Multicenter double-blind placebo-controlled randomized parallel group clinical study of efficacy and safety of Prospekta in the treatment of cognitive behavioral and psychiatric disorders in subjects with vascular dementia

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-MAP-003**
Version 1 date:	**April 06, 2020**
Version 2 date:	**February 08, 2021**
ClinicalTrials.gov Id:	**NCT04552041**

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 cognitive, behavioral and psychiatric disorders in subjects with vascular dementia.

Phase: III

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

Protocol No. MMH-MAP-003

Study purposes

- To evaluate efficacy of Prospekta in the treatment of cognitive, behavioral and psychiatric disorders in vascular dementia.
- To evaluate the safety of Prospekta in the treatment of cognitive, behavioral and psychiatric disorders in vascular dementia.

Study objectives

- Evaluate and compare changes in cognitive functions in two groups (Prospekta and Placebo) after 24-weeks of treatment.
- Evaluate and compare changes in behavioral and psychiatric dementia symptoms in two groups (Prospekta and Placebo) after 24-weeks of treatment.
- Evaluate and compare the presence and nature of adverse events (AEs) in two groups (Prospekta and Placebo), including central nervous system AEs during therapy, their relationship with the study drug and other characteristics.

Endpoints

Primary endpoint

1. Change in mean MoCA score after 24-week therapy (vs. baseline).

Secondary endpoints

1. Change in mean NPI-C score after 24-week therapy (vs. baseline).

Additional endpoints

1. Change in mean MoCA score after 12-week therapy.
2. Change in mean NPI-C score after 12-week therapy.

3. Mean CGI-EI score after 24-week therapy.

Safety assessment

- Changes in vital signs during the study.
- Occurrence and nature of adverse events (AEs) during the treatment, their intensity (severity), relation to the study drug, outcome.

Study design

Design: double-blind placebo-controlled randomized parallel-group clinical trial. The study will enroll male and female patients aged 60-85 years inclusively diagnosed with vascular dementia verified at Visit 1 according to the criteria of The National Institute of Neurological Disorders and Stroke National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences - NINDS-AIREN. Severity of vascular dementia should be moderate or mild (10-24 points according to Mini-Mental State Examination - MMSE), without signs of depression (total Cornell Scale for Depression in Dementia (CSDD) score ≤10).

After signing patient information sheet (informed consent form) to participate in the study, at Visit 1 (from day -14 to day 1) complaints and medical history will be collected, objective examination, recording vital signs - blood pressure (BP), respiration rate (RR), heart rate (HR) will be performed and compliance of the patient's diagnosis with NINDS-AIREN vascular dementia criteria will be evaluated. The study investigator will assess cognitive disorders using MMSE and Montreal Cognitive Assessment (MoCA). The study investigator and the patient's caregiver will fill Neuropsychiatric Inventory Clinician (NPI-C), and CSDD scales. The patient will undergo brain MRI (in the absence of brain MRI data within the previous 12 months before inclusion in the study).

Concomitant therapy and concomitant diseases and conditions will be recorded.

If inclusion/exclusion criteria are met, the patient will be randomized to one of the two groups: group 1 will receive Prospekta 2 tablets twice daily; group 2 will receive Placebo using the study drug dosing regimen.

Treatment duration will be 24 weeks during which 6 Visits will be made. At visits 2 and 3 (week 4±3 days and week 8±3 days) the study investigator will make a phone call and collect the complaints, monitor the prescribed and concomitant therapy, evaluate therapeutic safety.

At visit 4 (week 12±7 days) the study investigator will collect complaints, record objective examination findings and vital signs, monitor the prescribed and concomitant therapy, evaluate therapeutic safety and compliance, dispense the study drug until the next visit. The study investigator and caregiver will fill NPI-C.

At visits 5 and 6 (week 16±3 days and week 20±3 days) the study investigator will make a phone call and collect the complaints, monitor the prescribed and concomitant therapy, evaluate therapeutic safety.

At visit 7 (week 24±7 days) the study investigator will collect complaints, perform objective examination, record vital signs, monitor the prescribed and concomitant therapy, evaluate therapeutic safety, evaluate compliance. The study investigator will fill MoCA and Clinical Global Impression Efficacy Index (CGI-EI). The study investigator and caregiver will fill NPI-C. During the study the treatment for concomitant diseases will be allowed with the exception of the drugs specified in the section "Prohibited concomitant therapy".

