Multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of Prospekta in the treatment of patients with post-COVID-19 asthenia

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-MAP-006**
Version date:	**August 16, 2021**
ClinicalTrials.gov Id:	**NCT05074888**

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", World Medical Association Declaration of Helsinki, relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

Multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of Prospekta in the treatment of patients with post-COVID-19 asthenia

Phase: III

Sponsor: Company «MATERIA MEDICA HOLDING», Moscow, Russia

Protocol No. MMH-MAP-006

Objective of the study

- To evaluate the efficacy of Prospekta in the treatment of asthenia in patients after the coronavirus infectious disease (COVID-19);
- To evaluate the safety of Prospekta in the treatment of asthenia in patients after the coronavirus infectious disease (COVID-19).

Endpoints

Primary endpoint

1. Change in the mean FSS score after 4 weeks of treatment.

Secondary endpoints

1. Change in the 6-minute walk distance after 4 weeks of treatment.
2. Change in the severity of anxiety and depression as estimated by the HADS subscales after 4 weeks of treatment.
3. Change in the mean FSS score in the course of the 4-week follow-up.
4. Change in the 6-minute walk distance in the course of the 4-week follow-up.
5. Change in the severity of anxiety and depression as estimated by the HADS subscales in the course of the 4-week follow-up.
6. Changes in vital signs after 4 weeks of treatment and in the course of the 4-week follow-up.
7. Occurrence and nature of adverse events, their intensity (severity), causal relationship to the study drug, and outcome.

Safety assessment

- Presence and nature of adverse events during the therapy, their intensity (severity), relation to the product, outcome.
- Changes in vital signs.

Study design

Design – double blind placebo-controlled randomized parallel-group clinical study.

The study will enroll adult patients of either gender aged 18 to 65 years after new coronavirus infection of 2019 (COVID-19) with symptoms of asthenia that appeared during or after an acute coronavirus infection (COVID-19) and persisting 4 to 12 weeks from the onset of coronavirus infection.

After the patient signs the patient information sheet and the informed consent form for participation in the study, complaints, medical history, physical examination, registration of vital signs are collected, the patient fills in the Fatigue Severity Scale (FSS) and Hospital Anxiety and Depression Scale (HADS). A six-minute walk test (6MWT) is carried out. The physician evaluates the severity of asthenia with FSS scale and records concomitant medications, co-morbidities and concurrent conditions.

If a patient meets all inclusion criteria and does not have any of the exclusion criteria at Visit 1 (Day 1), he/she is randomized to one of two groups: Group 1 - patients receive Prospekta at a dose of 1 tablet twice daily for 4 weeks; Group 2 - patients receive placebo on the study drug regimen.

The trial will use electronic patient diaries (EPD). The patient should record any possible deterioration (if applicable) in the EPD. At Visit 1 (Day 1), the physician will provide guidance on how to work with EPD, so that the patient can use it independently in the future.

At Visit 2 (Week 4 ± 3 days), the physician will collect patient’s complaints, record physical examination data and vital signs as well as any changes in concurrent diseases and conditions. The patient fills out the FSS and HADS scales. A 6MWT is carried out. The physician monitors the prescribed treatment and use of concomitant medications, evaluates the safety of the study treatment and patient's compliance, filling out the diary.

The patient stops taking the study drug. At the end of the study treatment period, the patient is monitored for 4 weeks (follow-up period).

At Visit 3 (final visit, Week 8 ± 3 days), the physician collects patient’s complaints, records physical examination data and vital signs, changes in concomitant diseases and conditions. The patient fills in the FSS and HADS scales. A 6MWT is carried out. The physician evaluates the safety of the study treatment, checks the completion of the diary.

During the study the patients are allowed to take medications for their chronic conditions, except for medicines listed as "Prohibited concomitant treatment".

Inclusion and exclusion criteria

Inclusion criteria

1. Adults of either gender aged 18 to 65 years inclusive.
2. Patients within 4–12 weeks of the confirmed COVID-19 onset.
3. Symptoms of asthenia that appeared during or after an acute new coronavirus infection (COVID-19), persisting from 4 to 12 weeks from the onset of coronavirus infection.
4. Presence of asthenia (≥36 on the FSS scale).
5. Patients who agreed to use a reliable method of contraception during the study (for men and women with reproductive potential).
6. Presence of a signed information sheet and informed consent form for participation in the clinical trial.

