Statistical Analysis Plan

International multicentre randomised double-blind placebo-controlled adaptive design clinical trial to evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) in patients with chronic cerebral ischemia (MEMO)

NCT Number: NCT06834490

Pharmasoft

November 06, 2020

Plan of statistical analysis of efficacy and safety parameters, version 2.0 dated 06.11.2020, according to the results of "International multicentre randomised double-blind placebo-controlled adaptive design clinical trial to evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) in patients with chronic cerebral ischemia (MEMO)" under protocol #PHS-CICADIS-005-MEX-SOL-TAB, version 5.0 dated 30.04.2020.

Yaroslavl - 2020

Approval sheet for the Plan of statistical analysis of efficacy and safety parameters, version 2.0 dated 06.11.2020, according to the results of "International multicentre randomised double-blind placebo-controlled adaptive design clinical trial to evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) in patients with chronic cerebral ischemia (MEMO)" under protocol #PHS-CICADIS-005-MEX-SOL-TAB, version 5.0 dated 30.04.2020.

Project Manager

A.A. Khokhlov (signed)	06.11.2020
signature	date

Statistician

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signature	date

Responsible Sponsor's representative

signature	date

Table of Contents

List of tables

List of abbreviations

ANOVA - Analysis of variance;

BAI - Beck Anxiety Inventory;

CGI - Clinical Global Impressions Scale;

GCP - Good clinical practice;

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Medicinal Products for Human Use;

ITT - Intention to treat;

MedDRA - Medical Dictionary for Regulatory Activities;

MFI-20 - Multidimensional Fatigue Inventory;

PP - Per Protocol, the population of patients who completed the trial according to the protocol;

SF-36 - quality of life assessment questionnaire;

SOC - System Organ Class MedDRA;

T° - body temperature;

TESS - Treatment Emergent Signs and Symptoms;

BP - Blood Pressure;

ALT - alanine aminotransferase;

AST - aspartate aminotransferase;

CI - confidence interval;

BMI - Body Mass Index;

CRF – Case Report Form;

AE - Adverse event;

ESR - erythrocyte sedimentation rate;

SAE - serious adverse event;

HR - respiratory rate;

HR - heart rate;

CCI - chronic cerebral ischaemia;

ECG - electrocardiography.

The statistical tables will provide the following parameters for descriptive statistics:

N - number of valid cases;

M - arithmetic mean;

95% CI, L - the lower boundary of the 95% confidence interval;

95% CI, U - the upper limit of the 95% confidence interval;

Me - median;

Min - minimum value;

Max - maximum value;

Q_1 - lower quartile;

Q_3 - upper quartile;

Range - range of variation;

QRange - interquartile range;

SD - standard deviation;

CV - coefficient of variation.

1. Trial background

Title: International multicentre randomized double-blind placebo-controlled adaptive design clinical trial to evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC Pharmasoft LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC Pharmasoft LLC, Russia) in patients with chronic cerebral ischemia (MEMO)

Protocol No.: PHS-CICADIS-005-MEX-SOL-TAB

Version: 5.0 dated 30.04.2020.

Sponsor: RPC PHARMASOFT LLC, Russia

Investigational product: Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (Pharmasoft, Russia) and Mexidol® Forte 250 film-coated tablets, 250 mg (Pharmasoft, Russia)

Comparator product: NaCl 0.9% solution for intravenous and intramuscular administration and placebo film-coated tablets identical to the investigational product

Trial design: international multicentre randomized placebo-controlled adaptive design clinical trial

Number of patients: 318 (for the first phase)

Type of Trial: Phase III Trial (efficacy and safety trial)

Trial purpose:

To evaluate the efficacy and safety of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (Pharmasoft, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (Pharmasoft, Russia) in patients with chronic cerebral ischemia

Trial objectives:

1. To assess the dynamics of cognitive impairment reduction using the MoCA scale.
2. To assess the dynamics of the patients' quality of life using the SF-36 questionnaire.
3. To assess the dynamics of asthenic disorders detection using the MFI-20.
4. To assess the dynamics of the level of anxiety on the Beck Anxiety Inventory.
5. To assess the dynamics of autonomic changes according to the Wein questionnaire.
6. To assess the safety of therapy with the investigational products based on the presence and severity of adverse events recorded during the trial.
7. To assess the dynamics of cognitive impairment by the Digit Symbol Substitution Test.
8. To assess the dynamics of motor disorders using the Tinetti test
9. To assess the dynamics of the overall clinical impression using The Clinical Global Impressions Scale

Criteria for assessing efficacy and safety:

Primary efficacy criterion:

Mean change in Montreal Cognitive Assessment Scale (MoCA) score at patient completion of the erial (Visit 5) vs. baseline (Visit 0).

Secondary efficacy criteria:

- Dynamics of the severity of cognitive impairment on the MoCA scale between Visit 0 and Visits 2 and 4.

- Dynamics of patients' quality of life according to the SF-36 questionnaire between Visit 1 and Visits 2, 4, 5.
- Dynamics of asthenic disorders severity according to the MFI-20 between Visit 1 and Visits 2, 4, 5.
- Dynamics of anxiety level on Beck Anxiety Inventory between Visit 1 and Visits 2, 4, 5.
- Dynamics of autonomic changes according to the Wein questionnaire between Visit 1 and Visits 2, 4, 5.
- Dynamics of cognitive impairment by the Digit Symbol Substitution Test between Visit 1 and Visits 2, 4, 5.
- Dynamics of motor changes on the Tinetti test between Visit 1 and Visits 2, 4, 5.
- Dynamics of the Clinical Global Impressions Scale (The Clinical Global Impressions Scale) between Visit 1 and Visits 2, 5.

Safety criteria:

Safety of therapy with the investigational product based on the presence and severity of adverse events recorded during the trial at all visits.

2. Purpose of data statistical analysis

The purpose of developing this Statistical Analysis Plan is to describe the planned data analysis for Protocol #PHS-CICADIS- 005-MEX-SOL-TAB, version 5.0 dated 30.04.2020, for inclusion of the results in the Clinical Trial Report.

The results obtained according to the planned statistical analysis of the data presented in this document will be used in the submission of the registration dossier for the drug to the regulatory authorities, as well as in the writing of publications on the materials of the conducted clinical trial.