Inclusion and exclusion criteria

Inclusion criteria

1. Subjects aged 60-85 years old inclusively.
2. Subjects with verified diagnosis of vascular dementia.
3. Presence of all the vascular dementia criteria according to NINDS-AIREN:
   A. Presence of dementia, which is defined as a decline in cognitive function relative to the previous level of functioning, manifested by impairments in memory and two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control and praxis), preferably established during a clinical trial and confirmed by neuropsychological testing.

      The cognitive impairment must be so severe that it affects daily activity, reducing it independently of the physical consequences of the stroke.
   B. The presence of cerebrovascular disease, confirmed by signs of focal damage on neurological examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopsia or dysarthria associated with stroke (either a history of stroke or absence of such anamnestic information), and neuroimaging (CT or MRI) signs of cerebrovascular disease, including multiple infarcts in the territory of large vessels, or a single infarction in a strategically important area (angular gyrus, thalamus, basal ganglia, or the territory of the anterior or posterior cerebral arteries), as well as multiple lacunae in the region of the basal ganglia or white matter, or significant damage to the periventricular white matter, or a combination of the above lesions.
   C. There is an association between dementia and cerebrovascular disease as follows:
      a) onset of dementia within 3 months of stroke;
      b) sharp deterioration of cognitive functions; or fluctuating, stepwise progression of cognitive impairment.

4. Availability of permanent caregiver throughout the study (nurse or relatives).
5. Total Mini-Mental State Examination (MMSE) score - 10-24.
6. Total MoCA score <26.
7. Total NPI-C aggression and agitation domain score ≥14.
8. Absence of depression (total Cornell Scale for Depression in Dementia (CSDD) score ≤10).
9. Brain MRI confirming the diagnosis of vascular dementia within 1 year prior to enrollment (or brain MRI performed at enrollment visit).
10. Patients giving their consent to use reliable contraception throughout the study (for males).
11. Availability of signed patient information sheet and informed consent form for participation in the clinical trial.

Exclusion criteria

1. Signs of intracerebral hemorrhage, brain tumours causing dementia.
2. Alzheimer's disease, Parkinson disease, Lewy body dementia, multiple system atrophy, Jacob-Creutzfeld disease, Pick's disease, corticobasal degeneration.
3. Injuries of head (S00-S09) associated with impaired consciousness, cerebral contusion or open craniocerebral traumas.
4. Toxicity-related dementia (including drug-induced), multiorgan failure or metabolic and toxic disorders (chronic hypothyroidism, decompensated diabetes mellitus, avitaminoses, etc.).
5. Other psychiatric diseases besides dementia: mental disorders and behavioral disorders due to use of psychoactive substances (F10-19) schizophrenia, schizotypal and delusional disorders (F20-29).
6. Mental retardation (F70-79).
7. Inflammatory lesions of the brain with persistent neurological deficit.
8. Malignant neoplasms.
9. Previously diagnosed cardiovascular diseases with functional class IV (according to New York Heart Association, 1964).
10. Unstable angina pectoris, myocardial infarction or ischemic stroke within the last 6 months.
11. Female patients with childbearing potency.
12. Allergy/intolerance of any of the study drugs components including secondary to lactase deficiency.
13. Any conditions which, according to the investigator opinion, may interfere with the patient's participation in the study.
14. History of treatment noncompliance, mental diseases, alcoholism or drug abuse which will prevent from following the study procedures, according to investigator's opinion.

15. Participation in clinical trials for 3 months prior to enrollment in this study.
16. Use of any medications specified in "Prohibited concomitant medications" within 1 month before enrollment.
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. Patients 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 refusal of the patient/caregiver to comply with the protocol requirements.
3. Necessity in medications prohibited within the study.
4. An adverse event requiring discontinuation of the study drug.
5. Eligibility error.
6. Patient's/caregiver's desire to complete the study early for any reason.
7. Participation in any other clinical trial.
8. Cases not specified by the protocol when, according to the investigator’s opinion, further participation in the study harms the patient.
9. Unblinding.

Number of subjects

It is planned to include 406 patients (203 per group), which is expected to yield at least 324 patients (162 in Prospekta and Placebo groups) completing all protocol procedures.

Interim analysis

Unblinded interim analysis is preplanned in the study: at the 30% of enrolled patient. Type 1 error at the analyses is in governed by O'Brien-Fleming spending function, for type II error – the Pocock spending function is selected. Early study termination is planned due to both acceptance and rejection of null hypothesis. Interim analysis will be carried out on the data from the number of completing subjects established by the protocol. Number of subjects for interim analysis: 98 subjects (Prospekta – 49, Placebo – 49). Number of subjects for final analysis: 324 subjects (Prospekta – 162, Placebo – 162).