Exclusion criteria

1. History / suspicion of cancer of any localization (with the exception of benign neoplasms).
2. More than 75% of lung tissue damage during the period of COVID-19 disease (CT 4).
3. Cerebrovascular diseases with the development of moderate to severe cognitive impairments.
4. Uncontrolled arterial hypertension characterized by the following blood tension values: systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 110 mm Hg.
5. Myocardial infarction, stroke in the previous 6 months.
6. Nervous system disorders with persistent neurological impairment.
7. Autoimmune diseases.
8. Decompensated diseases of the cardiovascular system, liver, kidney, gastrointestinal tract, and metabolic, respiratory, endocrine or hematological diseases, peripheral vascular disorders.
9. Any severe comorbidity, which, in the opinion of the investigator, may affect patient participation in the clinical trial.
10. Hypersensitivity to any of the components of the study drug.
11. Hereditary lactose intolerance, lactose malabsorption, including congenital or acquired lactase or other disaccharidase deficiency, galactosemia.
12. Pregnancy, breast-feeding; childbirth less than 3 months prior to the inclusion in the trial, unwillingness to use contraceptive methods during the trial (for men and women with reproductive potential).
13. Patients, who, from the investigator's point of view, will not comply with study observation requirements or study drug administration procedures.

14. Prior history of mental illness, alcoholism or drug abuse that the investigator's opinion will interfere with successful study procedures.
15. Use of any medications listed in "Prohibited concomitant treatment" within 1 week before enrollment.
16. Participation in other clinical studies within 3 months prior to enrollment in the study.
17. Patients who are related to any of the on-site research personnel directly involved in the conduct of the trial or are an immediate relative of the study investigator. "Immediate relative" means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
18. Participants who work 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. Inability or patient’s refusal to comply with the protocol requirements.
3. Necessity in medications prohibited within the study.
4. An adverse event requiring discontinuation of the study product.
5. Patient’s decision to complete the study ahead of schedule due to lack of the therapy efficacy or any reasons.
6. Pregnancy.
7. Cases not specified by the protocol when, according to the investigator’s opinion, further participation in the study harms the patient.
8. Eligibility error.
9. Enrollment of the subject into another clinical study.
10. Unblinding.

Number of subjects

It is expected that **272** trial subjects will sign the informed consent.

At least **260** of the participants will be randomized.

Interim analysis

A non-blind interim analysis will be carried out after 62 PP subjects complete the trial. Based on the results, the sample size may be increased up to 680 subjects (with the maximum number of randomized subjects being n=646).

Treatment

Group 1

Name of the medicinal product: Prospekta

Active ingredient: brain-specific protein S-100, modified – 10 000 UMA*

** UMA – Units of Modifying Activity*

Excipients: Lactose monohydrate - 0.267g

Microcrystalline cellulose - 0.030 g

Magnesium stearate - 0.003 g

Method of administration: Per os. One tablet per intake 2 times a day (approximately at the same time), outside of meal (between meals or 15 minutes prior to meal or drinking). The tablet should be held in mouth until completely dissolved. The duration of therapy is 4 weeks.

Dosage form: Tablets.

Description: Flat cylinder-shaped scored beveled edge white to off-white tablets with smooth even surface.

Storage conditions: At temperature ≤ 25 ºC.

Group 2

Name of the medicinal product: Placebo

Active ingredient: No

Excipients: Lactose monohydrate - 0.267 g

Microcrystalline cellulose - 0.030 g

Magnesium stearate - 0.003 g

Method of administration: Per os. One tablet per intake 2 times a day (approximately at the same time), outside of meal (between meals or 15 minutes prior to meal or drinking). The tablet should be held in mouth until completely dissolved. The duration of therapy is 4 weeks.

Dosage form: Tablets.

Description: Flat cylinder-shaped scored beveled edge white to off-white tablets with smooth even surface.

Storage conditions: At temperature ≤ 25 ºC.

Treatment duration

Prospekta/Placebo treatment duration is 4 weeks.

Observation period

The total length of patient observation is 8 weeks (screening + randomization – up to 1 day, treatment –4 weeks, follow-up – 4 weeks).

