Multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of Divaza for adjustment of oxidative disorders in patients with cerebral atherosclerosis

Phase IV

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-DV-010**
Version date:	**December 05, 2017**

ClinicalTrials.gov Id: NCT03485495

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

Multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of Divaza for adjustment of oxidative disorders in patients with cerebral atherosclerosis

Phase: IV

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

Protocol No. MMH-DV-010

Objective of the study

- To obtain additional data on efficacy and safety of Divaza for adjustment of oxidative disorders in patients with cerebral atherosclerosis.

Endpoints

Primary endpoint

- Change in mean value of lipoprotein resistance to LP after 12-week therapy vs. baseline.

Secondary endpoint

- Proportion of patients with improved cognitive function (MoCA score + 1 or more) after 12-week therapy versus baseline.

Exploratory endpoints

- Change in mean level of preformed LP products, predominantly lipid hydroperoxides after 12-week therapy versus baseline.
- Change in mean value of lipoprotein ability for oxidation after 12-week therapy versus baseline.
- Change in mean value of NO product serum concentration after 12-week therapy versus baseline.
- Change in mean value of platelet aggregation after 12-week therapy versus baseline.
- Change in mean IMCT value after 12-week therapy versus baseline.

Safety assessment

- Occurrence and nature of adverse events during the therapy, their intensity (severity), causal relationship to the study drug, and outcome.

Study design

Design – a multicenter randomized double-blind placebo-controlled parallel-group clinical trial.

The study will enroll the patients of either gender aged 40-75 years old inclusively with verified atherosclerotic cerebrovascular lesions (ICD-10 code – "Cerebral atherosclerosis" [I67.2]), with cognitive disorders (MoCA<26), without relevant incapacity (mRs≤1).

At screening visit (Visit 1, from day - 5 to day 0), after signing patient information sheet (informed consent form) for participation in the clinical study the patient's complaints and medical history will be collected and objective examination will be carried out. The investigator will assess intensity of cognitive disorders using MoCA, extent of functional capacity using mRs[1].

If the patient meets inclusion criteria and has no exclusion criteria at Visit 2 (Day 0) he/she will be randomized to one of two groups: group 1 will receive Divaza at 2 tablets 3 times a day; group 2 - placebo using study drug scheme.

Laboratory examination will be performed.

1. oxidant and antioxidant systems (Fe^{2+}-induced chemoluminescence method, ELISA) defining:

1.1. level of preformed LP products, predominantly lipid hydroperoxides;

1.2. low and very low density lipoprotein resistance to LP;

1.3. lipoprotein potential for oxidation;

1.4. serum NO product concentration (Griess reaction).

2. compensatory potential of endothelium and its ability for adequate regulation of vascular tone with[2]:

2.1. determination of platelet aggregation with bandage sign;

2.2. MAH duplex scanning.

Procedures of Visit 2 may be performed on day of Visit 1 if general rules for blood collection are met, at that previously performed procedures will not be repeated.

[1] If applicable.

[2] Will be performed in FSBRI Research Center of Neurology only.

The first administration of Divaza or Placebo will be performed at Visit 2 at medical site in the investigator's presence. The patient monitoring and therapy will last for 12 weeks during which 3 additional visits will be made.

At Visit 3 (Week 4±5 days) the investigator will collect the complaints, perform objective examination, evaluate intensity of cognitive disorders (MoCA). The investigator will monitor the prescribed, basic and concomitant therapy, evaluate therapeutic safety.

At Visit 4 (Week 8±5 days) the investigator will make a phone call to the patient to evaluate safety of the treatment.

At the final Visit 5 (Weeks 12±5 days) the investigator will evaluate intensity of cognitive disorders (MoCA). Laboratory examination of oxidant and antioxidant systems, compensatory potential of endothelium and its potential for adequate vascular tone regulation. The investigator will monitor the prescribe, basic and concomitant therapy, evaluate therapeutic safety and treatment compliance.

During the study basic, concomitant therapy will be allowed except for the products indicated in the section "Prohibited concomitant therapy".

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of both genders aged 40-75 years old inclusive.
2. Diagnosis of cerebral atherosclerosis verified by all three signs:
    - underlying vascular disease (atherosclerosis and/or hypertension) and focal neurological symptoms combined with cerebral symptoms (headache, dizziness, tinnitus, impaired memory, working capacity);
    - ultrasound signs of atherosclerotic cerebrovascular lesions (according to MAH duplex scanning within 6 months preceding the patient enrollment into the study);
    - signs of morphological changes in the brain based on neuroimaging (CT/MRI 1.0-1.5 T) (subcortical and periventricular leukoaraiosis and/or focal changes in grey matter and white matter in the form of postischemic cysts and/or lacunar strokes and/or diffuse atrophic changes in the form of dilated cardiovascular system or subarachnoidal spaces).
3. Cognitive disorders (MoCa <26).
4. Patients with unchanged dose and combination of basic therapy of cerebral atherosclerosis and hypertension during the previous month.
5. Patients who gave their consent to use reliable contraception during the study.
6. Availability of signed patient information sheet and informed consent form for participation in the clinical trial.