Treatment

Group 1

Name of the medicinal product: Prospekta

Active ingredient: Affinity purified antibodies to brain-specific protein S-100, modified – 10 000 MAU*

** MAU – modifying action units*

Excipients: Lactose monohydrate (Ph.Eur., USP[1] NF, BP[2]) - 0.267 g

Microcrystalline cellulose (Ph. Eur., USP NF, BP) - 0.030 g

Magnesium stearate (Ph.Eur., USP NF, BP) - 0.003 g

Method of administration: Tablet for oral use. 2 tablets twice daily (approximately at the same time), outside the meal (between meals or 15 minutes before meals or fluids). Keep the tablets in mouth until completely dissolved.

Dosage form: Tablets.

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

Storage conditions: Store at a temperature not exceeding 25°C.

Group 2

Name of the medicinal product: Placebo

Active ingredient: No

Excipients: Lactose monohydrate (Ph.Eur., USP NF, BP) - 0.267 g

Microcrystalline cellulose (Ph. Eur., USP NF, BP) - 0.030 g

Magnesium stearate (Ph.Eur., USP NF, BP) - 0.003 g

Method of administration: Tablet for oral use. 2 tablets twice daily (approximately at the same time), outside the meal (between meals or 15 minutes before meals or fluids). Keep the tablets in mouth until completely dissolved.

Dosage form: Tablets.

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

Storage conditions: Store at a temperature not exceeding 25°C.

Treatment duration

Prospekta/Placebo treatment duration is 24 weeks.

Observation period

In total the patients will be monitored for 24-26 weeks (screening up to 2 weeks, therapy - 24 weeks).

[1] USP – current US Pharmacopoeia.
[2] BP – current British Pharmacopoeia.

Symptomatic (Standard) treatment

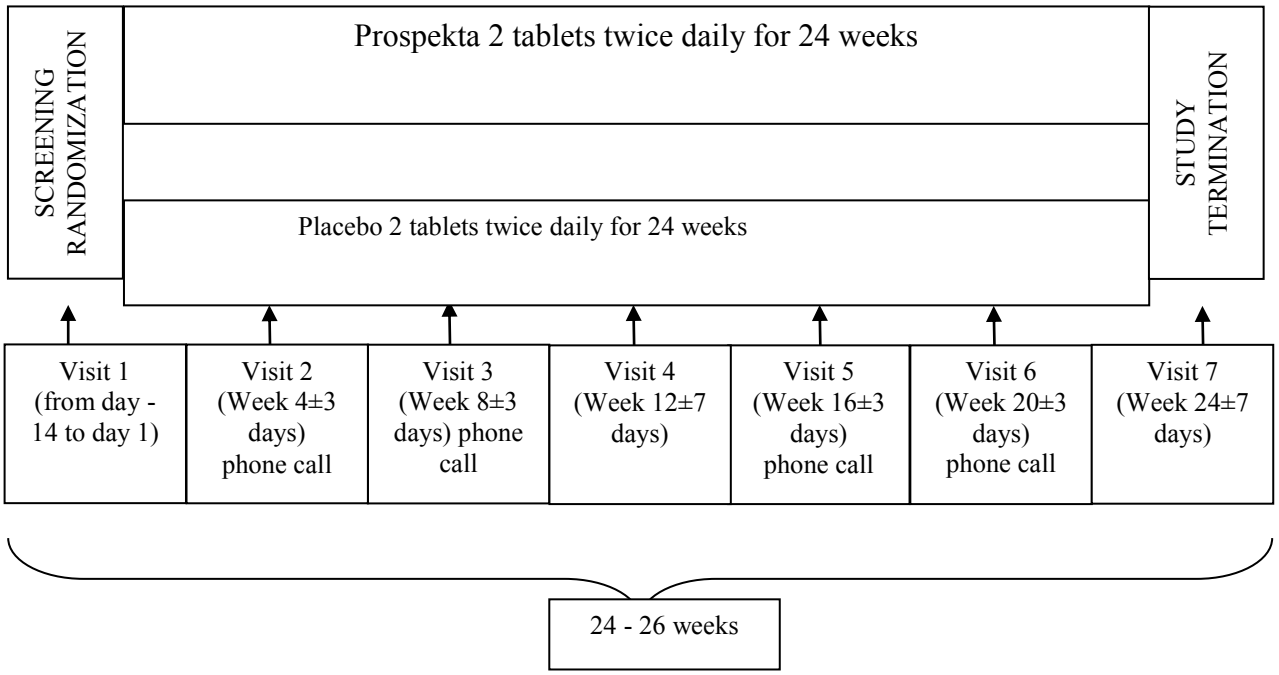
During the study, the patient may receive therapy for concomitant diseases and conditions, with the exception of medications specified in the section "Prohibited Concomitant Treatments."