Symptomatic (Standard) treatment

During the course of the study, the patient may receive therapy for concomitant diseases and conditions, with the exception of drugs listed in the "Prohibited Concomitant Treatment" section.

Prohibited concomitant therapy

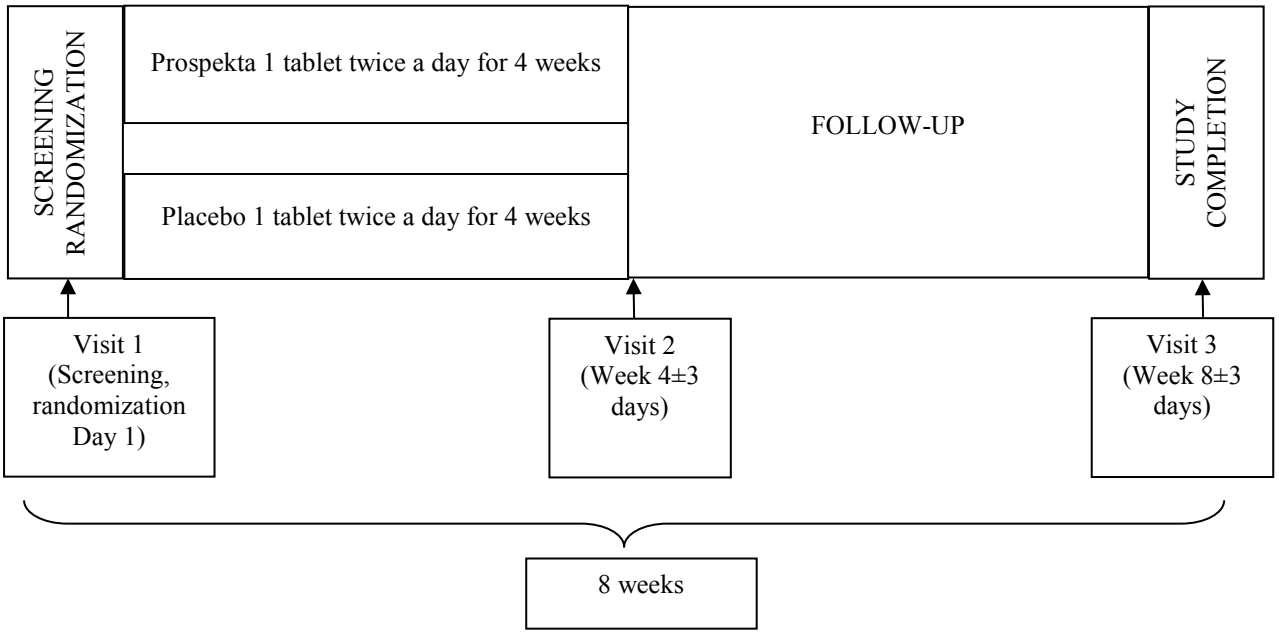
Within 1 week prior to enrollment and during the study (beginning from signing patient information sheet and informed consent form) subjects are forbidden to take any therapy that can affect the psychoemotional and psychophysical status of the patient, the processes of excitation-inhibition in the central nervous system (parenthesized is the ATC group):

1. Antiepileptic drugs (ATC group – N03A)
2. Muscle relaxants (M03)
3. Anticholinergic agents (N04A)
4. Dopaminergic agents (N04B)
5. Actovegin (B06)
6. Psycholeptics (N05), including anxiolytics (tranquilizers), hypnotics and sedatives
7. Psychoanaleptics (N06), including antidepressants, psychostimulants and nootropics including:
    - pyrrolidine derivatives (racetams) – piracetam, etiracetam, aniracetam, etc.
    - dimethylaminoethanol derivatives (acetylcholine precursors) - deanol aceglumate, meclofenoxate
    - pyridoxine derivatives - pyritinol, biotredin
    - GABA derivatives and analogues – gamma-aminobutyric acid, nicotinoyl gamma-aminobutyric acid, gamma-amino-beta-phenylbutyric acid hydrochloride, hopantenic acid, calcium gamma-hydroxybutirate
    - gingko biloba
    - neuropeptides and their analogues - methionyl-glutamyl-histidyl-phenylalanyl-propyl-glycyl-proline
    - amino acids and substances affecting excitatory amino acid system – glycine, pyrodoxine+threonine
    - 2-mercantobenzimidazole derivatives – ethylthiobenzymidazole hydrobromide
    - idebenon
    - vinpocetine