Plan for statistical analysis of efficacy and safety parameters

This trial is being conducted in accordance with:

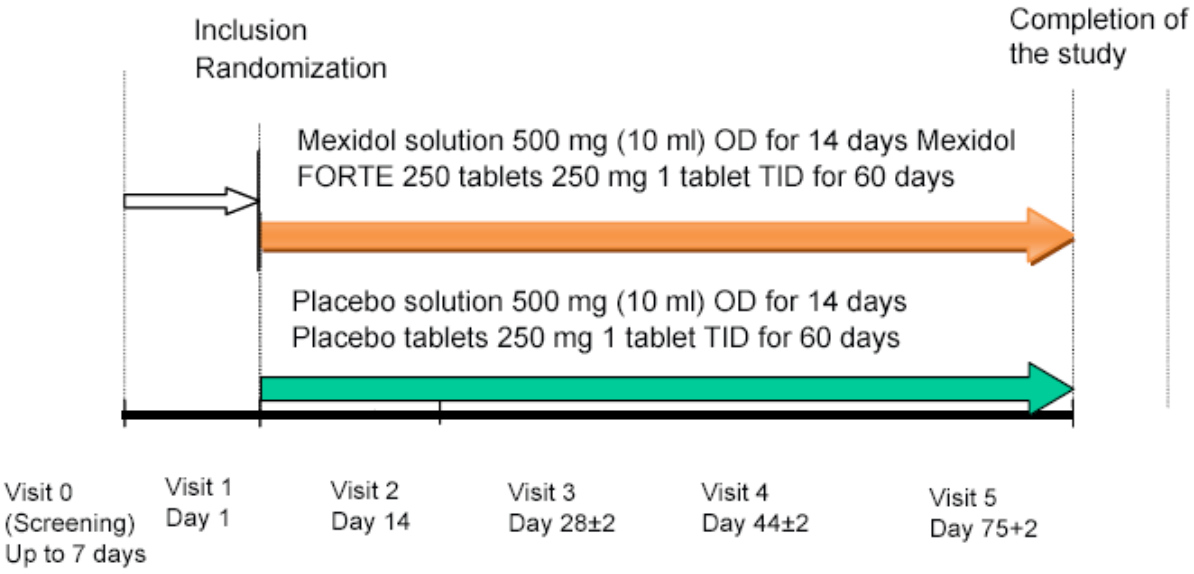
- Clinical Trial Protocol, in strict compliance with the Constitution of the Russian Federation;
- Ethical principles of the 1964 Declaration of Helsinki of the World Medical Association, as revised in 2013.
- Federal Law N 61-FZ dated 12 April 2010 "On Circulation of Medicines" (current version);
- National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice";
- Order of the Ministry of Health of the Russian Federation No. 200n dated 01 April 2016 "On Approval of the Rules of Good Clinical Practice";
- Resolution of the Government of the Russian Federation dated 13 September 2010 N 714 "On Approval of Standard Rules for Compulsory Life and Health Insurance for Patients Participating in Clinical Trials of a Medicinal Product" (current version);
- Order of the Ministry of Health of the Russian Federation No. 986n of 29 November 2012 "On Approval of the Regulations on the Ethics Council";
- Decision of the Council of the Eurasian Economic Commission of 03.11.2016 No. 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union".

Statistical evaluation of efficacy and safety parameters will be performed in accordance with the Drug Evaluation Guidelines (Volume I. - FGBU NCESMP, Moscow, 2014), Guidelines on the principles of application of biostatistics in clinical trials of medicinal products (Annex to the recommendation of the EEC Collegium from 03.11.2020 No. 2014) and general recommendations on biomedical statistics (ICH Topic E9 Statistical Principles for Clinical Trials, CPMP/ICH/363/96, 1998; Sergienko V.I., Bondareva I.B. Mathematical Statistics in Clinical Trials, Moscow: GEOSTAR-Media, 2006; Glantz S. Medical and Biological Statistics, Moscow: Practice, 1999).

3. Deviations from protocol

All changes to the original statistical plan with their rationale will be reflected in the Clinical Trial Report. No changes will be made to the list of parameters to be evaluated. If there is a deviation from the planned statistical analysis, all changes will be identified compared to the methods described in the statistical analysis plan. Similarly, if any additional changes are required after the analysis has been performed, this will be reflected in the Clinical Trial Report.

4. Trial procedures



5. Randomization

Table 1. Randomization scheme

Patient randomization number	Group
01	2
02	1
03	1
04	2
05	2
06	1
07	1
08	2
09	1
10	1
11	2
12	2
13	1
14	2
15	1
16	1
17	2
18	2
19	2
20	1
21	2
22	2
23	1
24	1
25	1
26	2
27	2
28	1

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
29	2
30	1
31	1
32	1
33	2
34	1
35	2
36	2
37	1
38	2
39	2
40	2
41	1
42	1
43	1
44	2
45	1
46	1
47	2
48	2
49	2
50	1
51	1
52	1
53	2
54	2
55	2
56	1
57	1
58	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
59	1
60	2
61	1
62	1
63	2
64	1
65	2
66	2
67	1
68	1
69	1
70	2
71	2
72	2
73	1
74	2
75	1
76	1
77	2
78	2
79	2
80	1
81	1
82	2
83	1
84	2
85	1
86	1
87	1
88	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
89	2
90	2
91	2
92	1
93	1
94	1
95	2
96	2
97	2
98	2
99	2
100	1
101	1
102	1
103	1
104	1
105	2
106	1
107	2
108	2
109	1
110	2
111	2
112	2
113	1
114	1
115	2
116	1
117	2
118	1

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
119	2
120	1
121	1
122	1
123	2
124	2
125	2
126	1
127	2
128	2
129	1
130	2
131	1
132	1
133	1
134	1
135	2
136	2
137	1
138	2
139	2
140	1
141	1
142	2
143	2
144	1
145	1
146	1
147	1
148	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
149	2
150	2
151	1
152	2
153	2
154	1
155	2
156	1
157	2
158	1
159	1
160	1
161	2
162	2
163	1
164	2
165	2
166	1
167	1
168	2
169	1
170	2
171	1
172	2
173	1
174	2
175	2
176	1
177	2
178	1