Prohibited concomitant therapy

One month prior to the enrollment as well as during the study (from signing of informed consent form and screening) any therapy affecting cognitive and mental status of the subject the following products will not be allowed (ATC group is indicated in brackets):

1. Anchicnolonergic agents (N04A).
2. Psycholeptics (N05) including:
    - antipsychotics (N05A)
    - anxiolytics (N05B)
    - hypnotic and sedative drugs (N05C)
    - other hypnotics and sedatives (N05CM) including those of herbal origin.
3. Psychoanaleptics (N06) including:
    - antidepressants (N06A)
    - psychostimulants and nootropics (N06B) including other psychostimulants and nootropics (N06BX)
    - anti-dementia drugs (N06D).
4. Other nervous system drugs (N07) including:
    - parasympathomimetics (N07A)
    - antivertigo preparations (N07C)
    - other nervous system drugs (N07X).
5. Heme products (B06AB): Actovegin.
6. Purine derivatives (C04AD): Pentoxifylline.
7. Dihydropyridine derivatives (C08CA): Nimodipine.
8. Substances of other pharmacological group with a nootropic ingredient including:
    - general tonic agents and adaptogens – herbal; melatonin, lecithin, acetylaminosuccinic acid etc.
    - antihypoxants and antioxidants – ethylmethylhydroxypyridine succinate, citicoline, all vitamins, etc.
    - metabolic agents.
9. Drugs that previously caused allergic reactions in patient.
10. Products containing ultrahigh dilutions (Tenoten, Proproten-100, Divaza, etc.).
11. Homeopathic products with nootropic or psychoactive effect.
12. Any unauthorized product and/or vaccine.

Study design scheme



Schedule of study procedures

Procedure/ visit	Visit 1 From day -14 to day 1	Visit 2 Week 4 ±3 days (phone)	Visit 3 Week 8± 3 days (phone)	Visit 4 Week 12 ± 7 days	Visit 5 Week 16 ±3 days (phone)	Visit 6 Week 20 ±3 days (phone)	Visit 7 Week 24 ±7 days
Informed consent	+						
Patient registration in IVRS and assignment of a personal code	+						
Demographics	+						
Collection of complaints	+	+	+	+	+	+	+
Medical history	+						
Concomitant conditions and diseases	+	+	+	+	+	+	+
Physical examination	+			+			+
Vital signs (HR, RR, BP)	+			+			+
Matching vascular dementia diagnosis with NINDS-AIREN criteria	+						

Head MRI or analysis of findings of MRI made within 1 year prior to enrollment	+						
Concomitant therapy	+	+	+	+	+	+	+
Filling MoCA	+			+			+
Filling MMSE	+						
Filling NPI-C	+			+			+
Filling CSDD	+						
Inclusion/exclusion criteria	+						
Randomization	+						
Dispensing of study drug	+			+			
Study drug accountability and return				+			+
Treatment compliance				+			+
Evaluation of study treatment safety	+	+	+	+	+	+	+
Filling CGI-EI scale							+
Visit completion	+	+	+	+	+	+	+
Study completion							+[3]

Statistical Analyses

Samples

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

The sample including all patients 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 drug administration will be recorded.

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

1) non-compliance with inclusion/exclusion criteria;
2) patient did not take any dose of study drug;

[3] In case of early discontinuation the procedure may be performed at visits 1-7.

3) absence of any patient data after administration of study drug.

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 study therapy.***

Per Protocol set. This sample includes all patients who received full protocol therapy and completed all scheduled visits. This set will be used for ***Per Protocol analysis (PP analysis) of efficacy of study therapy***. *Per Protocol set* will not include the patients 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/issue of the study drug.
3. Prescription of prohibited therapy.
4. Increase or decrease of 25% or more in the amount of study therapy received.
5. Inability to assess patient's objective compliance (adherence to therapy) according to the formula (e.g. loss of packaging).
6. Major discrepancies between source documents and CRF detected during monitoring or other authorized inspection.
7. Violations of the Informed consent procedure.
8. Non-compliance with the clinical study protocol procedures.
9. Inability to collect all patient'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. Other protocol deviations resulting in full or partial data invalidity.