- polypeptides and organic composites - bovine cortical polypeptides, cerebrolysin
- memantine (N06DX01)

8. Glucocorticoids of systemic action (except for topical steroids)
9. Tonics (A13)
10. Anabolic agents for systemic use (A14)
11. Other nervous system drugs (N07) including:
    - parasympathomimetics (N07A)
    - other nervous system drugs (N07X)
12. Substances of other pharmacological group with a nootropic ingredient including:
    - tonics and adaptogens – redberry, melatonin, lecithin, acetylaminosuccinic acid etc.
    - antihypoxants and antioxidants – ethylmethylhydroxypyridine succinate, citicoline, vitamin E, etc.
    - metabolic agents.
13. Homeopathic preparations for the treatment of nervous system disorders
14. Any unregistered product and/or vaccine
12. Drugs that previously caused allergic reactions in patient.

Study design scheme



Schedule of study procedures

Procedure/Visit	*Visit 1 Screening, Randomization (Day 1)*	*Visit 2 (Week 4±3 days)*	*Visit 3 (Week 8±3 days)*
Informed consent	+		
Registration patient in IVWRS and assignment of a personal code	+		
Demographics	+		
Collection of complaints	+	+	+
Medical history	+		
Concomitant conditions and diseases	+	+	+
Physical examination	+	+	+
Vital signs (HR, RR, BP)	+	+	+
Registration of therapy for concomitant diseases	+	+	+
Filling FSS scale	+	+	+
Six Minute Walk Test	+	+	+
Filling HADS scale	+	+	+
Pregnancy test	+		
Inclusion/exclusion criteria	+		
Randomization	+		
Study drug supply	+		
Study drug accountability and return		+	
Compliance assessment		+	
Evaluation of treatment safety	+	+	+
Visit completion	+	+	+
Study completion			+

Statistical Analysis

Samples

Total set includes all the subjects who have signed informed consent form (ICF). This sample will consider all adverse events (AEs) throughout the study, including those occurred prior to the study therapy.

The sample including all subjects who received at least one dose of the study drug to be used for ***analysis of the study treatment safety and tolerability*** (*Safety population*), as all AEs identified after the study product administration will be registered.

Full Analysis Set. This sample will consist of all enrolled subjects, except for those who met at least one of the following criteria:

1) non-compliance with inclusion/exclusion criteria;
2) subject failing to take any dose of the study drug;
3) lack of any data on the subject after the study drug administration.

Patients who had at least one of the listed events may be excluded from the analysis.

This was the best set for the Intention-to-treat method, so it will be used in the ***Intention-to-treat efficacy analysis (ITT-analysis) of the test therapy.***

Per Protocol set. This set will comprise all the subjects receiving per protocol therapy in full and completing all the scheduled visits. This set will be used for ***efficacy Per Protocol analysis (PP-analysis)***. *Per Protocol set* will not include the subjects whose data are fully or partially invalid for analysis due to a protocol deviation.

Protocol deviations resulting in full or partial data invalidity:

1. Violation of visit schedule.
2. Inappropriate distribution/dispensing of the study drug.
3. Prescription of prohibited therapy.
4. Increase or decrease by 25% or more in the amount of study therapy taken.
5. Inability to assess the subject's compliance using the formula (e.g. loss of pack with the product).
6. Major discrepancies between source documents and CRF detected during monitoring or another authorized check.
7. Violations of the informed consent procedure.
8. Non-compliance with the clinical study protocol procedures.
9. Inability to collect all subject's data used for evaluation of the study endpoints (e.g. lack of entries in source documents required for verification of inclusion/exclusion criteria, safety and efficacy criteria).
10. Any other deviation from the protocol that falls under the definition of «major deviation».

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software.[1]

Interim Analysis

A “non-blinded” interim analysis is planned in the protocol for 25% of the sample (0.25 information, for 31 subjects of the CT PP per group).

[1] Holder of license: OOO "NPF "Materia Medica Holding", No. 70100045.