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
179	2
180	1
181	1
182	2
183	2
184	1
185	1
186	2
187	2
188	2
189	1
190	1
191	1
192	2
193	2
194	1
195	1
196	1
197	2
198	2
199	1
200	1
201	2
202	2
203	2
204	1
205	1
206	2
207	1
208	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
209	1
210	2
211	2
212	1
213	2
214	2
215	1
216	1
217	2
218	1
219	1
220	1
221	2
222	2
223	2
224	2
225	2
226	1
227	1
228	1
229	1
230	2
231	2
232	1
233	1
234	2
235	1
236	2
237	2
238	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
239	1
240	1
241	1
242	2
243	1
244	2
245	1
246	2
247	1
248	2
249	1
250	2
251	2
252	1
253	1
254	1
255	2
256	1
257	2
258	2
259	2
260	1
261	2
262	1
263	2
264	1
265	1
266	2
267	2
268	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group
269	1
270	1
271	2
272	2
273	1
274	1
275	2
276	1
277	1
278	2
279	1
280	1
281	2
282	2
283	1
284	1
285	2
286	2
287	2
288	1
289	2
290	1
291	1
292	2
293	2
294	1
295	2
296	1
297	1
298	2

Patient randomization number	Group
299	2
300	1
301	2
302	1
303	2
304	1
305	1
306	2
307	1
308	2
309	1
310	2
311	2
312	1
313	2
314	1
315	1
316	2
317	1
318	2

As it was not possible to use randomization numbers 295 to 306 and 315 to 318 in the electronic system for technical reasons, these numbers were replaced by additionally generated records (#319- 334), while maintaining balance across treatment groups. This procedure has been approved by the Trial Sponsor. The distribution of additional randomization numbers is shown in Table 2.

Table 2. Distribution of additional randomization numbers

Patient randomization number	Group
319	1
320	1
321	2
322	2
323	1
324	2
325	2
326	1
327	1
328	2
329	2
330	1
331	1
332	2
333	1
334	2

The double-blinding condition is observed throughout the trial. The treatment code for any patient may be opened by the investigator, Sponsor or their authorized persons only if absolutely necessary to establish the true nature of the intervention received. Blinding can only be removed if the patient's choice of subsequent treatment depends on the drug the patient has been taking.

The drug codes remain unknown to the Investigator until the database is closed. The full randomization scheme with transcription of drug codes is kept by the project manager and the medical writer until the database is closed.

6. Main and additional trial parameters to be assessed in the course of the trial

Efficacy will be evaluated using primary and secondary efficacy criteria.

The primary efficacy criterion **(primary endpoint**) is the mean change in Montreal Cognitive Assessment Scale (MoCA) score at patient completion of the trial (Visit 5) vs. baseline (Visit 0).

The primary efficacy variable will be analysed based on the statistical hypothesis of superiority. The primary efficacy variable will be analysed in the ITT population as well as in the PP population.

Two-sided confidence intervals will be used as part of the primary efficacy analyses. Differences will be considered statistically significant at the p level <0.05.

The secondary efficacy evaluation criteria chosen are:

- Dynamics of the severity of cognitive impairment on the MoCA scale between Visit 0 and Visits 2 and 4.
- Dynamics of patients' quality of life according to the SF-36 questionnaire between Visit 1 and Visits 2, 4, 5.
- Dynamics of asthenic disorders severity according to the MFI-20 between Visit 1 and Visits 2, 4, 5.
- Dynamics of anxiety level on Beck Anxiety Inventory between Visit 1 and Visits 2, 4, 5.
- Dynamics of autonomic changes according to the Wein questionnaire between Visit 1 and Visits 2, 4, 5.

- Dynamics of cognitive impairment by the Digit Symbol Substitution Test between Visit 1 and Visits 2, 4, 5.
- Dynamics of motor changes on the Tinetti test between Visit 1 and Visits 2, 4, 5.
- Dynamics of the Clinical Global Impressions Scale (The Clinical Global Impressions Scale) between Visit 1 and Visits 2, 5.

For statistical analysis of quantitative features, the conformity to the law of normal distribution will be preliminarily assessed using the Shapiro-Wilk test. For indicators whose distribution conforms to the law of normal distribution, the arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, and variation spread will be calculated as parameters of descriptive statistics. For indicators whose distribution will differ from normal, the median, 25th and 75th percentiles, minimum and maximum values, and interquartile range will be calculated as parameters of descriptive statistics. In order to test the hypothesis of homogeneity of variance, Levene's test will be applied. Comparative analyses of performance measures (quantitative variables) will be performed by comparing mean values reflecting clinically important patient parameters in the main and control groups. Comparison of the mean values of each parameter in the two groups will be made using the Mann-Whitney U-criterion (non-parametric statistics) or the Student's t-test (under normal distribution). Comparisons of the rates within the group before and after treatment will be made using the T-test for related samples, or the Wilcoxon criterion.

Plan for statistical analysis of efficacy and safety parameters

Qualitative traits can be analysed using Pearson's $\chi 2$ criterion, the $\chi 2$ criterion with Yates correction and Fisher's exact test (if the frequency of a trait in at least one of the subgroups is 5 or less). Differences with p values of <0.05 will be considered statistically significant.

Standard methods of descriptive statistics will be used to describe the demographic and clinical parameters of the trial population, which are determined by the type of parameters being described. Descriptive statistics will include mean, standard deviation, minimum and maximum values, - for quantitative variables; number, proportion, distribution - for qualitative variables.

Concomitant therapy drugs will be coded by generic name using the WHO dictionary of medicines. Medications will be listed by treatment group.

A subanalysis is planned for patients with diabetes mellitus and metabolic syndrome.

Subanalysis by age will be done with the formation of the following subgroups: 40-60 years old, 61-75 years old.

A subanalysis will be performed in patients with CCI that developed without a previous stroke and with CCI that developed after a previous stroke

An interim analysis will be conducted once efficacy and safety data from 318 patients are available. As part of the interim analysis, the primary efficacy criterion under trial will be evaluated.