Exclusion criteria

1. History of subarachnoidal/parenchymatous/ventricular hemorrhage, cerebral tumour or another disease resulting in neurological disorders.
2. Ischemic-type stroke or any other acute cerebrovascular accident less than 6 months prior to the study with Modified Rankin Scale (mRs) > 1[3].
3. Cardiac sources of high risk or medium risk embolism (TOAST criteria).
4. Signs of acute or exacerbated chronic infectious diseases at or less than 2 weeks prior to screening.
5. History of CNS diseases including:
    - Inflammatory CNS diseases (G00-G09)
    - Systemic Atrophies Primarily Affecting the CNS (G10-G13)
    - Other degenerative diseases of the nervous system (G30-G32)
    - Demyelinating diseases of the CNS (G35-G37).
6. Dementia (F00–F03).
7. Previously diagnosed cardiovascular diseases with functional class III or IV (according to New York Heart Association, 1964).
8. Hypothyroidism, diabetes mellitus and other somatic diseases at decompensation stage.
9. Uncontrollable hypertension: SBP > 180 mm Hg and/or DBP > 110 mm Hg.
10. Diseases of lower limb veins (lower limb varicose veins, deep venous thrombosis, etc.) at decompensation stage.
11. Any other severe concomitant pathology which, according to the investigator, may interfere with the patient's participation in the study.
12. History/suspicion of oncology of any location (except for benign neoplasms).
13. Allergy/intolerance of any component of the drug products used in the therapy.
14. Hereditary lactose intolerance.
15. Malabsorption syndrome, including congenital or acquired lactase deficiency (or any other disaccharidase deficiency) and galactosemia.
16. Pregnancy, breast-feeding.
17. History of treatment non-compliance, psychiatric disorders, alcoholism or drug abuse which, according to the investigator, may interfere with the study procedures.
18. Use of any medicine indicated in the section "Prohibited concomitant treatment" within 1 month prior to enrollment.
19. Participation in other clinical trials in the previous 3 months.

[3] If the patient did not have a stroke, this scale will not be filled.

20. Patients who are related to any of the on-site research personnel directly involved in the study or are an immediate relative of the study investigator, or has another conflict of interests. ‘Immediate relative’ means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
21. Patients who work for OOO “NPF “MATERIA MEDICA HOLDING” (i.e. the company's employees, temporary contract workers, appointed officials responsible for carrying out the research or immediate relatives of the aforementioned).

Criteria for Withdrawal or Termination

1. Screening failure.
2. Acute or exacerbated chronic infectious or inflammatory disease with the symptoms persisting for more than 7 days.
3. Modification of the dose and/or combination of basic products.
4. Patient's inability or refusal to follow protocol requirements.
5. Necessity in medical products prohibited within the study.
6. Development of adverse event requiring cancellation of the study drug.
7. Incorrect inclusion of ineligible patient.
8. Pregnancy.
9. Desire of patient to complete the study ahead of schedule for any reason.
10. Participation in another clinical study.
11. Cases not specified by the protocol where the investigator decides that further participation may harm the patient.
12. Unblinding.

Number of subjects

It is planned to include 124 subjects which is expected to allow completion of all protocol procedures by at least 98 subjects (49 in each group).

Interim analysis

The protocol does not schedule any unblinded interim analyses, however, at the sponsor’s decision a 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: Divaza

Active ingredient: Affinity purified antibodies to brain-specific S-100 protein - 0.006 g*; affinity purified antibodies to endothelial NO synthase - 0.006 g*

Excipients: Lactose monohydrate (lactose) - 0.267g; microcrystalline cellulose - 0.03 g; magnesium stearate - 0.003 g

Method of administration: Tablet for oral use. Two tablets per intake 3 times a day (approximately at the same time), outside of meal (between meals or 15 minutes before eating or drinking). The tablets should be held in mouth until completely dissolved.

Dosage form: Tablets

Description: Scored and beveled flat cylindrical tablets, white to off-white

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

Group 2

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: Lactose monohydrate (lactose) - 0.267 g, microcrystalline cellulose - 0.03 g; magnesium stearate - 0.003 g

Method of administration: Tablet for oral use. Two tablets per intake 3 times a day (approximately at the same time), outside of meal (between meals or 15 minutes before eating or drinking). The tablets should be held in mouth until completely dissolved.