It is assumed that the study can be stopped due to the rejection of the null hypothesis with the O'Brien-Fleming type I error spending function. Based on the results of this analysis (if the stop parameters are not reached), it is assumed that the study will be adapted to determine the required additional sample size. The additional sample size will be determined according to the following algorithm[2]:

1) The conditional power is calculated in the interim analysis;

2) Depending on the value obtained, one of the three options for further research described below will be selected.

At the discretion of the sponsor, a blind interim analysis may be performed to refine the population parameters and possibly further refine the sample size (upward only).

Evaluation of sample size

The sample size was assessed in accordance with the following rules and assumptions:

1. Statistical assumptions
   - 1.1 the power of statistical tests «P = (1 − β)» is 80% (the probability of correct rejection of the null hypothesis is 0.8)
   - 1.2 the probability of type 1 error «α» is less that 5% (the probability of false acceptance of the alternative hypothesis is less than 0.05);
   - 1.3 the statistical criteria used for intergroup comparisons are two-sided unless otherwise noted;
   - 1.4 ratio between sample sizes of Prospekta and Placebo sample sizes is 1:1 (1 Prospekta subject per 1 Placebo subject);
   - 1.5 it is assumed to conduct a «non-blinded» interim analysis with the possibility of early termination due to the efficiency of 25% of the sample. Error spending function - O'Brien-Fleming boundary;
   - 1.6 it is assumed that the sample size can be adapted after the interim analysis based on the estimated conditional power (simultaneously with the interim analysis);
   - 1.7 statistical hypotheses - null and alternative hypotheses on the difference between investigational product and placebo under the dosing regimen used:

Primary Criteria:

$$H_0: M_1 - M_2 = 0$$

$$H_a: M_1 - M_2 \neq 0$$

[2] Mehta, C.R. and Pocock, S.J. (2011), Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist. Med., 30: 3267-3284. https://doi.org/10.1002/sim.4102.

where **M_1 and M_2** are values of change in the mean score of the questionnaire in the Placebo and Prospekta groups;

The following SAS code was used to determine the required sample size[3]:

executable SAS code (also defines critical statistics for the corresponding analyses)

```
Proc seqdesign errspend
Design nstages = 2
Info = cum (0.25,1)
Method (alpha) = UNI (rho = 0.5 tau = 0)
Method (beta) = UNI (rho = 0 tau = 0)
Stop = reject
Alpha = 0.05
Beta = 0.2
Samplesize model = twosamplemeans (meandiff = 0.65 stddev = 1.81)
Run.
```

1.8 the full sample size is determined by the formula:

$$N=Npp/(1-К_в)$$

where **N** – terminal sample size; N_{PP} – sample size in c. 1.7 i.e. scheduled number of subjects completing the study per protocol; $К_в$ – withdrawal rate.

2. Assumptions on expected clinical study effects:

It is assumed that there is **an inter-group difference between the changes in the mean score of the FSS** 0.65[4] questionnaire in favor of the Prospekta (the adaptation process assumes a possible deterioration in the effect prediction size to 0.41).

Population standard deviation of change: assumed to be 1.81[5]. Thus, for the first stage (before adaptation), the size of each of the groups of 122[6] clinical study subjects is required (PP sample). Considering the possible elimination of about 10% of the subjects in the study for various reasons[7], at least **272** subjects will be required to sign informed consent, of which 260 subjects of clinical trial will be randomized (**130** subjects of clinical trials to each group) (see item 1.8, the final complete elimination rate will be $К_{в.}$ = 0.1).

[3] Minimum size for this study

[4] The change in the average FSS score was indicated during the study, for the calculation of which the sum of points on nine points is divided by 9 (the average score lies in the range [1; 7]).

[5] Conservative assessment of the standard deviation: upper limit of 95% of the confidence interval of the standard deviation of the change in the mean score of the 9x questionnaire [1; 7] (measurements are considered independent, answers to individual questions are evenly distributed, the number of degrees of freedom for the distribution of the standard deviation of the average score is 8).

[6] Minimum size.

[7] Of these, the dropout of patients in the screening process (5%).