For the intermediate analysis, the critical Z values will be 0.40 and 2.75, respectively. During the interim data analysis, Z is calculated from the current values of the effect size. If $|Z| \leq 0.40$, the trial will be stopped due to "futility" (futility: the effect of the investigational product is not strong enough according to the chosen endpoint, the null hypothesis could not be rejected). If $|Z| > 2.75$, the Trial will be stopped due to "superiority" and the null hypothesis will be rejected (the investigational product will be considered superior to placebo in terms of efficacy). Otherwise, the trial will be continued, the null hypothesis will be tested for the value of 1.96 for the full sample size: if $|Z| > 1.96$, it will be concluded that the null hypothesis is rejected, if $|Z| \leq 1.96$, it will be concluded that the trial failed to reject the null hypothesis. In such a case, a new version of the statistical analysis plan will be prepared with an updated randomization scheme for the full sample size. An updated version of the statistical analysis plan will be coordinated with the Sponsor. For the second stage, the sample size will be 300 people in one group (600 people in total).

All safety data will be analysed on the safety population.

Further analysis of AEs, including SAEs, will consist of determining the total number of AEs, total number of patients with AEs, number of AEs associated with the trial therapy, number of AEs that required cancellation of therapy or changes in therapy parameters, and number of patient-initiated dropouts.

The frequency and severity of both all AEs and drug-related AEs (i.e., with the association rated as at least "possible"). AEs will be coded according to MedDRA and will be classified using System Organ Classes and preferred term (SOC - System Organ Class MedDRA - the highest level of classification of AEs taking into account the etiology, localization of manifestations and classification objectives).

Frequency tables with data on discontinuation of therapy or changes in therapy parameters due to AEs will be presented. The choice of statistical criterion will be determined by the conformity/nonconformity to the normal distribution law and the dependence/independence of the samples being compared. Comparisons of safety performance between trial groups will be made using the χ-square test (for qualitative data) and the t-test for data whose distribution follows the law of normal distribution, or its non-parametric analogue (for data whose distribution does not follow the law of normal distribution). The Mann-Whitney U-criterion will be used as the non-parametric analogue of the t-criterion.

The feasibility of using a number of statistical methods will be assessed after data collection has been completed, as the nature of the data distribution, sample homogeneity, etc. is not known in advance. During the course of the analysis, the list of methods to be used may be modified and supplemented if necessary for the qualitative processing of the data.

7. Statistical hypothesis

In accordance with the aim of the trial, statistical analysis of the results is planned to compare the efficacy of the therapy regimen including Mexidol® and Mexidol® FORTE 250 in the treatment of patients with chronic cerebral ischemia.

The present trial intends to assess the efficacy of therapy by the mean difference in Montreal Cognitive Assessment Scale (MoCA) scores at patient completion and trial initiation.

The following statistical hypotheses will be tested:

- null hypothesis (H_0): the efficacy of therapy with the investigational product is not superior to the efficacy of therapy with placebo: H^0: $\mu_m - \mu_p \leq 0$,

where μ_m and μ_p - mean values of change on the Montreal Cognitive Function Assessment Scale in the main group (μ_o) and placebo group (μ_p);

- alternative hypothesis (Ha): the efficacy of therapy with the investigational product is superior to that of therapy with placebo:

H^A: $\mu_m - \mu_p > 0$.

8. Estimation of the required sample size

There is a lack of information in the open literature that allows for accurate estimation of a drug's effect size according to the primary endpoint chosen. For the above reason, a group sequential design will be used to optimize the determination of the required sample size. The trial can be conducted in two stages: the maximum sample size N is divided into two parts. After the first part of the patients have completed the trial, an interim analysis will be performed. If, based on the results of the interim analysis, the sample size is sufficient to reject the null hypothesis or prove that the null hypothesis cannot be rejected, the trial will be terminated early. Otherwise, the trial will be continued and the final decision to accept or reject the null hypothesis will be made based on the data obtained from the full sample of patients.

Plan for statistical analysis of efficacy and safety parameters

Since the objective of this trial is to demonstrate the superiority of the investigational product over placebo, an asymmetric design was chosen in the planning of the trial. The cost function ("spending function") for group sequential design was selected from the Hwang, Shihand De Cani family with values γ= - 2 and γ= - 4 for the β- and α-cost functions, respectively, defining the lower and upper bounds of the acceptable range. The search for the required sample size and boundary conditions was performed using the gsDesign module (v.2.4-01,2011, AndersonK.) of the statistical software package R v.3.5.2. Input data corresponded to a fixed sample size in a simple study with no interim analyses. Calculation of the sample size for the trial without interim analysis was done based on the following formula:

$$n = (Z_\alpha + Z_\beta)^2 \cdot \frac{2 \cdot SD^2}{(\mu_m - \mu_p)^2},$$

where Z_α and Z_β - critical values of the normal distribution corresponding to the established error levels α and β (α- and β-errors are 0.05 and 0.2, respectively); SD - standard deviation [3 - 5].

In estimating the sample size, the standard deviation was assumed to be 4.3 scores. The specified value of the standard deviation is the maximum possible value for the analysed performance indicator.

Assuming a difference in drug efficacy of at least 1 score, which corresponds to the minimum value of clinically significant differences, the calculation based on the above values ($Z\alpha$=1.96, Z^{β}=0.842, SD=4.3, $\mu_m - \mu_\rho = 1$) resulted in a sample size providing statistical power of the trial of at least 80%, equal to 291 patients in each group (582 patients in total).

Plan for statistical analysis of efficacy and safety parameters

In order to avoid inflation of first-order error and to maintain the stated power level, the total sample size in a trial with a group sequential design should be higher than in a trial without interim data analysis. According to the calculation made, the sample size for the first phase of the trial will be 150 people in one group (300 people in total), for the second stage - 300 people in one group (600 people in total). In case of possible patient attrition during the trial, 318 patients will be randomized for the first phase. Interim analyses will be performed after completion of the trial by the phase I patients.

For the intermediate analysis, the critical Z values will be 0.40 and 2.75, respectively. During the interim data analysis, Z is calculated from the current values of the effect size. If $|Z| \leq 0.40$, the trial will be stopped due to "futility" (futility: the effect of the investigational product is not strong enough according to the chosen endpoint, the null hypothesis could not be rejected). If $|Z| > 2.75$, the trial will be stopped due to "superiority" and the null hypothesis will be rejected (the investigational product will be considered superior to placebo in terms of efficacy). Otherwise, the trial will be continued, the null hypothesis will be tested for the value of 1.96 for the full sample size: if $|Z| > 1.96$, it will be concluded that the null hypothesis is rejected, if $|Z| \leq 1.96$, it will be concluded that the trial failed to reject the null hypothesis. In such a case, a new version of the statistical analysis plan will be prepared with an updated randomization scheme for the full sample size. An updated version of the statistical analysis plan will be coordinated with the Sponsor. For the second stage, the sample size will be 300 people in one group (600 people in total).