Dosage form: Tablets

Description: Scored and beveled flat cylindrical tablets, white to off-white

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

Prohibited concomitant therapy

One month prior to enrollment and during the study (beginning from signing informed consent form and initiation of screening) it is prohibited to administer any therapy affecting neurological and oxidative status of the patient:

1. Products manufactured by OOO "NPF "Materia Medica Holding": Tenoten, Kolofort, Brizantin, Proproten, Afalaza, Impaza.
2. Antihypoxants and antioxidants including:
   - vitamin E and its derivatives – α-tocopherol acetate, etc.
   - vitamin C and its derivatives – ascorbic acid, ascovit, etc.

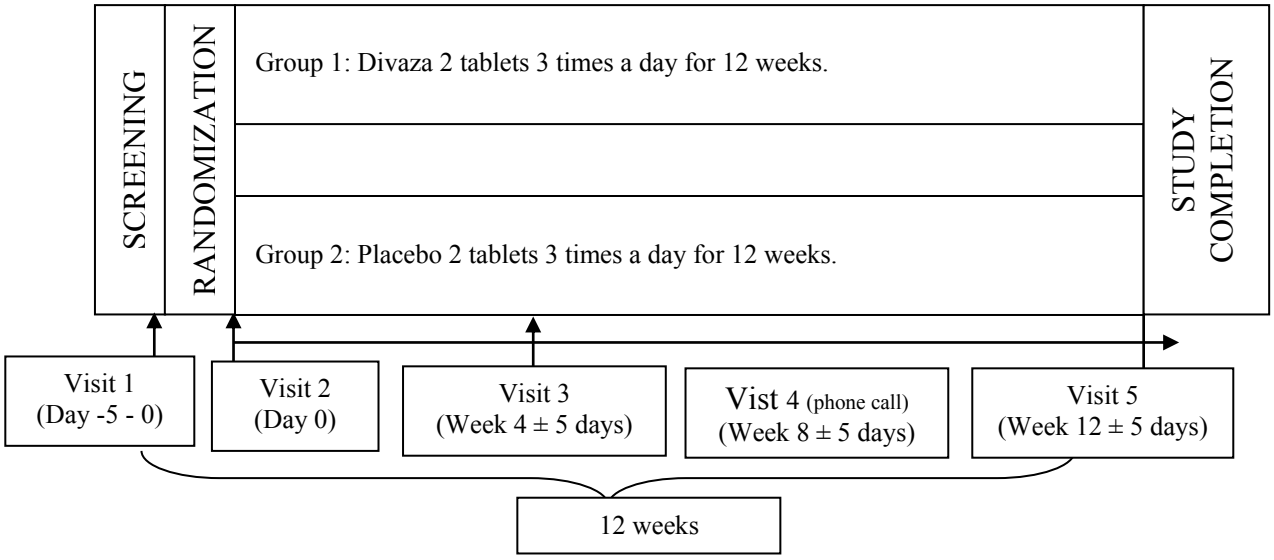
- vitamin A and its derivatives – retinol etc.
- glutathione
- deproteinized fetal hemoderivative - actovegin
- dihydroquercetin
- dimethyloxobutylphosphonyldimethylate derivative – dimephosphon
- carnitine and its derivatives - carnitine chloride
- oxygen
- levocarnitine and its derivatives – carniten, carnifit, levocarnil, elcar
- methylethylpyridinol and its derivatives – vixipin, cardioxipin, emoxipin, etc.
- morpholinyl-methyl-triazolyl thioacetate derivatives – thiotriazoline
- meldonium derivatives - mildronate
- sodium oxybutyrate
- sodium fumorste derivatives - confumin
- oxyethylammonium methylfenoxyacetate deritvatives – trecresan
- pentahydroxyethylnaftoquinone derivativrs – histochrome, echinochrome
- polydihydroxyphenylene thiosulfonate sodium – hypoxen, olifen, etc
- superoxide dismutase – rexod etc.
- thioctic acid derivatives – neurolipon, octolipen, polition, thiogamma, espalipon
- trimethazine and its derivatives – preductal, rimecod, trimectal, triducard, etc.
- pumpkin-seed oil – peponen, etc.
- ubidecarenone and its derivatives – kudesan, kudevita, etc.
- phenazone acid
- cytochrome C
- ethylmethyhydroxypyridine malate derivatives – ethoxydol
- ethylmethylhydroxypyridine succinate and its derivatives – mexidol, mexicor, mexiprim, neurox, cerecard, etc.
- ethylthiobenzimidazole hydrobromide.