Sample size adaptation

It is planned to adapt the sample size during the study according to the following algorithm[8]:

1) During the planned interim analysis (if the study was not completed due to the rejection of the null hypothesis based on the interim analysis boundary), the conditional power is calculated by the formula:

$$CPower = 1 - \Phi\left(\frac{z_\alpha * \sqrt{N_{min}} - z_1 * \sqrt{N_1}}{\sqrt{N_{min} - N_1}} - \frac{z_1 * \sqrt{N_{min} - N_1}}{\sqrt{N_1}}\right)$$

where Z_1 – value of Z-statistic obtained from interim analysis on N1 of the first participants from N_{min} (minimum study sample size);

$Z_\alpha = 1.9603$ (the value of statistics for the final analysis, taking into account the presence of an interim analysis);

$\Phi(x)$ – probability value of event X for standard normal distribution ($\sigma=1$, $\mu=0$).

2) Maximum allowable increase in sample size to no more than 612 is assumed[9].
3) Assumed minimum sample size $N_{min} = 260$.
4) Based on the above, one of the adaptation scenarios will be selected.
5) Optimistic scenario (conditional power CPower > 0.8, or equivalently Z1 > 1.3545): the sample size does not change ($N_{final} = N_{min}$).
6) Mid-range scenario (conditional power 0.397 < CPower < 0.8, or equivalently 0.8744 < Z_1 < 1.3545): the sample size changes according to the formula:

$$N_{final} = N_1 + \left(\frac{N_1}{z_1^2}\right) * \left(\frac{z_\alpha * \sqrt{N_{min}} - z_1 * \sqrt{N_1}}{\sqrt{N_{min} - N_1}} + z_\beta\right)^2$$

7) Pessimistic scenario (conditional power CPower < 0.3975, or equivalently Z_1 < 0.8744): sample size does not change ($N_{final} = N_{min}$).
8) The final statistical analysis is carried out with the critical values obtained during the assessment of the minimum sample size (Z_α= 1.9603).

Statistical criteria

All statistical calculations will be made using two groups of statistical criteria:

- parametric - to obtain effective estimates for random parameters in case the relevant conditions of method/model applicability are not violated (e.g. sphericity, normality, risk proportionality, etc.)
- nonparametric – in all other cases.

[8] Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples. Cyrus R. Mehta1,2, Stuart J. Pocock3. Statistics in Medicine 2000; 00:1–6.
[9] Taking into account the elimination - up to 680.

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).

The following parameters and approaches are to be used:

1. To evaluate the differences in continuous variables obtained in one group at two different visits – Student's test for matched samples.
2. To evaluate the time changes of the compared indicators - variance (ANOVA) or covariance (ANCOVA) analysis in modification with repeated measures (Repeated Measures).
3. In case of multiple comparisons of the groups various corrections for multiplicity will be used, e.g. Dunnett, Tukey, Scheffe, Holm adapted test, etc.
4. Generalized Linear Models and/or Mixed Linear Models will be used in case of abnormal data distribution.
5. Selection of the type of distribution, specification of factor and covariance structures of the model will be made using fit-statistics such as AIC (Akaike information criterion).

The following SAS software programs are supposed to be applied to the above listed tests and techniques:

- UNIVARIATE – normality verification of the distributions under comparison
- CORR, MEANS – calculation of descriptive statistics
- TTEST – Student's test with all modifications
- GLM – generalized linear models for analysis of time changes (ANOVA, ANCOVA)
- GENMOD – generalized linear models
- MIXED – mixed linear models.

Non-parametric criteria

Below are potential types of comparisons with relevant criteria:

1. To evaluate time changes in the parameters compared – Friedman test, nonparametric analogue of repeated measures analysis of variance.
2. For frequency analysis of contingency tables 2×2 – χ^2 (if the frequency under comparison > 5) or exact Fisher's test (if one of the frequencies under comparison < 5).
3. Cochran-Mantel-Haenszel test (modified χ^2 test for multiple comparisons) – to perform frequency analysis based on independent strata.
4. For frequency analysis of data on presence/absence of an event or outcome during repeated measurements (contingency tables with dependent strata) – survival analysis.

To perform the above-mentioned nonparametric statistical analysis the following SAS procedures are to be used:

- FREQ – Friedman test, χ^2 test and/or exact Fisher's 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, as well as maximum and minimum values, as well as 1, 2 and 3 quartiles (if necessary, other measures of central tendency and spread can be additionally given). The categorical variables will be presented as frequency tables by visits.
Outliers will be analyzed individually. The data will be grouped by visits.