9. Statistical estimation of efficacy parameters

Statistical processing of the data obtained during the trial will be carried out using specialised software, namely the programming language for statistical data processing R and StatSoft® Statistica v.12 (and above) statistical package.

Statistical analyses will be performed for data obtained from all included patients who received at least one dose of the investigational product. The data obtained will be summarised using discrete groups with case frequencies and percentages. Descriptive statistics will be presented at each visit for all quantitative safety data from the trial.

Indicators of descriptive statistics used in this trial will include:

Descriptive statistics will include:

for quantitative data:

- number of valid cases (N)
- arithmetic mean (M);
- standard deviation (SD);
- median (Me);
- minimum (Min);
- maximum (Max);
- range
- lower quartile (Q_1);
- upper quartile (Q3);

- interquartile range (QRange);

for ordinal data:

- median (Me);
- lower quartile (Q_1);
- upper quartile (Q_3);
- interquartile range (QRange);
- minimum (Min);
- maximum (Max);

for categorical data:

- frequency;
- portion (%).

In addition, calculation of 95% confidence intervals (95% CI, L; 95% CI, U) will be used.

The Shapiro-Wilk test will be used to assess the normality of the distribution for indicators with interval type of scale. Pearson's χ^2 (chi-square) exact test or Fisher's exact test (in case the absolute frequency of a trait is 5 or less) will be used to compare groups on qualitative traits.

To test the null hypothesis of no difference between groups for qualitative features not specified as direct measures of efficacy (secondary endpoints) as well as qualitative measures of safety, testing of the null hypothesis of no difference between groups is planned using the χ^2 test or Fisher's exact test.

The feasibility of using a number of statistical methods will be assessed after data collection has been completed, as the nature of the data distribution, sample homogeneity, etc. is not known in advance. During the course of the analysis, the list of methods to be used may be modified and supplemented if necessary for the qualitative processing of the data. All deviations from the statistical plan of the trial as well as their causes will be detailed in the statistical report. No changes will be made to the list of parameters to be evaluated.

10. Safety analysis

The protocol provides the following safety assessment parameters:

1. Number and severity of adverse events (AEs) / serious AEs (SAEs) - patients will be interviewed for adverse events by members of the investigational site team at each visit. Identified adverse events will be entered into the adverse event log, source documentation and recorded in the CRF. In case of adverse events, the investigator may decide to repeat the clinical examination and/or laboratory tests.
2. Physical examination data - dynamic assessment at all visits.
3. Vital signs (blood pressure, HR, respiratory rate, body temperature) - dynamic assessment at all visits
4. Data of clinical, biochemical blood tests (ALT, AST, glucose, urea, creatinine) - evaluation in dynamics at visits 0, 2, 5.
5. Clinical urinalysis data - assessment in dynamics at visits 0, 2, 5.

Patients will be monitored throughout the trial for the development of AEs. After the first dose of the investigational product, the Investigator will record any identified AEs and SAEs. AEs reported prior to the first dose of the investigational product will be listed separately and will not be included in the safety assessment of therapy.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). A complete list of patients who have discontinued the investigational product early will be provided specifying the reason for the discontinuation. Further analysis of AEs, including SAEs, will consist of determining the total number of AEs, total number of patients with AEs, number of AEs associated with the trial therapy, number of AEs that required cancellation of therapy or changes in therapy parameters, and number of patient-initiated dropouts.

The frequency and severity of both all AEs and drug-related AEs will be presented for system organ classes (SOC MedDRA - the highest level of classification of AEs, taking into account etiology, localization of manifestations and classification objectives). More frequent AEs will be evaluated for occurrence based on dose, dosing regimen, duration of treatment, demographics or other baseline characteristics, and efficacy outcomes. The time of occurrence of adverse events and their duration will also be analysed. Descriptive statistical methods will be used for the analyses.

The final distribution of patients, indicating the number of patients included in the efficacy analysis, will be presented in accordance with Example 1 of Appendix No. 5 to the Rules of Good Clinical Practice of the Eurasian Economic Union (Decision of the Council of the Eurasian Economic Commission of 03.11.2016 No. 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union").

The list of patients who prematurely discontinued the investigational product will be submitted in accordance with the form provided in Appendix No. 6 to the Rules of Good Clinical Practice of the Eurasian Economic Union (Decision of the Council of the Eurasian Economic Commission of 03.11.2016 No. 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union").

Plan for statistical analysis of efficacy and safety parameters

The list of patients and observations excluded from the efficacy analysis will be submitted in accordance with the form provided in Appendix No. 7 to the Rules of Good Clinical Practice of the Eurasian Economic Union (Decision of the Council of the Eurasian Economic Commission of 03.11.2016 No. 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union").

Frequency tables with data on discontinuation of therapy or changes in therapy parameters due to AEs will be presented.

Data obtained before the start and at the end of the trial will be compared to assess safety parameters.

The statistical report on the results of this trial will include tables showing the dynamics of clinical manifestations and instrumental examination data, the dynamics of vital functional parameters and comparison of the results of clinical and biochemical blood analysis and general urine analysis. The results of the evaluation of the incidence of adverse events will be given.

All data will be analyzed on the safety population.

The identification of AEs, including serious AEs, will consist of determining the total number of AEs;

total number of patients with AEs;

number of AEs with a possible and higher degree of association with the investigational product/procedure;

number of AEs that required discontinuation of therapy;

The frequency and severity of all AEs and drug-related AEs will be summarized for body systems. The experimental and control groups of patients will be compared in terms of the incidence of AEs and their severity. Data on patient dropouts from the trial due to the development of AEs (if any) will be tabulated.

Adverse event (AE) is any adverse change in the health status of a patient or subject of a clinical trial to whom a medicinal (investigational) product has been administered, regardless of the causal relationship with its use. An adverse event may be any unfavourable and unintended change (including a deviation of a laboratory indicator from the norm), symptom or disease, the time of occurrence of which does not exclude a causal relationship with the use of the medicinal product, regardless of the presence or absence of a relationship with the use of the medicinal product.

If any adverse event develops, the investigator should complete the relevant pages of the patient's CRF, assess the appropriateness of the patient's continued participation in the trial. Adverse events will be recorded from the time the first dose of the patient's investigational product is administered to the patient in the trial until completion of the trial.