3. Other antioxidants including:
   - acetylcysteine and its derivatives – fluimucil, mucobene, etc.
4. Peripheral vasodilating agents (ATC group C04) including nicotinic acid and its derivatives; purines (xanthinol nicotinate, pentoxyphylline), ergot alkaloids (nicergoline, α-dihydroergocriptine + caffeine), other vasodilating agents (vincamine, bencyclane, naftidrofuryl), papaverine, etamivan + etophylline + hexobendine.
5. Calcium channel blockers − nimodipine (C08CA06), instenone(C01EX).
6. Anticholinergic agents (N04A).

7. Dopaminergic agents (N04B).
8. Psycholeptics (N05) including anxiolytics (tranquilizers), hypnotics and sedative agents.
9. Psychoanaleptics (N06) including antidepressants, psychostimulants and nootropic agents including:
   - pyrrolidine derivatives (racetams) – piracetam, etiracetam, aniracetam, etc.
   - dimethylaminoethanol derivatives (acetylcholine precursors) – deanol aceglumate, meclofenoxate
   - pyridoxine derivatives – pyritinol, biotredin
   - derivatives and analogues of GABA – gamma-aminobutyric acid, nicotinoyl γ-aminobutyric acid, γ-amino-beta-phenylbutyric acid hydrochloride, hopantenic acid, calcium γ-hydroxybutyrate
   - ginkgo biloba
   - neuropeptides and their analogues - methyonyl-glutamyl-histidyl-phenylalanyl-prolyl-glycyl-proline
   - amino acids and substances affecting the system of excitatory amino acids – glycine, pyridoxine+threonine
   - derivatives of 2-mercaptobenzimidazole – ethylthiobenzimidazole hydrobromide
   - idebenone
   - vinpocetine derivatives - cavinton
   - choline alfoscerate derivatives - cerepro
   - popypeptides and organic composites - polypeptides of the cerebral cortex of cattle, cerebrolysin
   - cytoflavin.
10. Other products for the treatment of nervous system diseases (N07) including:
   - parasimpathomimetics (N07A)
   - antivertigo preparations (N07C)
   - other nervous system drugs (N07X).
11. The substances from other pharmacological groups with nootropic effect including:
   - general tonic agents and adaptogens – ginseng, melatonin, lecithin, acetylaminoauccinic acid, etc.
   - metabolic agents.
12. Corticosteroids for systemic use (H02A).
13. Corticosteroids for systemic use, combinations (H02B).
14. Homeopathic agents.
15. Any unregistered product and/or vaccine..

16. The products to which the patient had previously an allergic reaction.

Study design scheme



Schedule of study procedures

Visit / *Procedure*	**Visit 1 (from day -5 to day 0) Screening**	**Visit 2[4] (Day 0) Randomization**	**Visit 3 (Week 4 ± 5 days)**	**Visit 4 (phone call) (Week 8 ± 5 days)**	**Visit 5 (Week 12 ± 5 days)**
Informed consent	+				
Study subject registration in IVRS and assignment of a personal code	+				
Collection of complaints	+	+	+	+	+
Medical history	+				
Recording concomitant conditions and diseases	+	+			
Objective examination	+	+	+		+
Vital signs (HR, BR, BP)	+	+	+		+
Concomitant therapy	+	+	+	+	+
Inclusion/exclusion criteria	+				
Appointment of visit	+	+	+	+	
Randomization		+			
Study drug supply		+	+		
Study drug accountability and return, compliance assessment			+		+
Evaluation of treatment safety		+	+	+	+
Completing the Montreal Cognitive Assessment Scale	+		+		+

[4] If Visit 1 and Visit 2 procedures are performed on the same day, repeated procedures are not required.

(MoCA)					
Completing the Modified Rankin Scale (mRs)[5]	+				
Venous blood sampling for testing:		+			+
- levels of preformed LP products, predominantly lipid hydroperoxides		+			+
- low and very low-density lipoprotein resistance to LP		+			+
- lipoprotein ability for oxidation		+			+
- serum levels of NO products		+			+
- platelet aggregation with bandage sign[6]		+			+
Duplex MAH scanning[7]		+			+
Pregnancy test [8]	+				
End of patient participation in the study	+	+	+	+	+

Statistical Analyses

Samples

Total set includes all the patients who have signed ICF. This sample will consider all adverse events 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 adverse events 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) noncompliance with inclusion/exclusion criteria;
2) patient failing to take any dose of the study drug;
3) lack of any data on the patient after the study drug administration.