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software.[4]

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 a type I error is less that 5% (the probability of false acceptance of the alternative hypothesis is less than 0.05)
   - 1.3 type 1 error is distributed between the primary and secondary criteria in 1:1 ratio
   - 1.4 statistical criteria of comparisons will be two-sided, unless specified otherwise

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

1.5 calculation of the sample size will be based on the assumptions concerning the effect declared in the primary efficacy criterion of the protocol

1.6 ratio between Prospekta and Placebo sample sizes is 1:1 (1 Prospekta patient per 1 Placebo patient)

1.7 statistical hypotheses - null and alternative hypotheses on the difference between study drug and placebo under the dosing regimen used:

Primary endpoint:

$$\mathbf{H_0: \mu_1 - \mu_2 = 0}$$

$$\mathbf{H_a: \mu_1 - \mu_2 \neq 0}$$

where μ_1 - change in total MoCA score in Prospekta group, μ_2 - change in total MoCA score in Placebo group

Secondary endpoint:

$$\mathbf{H_0: \mu_1 - \mu_2 = 0}$$

$$\mathbf{H_a: \mu_1 - \mu_2 \neq 0}$$

where μ_1 - change in total NPI-C score in Prospekta group, μ_2 - change in total NPI-C score in Placebo group

1.8 calculation of sample size for statistical criteria was made using the following program code:

Proc seqdesign errspend;

Design nstages = 2

Info = cum (0.3,1)

Method (alpha) = UNI (rho = 0.5 tau = 0)

Method (beta) = UNI (rho = 0 tau = 0)

Stop = both

Alpha = 0.025

Beta = 0.2

Samplesize model = twosamplemean (meandiff = 1.3 stddev = 3.53)

Run

1.9 Full sample size will be determined using the formula:

$$N_T = N_{PP}/(1 - K_B)$$

where N_T – full sample size; N_{PP} – result of calculation in c. 1.8, i.e. scheduled number of patients completing the study per protocol; K_B – withdrawal rate.

2. Assumptions on expected treatment effects.

It is assumed that the difference between the changes in the mean total MoCA score in the Prospekta and Placebo after 24 weeks of treatment will be 1.3 points with a standard deviation of at least 3.53[5].

Therefore, group size needed to compare Prospekta and Placebo will be **162** subjects for each group. Given potential withdrawal of at least 20% patients (**K_B = 0.2**) during the study for various reasons, at least **406** subjects will be required to sign informed consent, with **203** patients per group (see cl. 1.9).

Minimum detectable effect for secondary criterion (change in total NPI-C score) at fixed sample size is supposed to be equal to: 7.36 (this being lower than clinically relevant change) at standard deviation of total score of 20 [13][6].

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.

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 methods and approaches are supposed to be used:

1. To evaluate the differences in continuous variables obtained in one group at two different visits – Student t-test for paired samples.
2. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or covariance (ANCOVA) modified with 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).

[5] The data were obtained from MMH-MAP-001trial blinded interim analysis.
[6] Assessment is based on bibliographic data in assumption, uniformity of mean change from time and reduction in correlation of measurements over time.

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 studying temporal dynamics (ANOVA, ANCOVA)
- GENMOD – generalized linear models
- MIXED – mixed linear models.

Non-parametric criteria

Below are the main potential types of comparisons with relevant criteria:

1. To evaluate time changes in the parameters compared – Friedman test, non-parametric analogue of analysis of variance with repeated measures.
2. For frequency analysis of contingency tables 2×2 – $\chi 2$ (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 $\chi 2$ 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 non-parametric statistical analysis the following SAS procedures are to be used:

- FREQ – Friedman test, $\chi 2$ 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 treatment.

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.

Incomplete/missing data

Missing data not requiring the patient exclusion from analysis will be processed as follows:

1. For sections of descriptive statistics the missing/incomplete data will be ignored specifying the number of complete and incomplete data points.
2. Efficacy criteria - after unblinding the interval data will be filled with the relevant **group median value**, categorical data - according to **worst case** approach. Prospekta group - worst outcome, Placebo group - best outcome. If allowed by the type of missing values (MCAR, MAR, etc.) and the type of variable, **multiple imputation** may be used.
3. Additional criteria will be processed similar to descriptive statistics.