's data.

1. Inappropriate distribution/supply of the study drug.
2. Prescription of prohibited therapy.
3. Increase or decrease in the study drug dosing by ≥ 25%.
4. Inability to assess the patient's compliance using the formula (e.g. loss of pack with the product).
5. Major discrepancies between source documents and CRF identified during monitoring or another authorized inspection.
6. Violation of the procedure of obtaining informed consent.
7. Non-compliance with the clinical study protocol procedures.
8. Inability to collect all the patient's data used for evaluation of the study endpoints[6] (e.g. lack of records in source documents required for verification of inclusion/exclusion criteria, safety and efficacy criteria).
9. Any other protocol deviations covered by the term “major deviation”.

Evaluation of sample size

It is expected that out of 360 patients randomized 200 patients will complete the study per protocol[7]. Taking into consideration the expected screening failures, the informed consent should be obtained from 400 patients.

The sample size was 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 false acceptance of an alternative hypothesis is less than 0.05);
    1.3 the applied statistical tests for group comparisons are two-sided, unless stated otherwise;
    1.4 the sample size is calculated based on the assumptions on the expected effect declared in the primary endpoint of this protocol;

[6] If, considering the lack of some data in primary endpoint variable, the fact of reaching the primary endpoint by the patient can still be determined, the patient will be eligible for PP analysis (e.g. the diary lacks some records but the time of recovery can still be determined).
7No more than 10% patients who signed PIS and ICF are expected to be screning failures for various reasons.

1.5 the ratio between the sample sizes of the study drug and placebo groups is 1:1 (1 study drug patient - 1 placebo patient);

1.6 statistical hypotheses: null and alternative hypotheses about the superiority of the study drug over placebo using the applied dosing regimen:

primary endpoint:

$$\mathbf{H_0: M_1\text{-}M_2 = 0}$$

$$\mathbf{H_a: M_1\text{-}M_2 \neq 0}$$

where : M_1 – average time to resolution of the symptoms in the Raphamin group, M_2 – average time to resolution of the symptoms in the Placebo group.

Sample analysis will be performed according to the following formulas:

$$\mathbf{n_1 = kn_2}$$

$$n_2 = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 * (1 + 1/k)\sigma^2}{\varepsilon^2}$$

where $\mathbf{n_2}$, $\mathbf{n_1}$ is sample size in study drug and placebo groups, respectively;

$\boldsymbol{\varepsilon = M_1\text{-}M_2}$ is the time difference between Raphamin and Placebo groups;

k – coefficient of Raphamin/Placebo sample ratio (k=1);

σ - standard deviation;

$\mathbf{z_{\alpha/2}}$ – tabular value of two-sided z-test for **α**;

$\mathbf{z_{\beta}}$ – tabular value of one-sided z-test for **β**;

1.7 Full sample size is determined using the formula:

$$\mathbf{N = Npp / (1 - R_w)},$$

where **N** – the final sample size;

$\mathbf{N_{PP}}$ – result of calculation in cl. 1.6, i.e. scheduled number of the patients completing the study per protocol;

$\mathbf{R_w}$ – withdrawal rate.

2. Assumptions on expected effects of the clinical study: The differences in duration of the disease between the groups is expected to be less than 1 day, with standard deviation in the groups of no more than 2.5[8] days.

Therefore, the number needed to compare study drug and placebo will be **200** patients for both groups. Given potential withdrawal of at least 50%[9] patients **($\mathbf{R_W}$ = 0.5)** during the study for

[8]Upper limit of confidence interval of standard deviation of the time to resolution of the symptoms for placebo group based on the results of study MMH-ER-009 "International multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of Ergoferon in the treatment of acute respiratory viral infections in children".

[9] This rate is composite: 10% patients will be screening failures or discontinue the study for other reasons specified in the relevant protocol section, in 44.4% remaining patients the diagnosis will not be confirmed by PCR. The rate was assessed based on PCR findings obtained in "Multicenter double-blind placebo-controlled randomized parallel-group study of efficacy and safety of MMH-407 in the treatment of acute respiratory viral infection" (MMH-407-001).

various reasons, at least **400** patients will be required to sign informed consent, with **200** subjects per group.

Statistical criteria

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

- parametric – to obtain effective evaluations for parameters of random values, if the relevant conditions of applicability of methods/models are not violated (e.g. sphericity, normality, proportionality of risks, etc.);
- non-parametric – in any other cases.

Parametric criteria

The application of parametric criteria will be accompanied by a check of models for applicability (e.g. Kolmogorov-Smirnov test, Shapiro-Wilk test, etc.).

The following parametric tests and approaches are to be used:

1. To evaluate the differences of continuous variables obtained in one group at two different visits – Student's test for matched samples.
2. To evaluate the temporal dynamics of the compared indicators – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.
3. In case of multiple comparisons between the groups will apply a variety of corrections for multiplicity (Dunnett, Tukey, Scheffe, Holm adaptive test), etc.
4. In case of abnormal data distribution, approaches with the Generalized Linear Models and / or Mixed Linear Models will be used.
5. Selection of the type of distribution, specification of the factor and covariance structures of the model will be made using fit-statistics such as AIC[10] (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 General Linear Models for studying temporal dynamics (ANOVA, ANCOVA);
- GENMOD – analysis of Generalized Linear Models;
- MIXED – analysis of Mixed Linear Models.

[10] Akaike information criterion (AIC).

Non-parametric criteria

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

1. To evaluate the temporal dynamics of the compared indicators – Friedman test, nonparametric analogue of repeated measures analysis of variance.
2. 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).
3. For the frequency analysis of cross tables with independent strata – Cochran–Mantel–Haenszel test (modification of the χ^2-test for multiple comparisons).
4. 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, PHREG – 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 (other measures of central tendency and variance may be provided where applicable). The data suggesting statistical conclusion will have the relevant confidence intervals. Extreme values (outliers) will be analyzed additionally. The data will be pooled according to visits. Categorical variables will be presented as per-visit frequency tables.