The investigator assesses the severity of an adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE) current version at the time of the trial. If an adverse event cannot be classified according to the CTCAE criteria, the investigator will select the closest description of the severity of the adverse event from those given in the classification based on personal clinical experience:

1 (Mild) - no symptoms or mild symptoms, only clinical or diagnostic monitoring is required; no intervention is indicated;

2 (Moderate) - only minimal, localized or non-invasive interventions are indicated; limitation of activities of daily living;

3 (Severe) - severe or clinically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization is indicated; loss of ability to work; limitation of self-care in daily life activities;

4 (Life-threatening/disability) - life-threatening consequences, urgent intervention required;

5 (Fatal) - death associated with an adverse event.

The investigator will need to assess the association of the development of the adverse event with the investigational product:

No - clearly and unquestionably related to extrinsic causes only, and does not meet the criteria for an unlikely, possible or probable relationship.

Yes - there is a definite temporal relationship with the use of the drug.

Criteria:

- may have been caused by a clinical condition or external factors or other prescribed treatments;
- clear temporal relationship between the cessation of use of the investigational product or by reducing the dose and recovering;
- resumes upon rechallenge;
- is consistent with the known nature of the response to the investigational product.

The association of an AE with the use of investigational products will be assessed using World Health Organisation (WHO) criteria:

Definite. Clinical manifestations of an AE, including abnormalities of laboratory parameters occurring during the period of drug administration, which cannot be explained by the presence of existing diseases and the influence of other factors and chemical compounds. Manifestations of an AE regress after withdrawal of the drug and reappear with repeated administration.

Probable. Clinical manifestations of an AE, laboratory abnormalities are related in time to drug intake, are unlikely to be related to comorbidities or other factors, and regress with drug withdrawal. The response to rechallenge is unknown.

Possible. Clinical manifestations of an AE that include changes in laboratory values that are temporally related to drug administration but can be explained by the presence of comorbidities or the administration of other drugs and chemical compounds. Information on response to drug withdrawal is unclear.

Doubtful. Clinical manifestations of an AE that include changes in laboratory values that occur in the absence of a clear temporal relationship to drug administration; other factors (drugs, diseases, chemicals) are present that may be responsible for their occurrence.

Conditional. Clinical manifestations of an AE, abnormalities of laboratory parameters attributed to an AE are difficult to assess. Additional data is needed for evaluation, or the data is currently being analysed.

Unclassifiable. Reports of suspected AE cannot be evaluated because there is insufficient information or it is contradictory. In the event of an AE, the Investigator should take and record their actions in primary and secondary documentation, e.g. prescribe additional medication (what, in what dose, for how long); extend the period of hospitalization of the patient, etc.

Serious AE (SAE) is any AE that:

- Resulted in death;
- Is life-threatening;
- Requires hospitalization or an extension of current hospitalization;
- Resulted in permanent or significant disability or disablement;
- Has resulted in the development of a congenital anomaly or malformation;
- Is a significant medical event that requires medical intervention to prevent one of the above outcomes.

Fatal outcomes, other AEs and other significant SAEs will be analysed and discussed.

If a patient develops an AE or SAE, it is mandatory that the appropriate forms are completed for the patient and attached to the patient's CRF. The safety assessment population will be used for all safety analyses.

Early withdrawn patients will be present in the patient list, and summarized by the main reason for withdrawal, and for each treatment group. Missing or omitted data will not be replaced.

Clinical laboratory assessments will be tabulated, presenting measures of descriptive statistics by trial visit, indicating changes from baseline. Laboratory abnormalities outside of normal values will be noted. Lists and summary descriptions of clinically significant haematological laboratory abnormalities will be presented. The feasibility of using a number of statistical methods will be assessed after data collection has been completed, as the nature of the data distribution, sample homogeneity, etc. is not known in advance. During the course of the analysis, the list of methods to be used may be modified and supplemented if necessary for the qualitative processing of the data. All deviations from the statistical plan of the trial as well as their causes will be detailed in the statistical report.

Vital signs will also be presented with descriptive statistics showing changes from baseline.

Based on the results of the trial, after the final statistical analysis, a conclusion will be made about the efficacy and safety of Mexidol® and Mexidol® FORTE 250 in comparison with placebo.

11. Patient populations to be analysed

The following patient populations will be included in the statistical analyses:

1. **Safety population**: all patients who have taken at least one dose of the investigational product;
2. **Intent-to-treat** (ITT): all randomized patients for whom there is an estimate of efficacy parameters for at least one visit other than the randomization visit,
3. **Per-protocol** (PP): patients who completed the trial according to the clinical trial protocol.

The primary efficacy variable will be analysed in the ITT population as well as in the PP population.

The final clinical trial report will include data on all patients included in the trial, including those who dropped out at any time without explanation.

12. Table templates

Table 3. Results of assessment of normality of distribution of indicators (template)

Indicators	Stage	Investigational product					
		Mexidol® + Mexidol® FORTE 250			Placebo		
		W	p	Distribution[1]	W	p	Distribution
Age	Visit 0			normal/other than normal			normal/other than normal
Height	Visit 0			normal/other than normal			normal/other than normal
Body weight	Visit 0			normal/other than normal			normal/other than normal
BMI	Visit 0			normal/other than normal			normal/other than normal
HR	Visit 0			normal/other than normal			normal/other than normal
	Visit 1			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 4			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
RR	Visit 0			normal/other than normal			normal/other than normal

[1] For indicators whose distribution in both groups is normal, Levene's test for homogeneity of variance will be performed.