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

Per Protocol set. This sample includes all patients who completed the therapy as per the study protocol, without any missing visits or major protocol deviations. This set will be used in the ***Per Protocol efficacy analysis of the test therapy.***

[5] If applicable.
[6] Will be performed for the patients in FSBRI Research Center of Neurology only.
[7] Will be performed for the patients in FSBRI Research Center of Neurology only.
[8] If applicable.

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 supply of the study drug.
3. Prescription of prohibited therapy.
4. ≥ 25% increase or reduction in the amount of the study therapy administered.
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. Violation of the procedure for obtaining Informed consent.
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. 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.[9]

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 I error ' α ' is less that 5% (the probability of false acceptance of the alternative hypothesis is less than 0.05);
   - 1.3 statistical criteria will be two-sided;
   - 1.4 calculation of sample size will be based on the assumptions on the expected effect declared in the primary and secondary endpoints of the protocol;
   - 1.5 ratio between Divaza and Placebo sample sizes is 1:1 (1 Divaza subject per 1 Placebo subject);
   - 1.6 statistical hypotheses will be as follows:
     - Binary values:

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null and alternative hypotheses on superiority of the study product under the dosing scheme used:

$$H_0: p_1=p_2$$

$$H_a: p_1\neq p_2$$

p_1 – proportion of patients in Divaza group with ≥ 1 improvement

p_2 – proportion of patients in Placebo group with ≥ 1 improvement

- Interval values

null and alternative hypotheses on superiority of the study product under the dosing scheme used:

$$H_0: \Delta\mu_1=\Delta\mu_2$$

$$H_a: \Delta\mu_1\neq\Delta\mu_2$$

where $\Delta\mu_1$ – mean reduction (initial – final score) in Divaza group

$\Delta\mu_2$ – mean reduction (initial – final score) in Placebo group;

1.7 calculation of sample size for statistical criteria will be made using the following formulas:

- Binary values:

$$n_1 = kn_2$$

$$n_2 = \frac{\left(z_{\frac{\alpha}{2}} + z_\beta\right)^2}{\epsilon^2}\left[\frac{p_1(1-p_1)}{k} + p_2(1-p_2)\right]$$

where n_1, n_2 are sample sizes for Divaza and Placebo groups

$\epsilon = p_1-p_2$ – expected difference between proportions of subjects with improvement in Divaza and Placebo groups

k – ratio of sample sizes (in this study equal to 1)

$z_{\alpha/2}$ – tabular value of two-sided z-criterion for α

$\backslash z_\beta$ – tabular value of one-sided z-criterion for β;

- Interval values:

$$n_1 = kn_2$$

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

where n_1, n_2 are sample sizes for Divaza and Placebo groups, respectively

$\varepsilon = \Delta\mu_1-\Delta\mu_2$ – expected difference between mean reductions of value between Divaza and Placebo groups

k – ratio of sample sizes (in this study k=1)

σ – standard deviation of reduction

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

z_{β} – tabular value of one-sided z-criterion for **β**;

1.8 the largest of the samples meeting the primary endpoint will be used for terminal PP sample size

$$N_{PP}=\max(n_1, n_2, \ldots, n_i);$$

1.9 final sample size will be determined using the formula:

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

where N_T – final sample size;

N_{PP} – result of calculation in cl. 1.7 – cl. 1.8, i.e. the scheduled number of the patients completing the study per protocol

C_w – withdrawal coefficient.

2. Assumptions on expected clinical study effects.

Primary endpoint: difference in changes in activity of endogenous antioxidant protection between Divaza and Placebo groups will be no less than **ε**=20.36 s at standard deviation of **σ**=32.1.

Secondary endpoint: Proportion of patients with reduced total MoCA score ≥ 1 in Divaza group will be no less than 82%, while in Placebo group the relevant value will be no more than 50%.

3. Total type I error is divided equally between the primary and secondary criteria.

To evaluate superiority of Divaza over Placebo, group size will be (**49, 42**) patients for each group, respectively, for the primary and secondary criteria.

Given potential withdrawal of at least 20% subjects (R_w**=0.2**) during the study for various reasons, at least **124** patients will be required to sign informed consent, with **62** patients per group.

Statistical criteria

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

- parametric - to evaluate continuous and interval random values;
- nonparametric – to obtain:
  - evaluations of equality/inequality in the proportion of the patients upon their comparison for various visits,
  - analysis of frequencies of the features compared,

  and

- evaluation of continuous and interval random values in case of non-compliance with normal random distribution.

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 paired samples.
2. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or modified repeated measures covariance (ANCOVA).
3. In case of multiple comparisons of the groups various adjustments for multiplicity will be used (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 – $\chi 2$ (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 nonparametric 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 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.