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational product					
		Mexidol® + Mexidol® FORTE 250			Placebo		
		W	p	Distribution[1]	W	p	Distribution
	Visit 1			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 4			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Systolic BP	Visit 0			normal/other than normal			normal/other than normal
	Visit 1			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 4			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Diastolic BP	Visit 0			normal/other than normal			normal/other than normal
	Visit 1			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 4			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Haemoglobin	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational product					
		Mexidol® + Mexidol® FORTE 250			Placebo		
		W	p	Distribution[1]	W	p	Distribution
	Visit 5			normal/other than normal			normal/other than normal
Haematocrit	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Erythrocyte count	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Platelet count	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
White blood cell count	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Eosinophils	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational product					
		Mexidol® + Mexidol® FORTE 250			Placebo		
		W	p	Distribution[1]	W	p	Distribution
Basophils	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Stab neutrophils	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Segmented neutrophils	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Lymphocytes	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Monocytes	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
ESR	Visit 0			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational product					
		Mexidol® + Mexidol® FORTE 250			Placebo		
		W	p	Distribution[1]	W	p	Distribution
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Blood glucose	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
ALT	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
AST	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Creatinine	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal
Urea	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational product					
		Mexidol® + Mexidol® FORTE 250			Placebo		
		W	p	Distribution[1]	W	p	Distribution
	Visit 5			normal/other than normal			normal/other than normal
Urine pH	Visit 0			normal/other than normal			normal/other than normal
	Visit 2			normal/other than normal			normal/other than normal
	Visit 5			normal/other than normal			normal/other than normal

Table 4. Statistical analysis of the primary endpoint (template)

Montreal Cognitive Assessment Scale (MoCA) scores	Mexidol® + Mexidol® FORTE 250				Placebo			
	Visit 0	Visit 5	Dynamics		Visit 0	Visit 5	Dynamics	
			Abs.	%			Abs.	%
N								
Mean								
95% CI, L								
95% CI, U								
Median								
Min								
Max								
Q_1								
Q_3								
Range								
QRange								
SD								
CV								
Intragroup comparison: comparison of data at the end of therapy with data at the start of therapy (statistical criterion"[2]) (p-level value)								
Comparison of drugs (statistical test[3]) (p-value)								
Indicator span diagram/ indicator scatter diagram or indicator trend diagram								

[2] T-test for related samples or Wilcoxon test depending on the type of distribution of the indicator
[3] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Plan for statistical analysis of efficacy and safety parameters

Table 5. Statistical analysis of secondary endpoints (MoCA scale) (template)

MoCA scores	Mexidol® + Mexidol® FORTE 250										Placebo									
	Visit 0	Visit 1	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0		Visit 5	Dynamics to Visit 0		Visit 0	Visit 1	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0		Visit 5	Dynamics to visit 0	
				Abs.	%		Abs.	%		Abs.	%				Abs.	%		Abs.	%		Abs.	%
N																						
Mean																						
95% CI, L																						
95% CI, U																						
Median																						
Min																						
Max																						
Q_1																						
Q_3																						
Range																						
QRange																						
SD																						
CV																						
Intragroup comparison: comparison of data at the end of therapy with data at the start of therapy (statistical criterion"[4]) (p-level value)																						
Comparison of drugs (statistical test[5]) (p-value)																						
Indicator span diagram/ indicator scatter diagram or indicator trend diagram																						

[4] T-test for related samples or Wilcoxon test depending on the type of distribution of the indicator
[5] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Plan for statistical analysis of efficacy and safety parameters

Table 6. Statistical analysis of secondary endpoints (SF-36, MFI-20, BAI, Wein questionnaire, Tinnetti test, Digit Symbol Substitution Test) (template)

Indicator	Mexidol® + Mexidol® FORTE 250										Placebo									
	Visit 0	Visit 1	Visit 2	Dynamics to Visit 1		Visit 4	Dynamics to Visit 1		Visit 5	Dynamics to Visit 1		Visit 0	Visit 1	Visit 2	Dynamics to Visit 1		Visit 4	Dynamics to Visit 1		Visit 5	Dynamics to Visit 1	
				Abs.	%		Abs.	%		Abs.	%				Abs.	%		Abs.	%		Abs.	%
N																						
Mean																						
95% CI, L																						
95% CI, U																						
Median																						
Min																						
Max																						
Q_1																						
Q_3																						
Range																						
QRange																						
SD																						
CV																						
Intragroup comparison: comparison of data at the end of therapy with data at the start of therapy (statistical criterion"[6]) (p-level value)																						
Comparison of drugs (statistical test[7]) (p-value)																						
Indicator span diagram/ indicator scatter diagram or indicator trend diagram																						

[6] T-test for related samples or Wilcoxon test depending on the type of distribution of the indicator
[7] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Table 7. Statistical analysis of secondary endpoints (Global Clinical Impression Scale) (template)

Value on the Global Clinical Impression Scale		Investigational product				
		Visit 0	Visit 1	Visit 2	Visit 4	Visit 5
00	Abs.					
	%					
01	Abs.					
	%					
...	Abs.					
	%					
Comparison of drugs (statistical test[8]) (p-value)						

Table 8. Baseline anthropometric indices (template)

Indicator	Mexidol® + Mexidol® FORTE 250				Placebo				General data			
	Age, years	Body weight, kg	Height, cm	BMI	Age, years	Body weight, kg	Height, cm	BMI	Age, years	Body weight, kg	Height, cm	BMI
N												
Mean												
95% CI, L												
95% CI, U												
Median												
Min												
Max												
Q1												
Q3												
Range												
QRange												
SD												
CV												

Table 9. Urinalysis values during the trial (template)

Indicator		Mexidol® + Mexidol® FORTE 250			Placebo		
		Visit 0	Visit 2	Visit 5	Visit 0	Visit 2	Visit 5
Normal	Abs.						
	%						
Deviations from normal (clinically insignificant)	Abs.						
	%						
Deviations from normal (clinically significant)	Abs.						
	%						
Inter-group differences		Statistical criterion			p-level	p-level	p-level

[8] Pearson's $\chi 2$ test/Fisher's exact test

Table 10. Results of physical examination during the trial (template)

Indicator[9]		Drug				
		Visit 0	Visit 1	Visit 2	Visit 4	Visit 5
Normal	Abs.					
	%					
Deviations from normal (clinically insignificant)	Abs.					
	%					
Deviations from normal (clinically significant)	Abs.					
	%					
Comparison of drugs (statistical test[10]) (p-value)						

[9] • General condition (satisfactory, moderately severe, severe, extremely severe, agonal).
• Skin and visible mucous membranes.
• Endocrine system.
•Lymphatic system.
•ENT organs.
•Respiratory system.
•Cardiovascular system.
•Gastrointestinal tract.
•Nervous System.
•Musculoskeletal system.
•Reproductive system.
•Urinary system.

[10] Pearson's $\chi 2$ test/Fisher's exact test

Plan for statistical analysis of efficacy and safety parameters

Table 11. Comparison of vital signs with the investigational product and placebo (template)

Indicator[11]	Drug				
	Visit 0	Visit 1	Visit 2	Visit 4	Visit 5
N					
Mean					
95% CI, L					
95% CI, U					
Median					
Min					
Max					
Q_1					
Q_3					
Range					
QRange					
SD					
CV					
Intragroup comparison: comparison of data at the end of therapy with data at the start of therapy (statistical criterion"[12]) (p-level value)					
Comparison of drugs (statistical test[13]) (p-value)					
Indicator span diagram/ indicator scatter diagram					

[11] BP, HR, RR, T°.
[12] T-test for related samples or Wilcoxon test depending on the type of distribution of the indicator
[13] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Table 12. Results of statistical analysis of blood and urine test results (template)

Indicator[14]	Drug		
	Visit 0	Visit 2	Visit 5
N			
Mean			
95% CI, L			
95% CI, U			
Median			
Min			
Max			
Q_1			
Q_3			
Range			
QRange			
SD			
CV			
Intragroup comparison: comparison of data at the end of therapy with data at the start of therapy (statistical criterion"[15]) (p-level value)			
Comparison of drugs (statistical test[16]) (p-value)			
Indicator span diagram/ indicator scatter diagram			

[14] Interval indicators measured according to the trial protocol
[15] T-test for related samples or Wilcoxon test depending on the type of distribution of the indicator
[16] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Table 13. ECG values during the trial (template)

ECG		Mexidol® + Mexidol® FORTE 250			Placebo		
		Visit 0	Visit 2	Visit 5	Visit 0	Visit 2	Visit 5
Normal	Abs.						
	%						
Deviations from normal (clinically insignificant)	Abs.						
	%						
Deviations from normal (clinically significant)	Abs.						
	%						
Inter-group differences		Statistical criterion					

Table 14. Results of parametric analysis of variance for repeated measurements (template)

Indicator, Repeated measures analysis of variance, factor	SS	DF	MS	F	p
Intercept					
Drug					
Visit					
Visit*Drug					
Error					

Table 15. Results of non-parametric analysis of variance (Friedman test) (template)

Indicator	Mexidol® + Mexidol® FORTE 250					Placebo				
Visit	Average rank	Sum of ranks	Mean	SD	p	Average rank	Sum of ranks	Mean	SD	p
Visit 0										
Visit 1										
Visit 2										
Visit 4										
Visit 5										

Table 16. Results of a posteriori multiple comparisons

Mexidol® + Mexidol® FORTE 250						Placebo					
Indicator	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 4**	**Visit 5**	**Indicator**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 4**	**Visit 5**
Visit 0	-					**Visit 0**	-				
Visit 1		-				**Visit 1**		-			
Visit 2			-			**Visit 2**			-		
Visit 4				-		**Visit 4**				-	
Visit 5					-	**Visit 5**					-

Table 17. Summary table of the incidence of reported NNDs in the group receiving Mexidol® + Mexidol® FORTE 250 by degree with randomization numbers of patients (N=)

AE/code, PT according to MedDRA version	Mild AE		Medium AE		Moderate AE		Life-threatening AE		Fatal AE		Total		Total
	R	UR	R	UR	R	UR	R	UR	R	UR	R	UR	R+UR

Table 18. Summary table of the incidence of reported AEs in the group taking placebo by severity with randomization numbers of patients (N=)

Adverse Event/Code, RT level under MedDRA v. 22.0 RU	Mild AE		Medium AE		Moderate AE		Life-threatening AE		Fatal AE		Total		Total
	R	UR	R	UR	R	UR	R	UR	R	UR	R	UR	R+UR

Plan for statistical analysis of efficacy and safety parameters

Table 19. Summary table of the incidence of AEs after taking each investigational product

Adverse Event/Code, RT level under MedDRA v. 22.0 RU	Mexidol + Mexidol® FORTE 250 N=		Placebo N=		P-value (Statistical criterion)
	n	%	n	%	

Table 20. List of all adverse events for each patient

Site number	Randomization number, full name	Demographic data		AE/code, PT according to MedDRA version	AE onset	Severity	Seriousness	Relationship	Actions taken in relation to the patient	Actions taken in relation to the Investigational drug	Concomitant therapy	Date the AE resolved	Outcome
		Age, y											
		gender											
		Weight, kg											
		Height, cm											
		race											

Table 21. Classification of AEs according to MedDRA v. 22.0 RU

Randomization number, initials	AE	MedDRA AE code, SOC level	MedDRA AE term, SOC level	MedDRA AE code, PT level	MedDRA AE term, PT level

Plan for statistical analysis of efficacy and safety parameters

Table 22. Summary table of the incidence of reported SAEs in the group receiving Mexidol® + Mexidol® FORTE 250 by degree with randomization numbers of patients (N=)

Adverse event/code, PT level according to MedDRA version	Mild AE		Medium AE		Moderate AE		Life-threatening AE		Fatal AE		Total		Total
	R	UR	R	UR	R	UR	R	UR	R	UR	R	UR	R+UR

Table 23. Summary table of the incidence of reported SAEs in the placebo group by grade with randomization numbers of patients (N=)

Adverse Event/Code, RT level under MedDRA v. 22.0 RU	Mild AE		Medium AE		Moderate AE		Life-threatening AE		Fatal AE		Total		Total
	R	UR	R	UR	R	UR	R	UR	R	UR	R	UR	R+UR

Plan for statistical analysis of efficacy and safety parameters

Table 24. Summary table of the incidence of SAEs after taking each investigational product

Adverse Event/Code, RT level under MedDRA v. 22.0 RU	Mexidol® + Mexidol® FORTE 250 N=		Placebo N=		P-value (Statistical criterion)
	n	%	n	%	

Table 25. List of all serious adverse events for each patient

Site number	Randomization number, full name	Demographic data		SAE/code, PT according to MedDRA version	AE onset	Severity	Seriousness	Relationship	Actions taken in relation to the patient	Actions taken in relation to the investigational product	Concomitant therapy	Date the AE resolved	Outcome
		Age, y											
		Gender											
		Weight, kg											
		Height, cm											
		Race											

Table 26. Classification of SAEs according to MedDRA v. 22.0 RU

Randomization number, initials	SAE	SAE MedDRA code, SOC level	SAE MedDRA term, SOC level	SAE MedDRA code, PT level	SAE MedDRA term, PT level