Statistical Analysis Plan

A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the efficacy and safety of Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA)

NCT Number: NCT06854601

Pharmasoft

September 27, 2019

Plan for statistical analysis of efficacy and safety parameters in the clinical trial

"A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the efficacy and safety of Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA)" under protocol No. PHS-ADHD-002-MEX-TAB, version 3.0 dated 19.07.2019.

Yaroslavl - 2019

Approval sheet for the plan of statistical analysis of efficacy and safety parameters, version 1.0 dated 27.09.2019, in a multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA) under protocol No. PHS-ADHD-002-MEX-TAB, version 3.0 dated 19.07.2019.

Project Manager

Ekaterina Yuryevna Sharonova (signed) *30.09.2019*
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History of changes to the document

Version number	Date of issue	Amendments	
		Section	Modifications made
1.0	27.09.2019	New document	

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List of abbreviations

ADHD Rating Scale-IV;

CGI-ADHD-S is a scale to assess the global clinical impression of ADHD severity;

CGI-I - Clinical Global Impression-Improvement Scale;

FAS - Full Analysis set;

MedDRA - Medical Dictionary for Regulatory Activities;

PP - Per Protocol;

SNAP-IV - scale to assess the severity of ADHD;

SCAS - Child Anxiety Scale - parental assessment;

SOC - System Organ Class MedDRA;

TESS - Treatment Emergent Signs and Symptoms;

BP - Blood Pressure;

ALT - alanine aminotransferase;

AST - aspartate aminotransferase;

GGT - gamma-glutamyltransferase;

CI - confidence interval;

BMI - Body Mass Index;

eCRF - electronic case report form;

AE - Adverse event;

ADHD - attention deficit hyperactivity disorder;

ESR - erythrocyte sedimentation rate;

SAE - serious adverse event;

RR - Respiratory rate;

HR - Heart rate;

ALP - alkaline phosphatase.

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

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: A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA).

Protocol No.: PHS-ADHD-002-MEX-TAB

Protocol version: 3.0 dated 19.7.2019.

Sponsor: RPC PHARMASOFT LLC, Russia

Investigational product: Mexidol® (ethylmethylhydroxypyridine succinate) film-coated tablets, 125 mg (RPC PHARMASOFT LLC, Russia).

Comparator product: Placebo (RPC PHARMASOFT LLC, Russia).

Trial design:

A multicentre, prospective, double-blind, randomised in three parallel groups with a 1:1:1 ratio clinical trial to evaluate the efficacy and safety of Mexidol® film-coated tablets, 125 mg using placebo controls. **Number of patients:** 333

Type of trial: phase II-III trial

Trial purpose:

Evaluation of efficacy and safety of two dosing regimens of Mexidol® film-coated tablets, 125 mg (PRC Pharmasoft LLC, Russia) vs. placebo in children aged 6 to 12 years inclusive with attention deficit hyperactivity disorder (ADHD).

Trial objectives:

Primary objectives:

1. To evaluate the efficacy of Mexidol® film-coated tablets, 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy in relation to the average change in the total score on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP-IV scale when administered at a dose of 125 mg OD.
2. To evaluate the efficacy of Mexidol® film-coated tablets, 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy in relation to the average change in the total score on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP-IV scale when administered at a dose of 125 mg BID.

Secondary objectives:

1. To evaluate the efficacy of Mexidol® film-coated tablets 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy when administered at a dose of 125 mg OD and 125 mg BID on the basis of the following parameters:
    a. Mean change on the SNAP-IV subscale - inattention;
    b. Mean change on SNAP-IV subscale - hyperactivity/impulsivity;
    c. Mean change on the SNAP-IV subscale - oppositional defiant disorder;
    d. Mean change on the SNAP-IV subscale - Conners' clinical index;
    e. Mean change on the Spence Children's Anxiety Scale (SCAS);
    f. Mean change on ADHD Rating Scale-IV;
    g. Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S);
    h. Assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores);
    i. The Clinical Global Impressions Scale - Improvement (CGI-I) score.
2. To evaluate the safety of Mexidol® film-coated tablets, 125 mg (RPC PHARMASOFT LLC, Russia) vs. placebo based on the assessment of frequency, severity and nature of adverse events.

Criteria for assessing efficacy and safety:

Given the purpose and **primary** objective of the present trial, the **primary endpoint** is the mean change in the sum of the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline.

Secondary endpoints:

- Mean change on the SNAP-IV inattention subscale after 6 weeks of therapy vs. baseline;
- Mean change on SNAP-IV subscale hyperactivity/impulsivity after 6 weeks of therapy vs. baseline;
- Mean change on the SNAP-IV subscale, oppositional defiant disorder, after 6 weeks of therapy vs. baseline;
- Mean change on the SNAP-IV subscale - Conners' clinical index;
- Mean change on the Spence children's anxiety scale (SCAS) after 6 weeks of therapy vs. baseline;
- Mean change on ADHD Rating Scale-IV scores after 6 weeks of therapy vs. baseline;
- Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale score after 6 weeks of therapy vs. baseline;
- Assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores);
- Clinical Global Impressions Scale - Improvement (CGI-I) score after 6 weeks of therapy vs. baseline.

The comparative efficacy of the investigational product and the comparator product on the primary endpoint will be assessed, with 95% confidence intervals calculated for the difference in mean changes in the sum of the total score on the inattention, hyperactivity/impulsivity subscales of the SNAP-IV scale.

Safety endpoints:

- Number of adverse events (AEs) and serious AEs (SAEs);
- Frequency and severity of AEs/SAE associated with investigational product/placebo.

Safety assessment will be based on patient and/or patient's parents interview, physical examination findings (including assessment of vital signs: BP, HR, RR), data from the Patient Diary and results of laboratory and instrumental examination (clinical and biochemical blood tests).

The clinical trial is double-blind, meaning that the investigational site staff and patients participating in the trial will not know which therapy (Mexidol® + placebo therapy, Mexidol® alone, or placebo alone) patients will receive.

2. Purpose of data statistical analysis

The purpose of developing this Statistical Analysis Plan is to describe the planned data analysis for Protocol #PHS-ADHD-002-MEX-TAB, version 3.0 dated 19.07.2019 for inclusion of 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.

This trial is being conducted in accordance with:

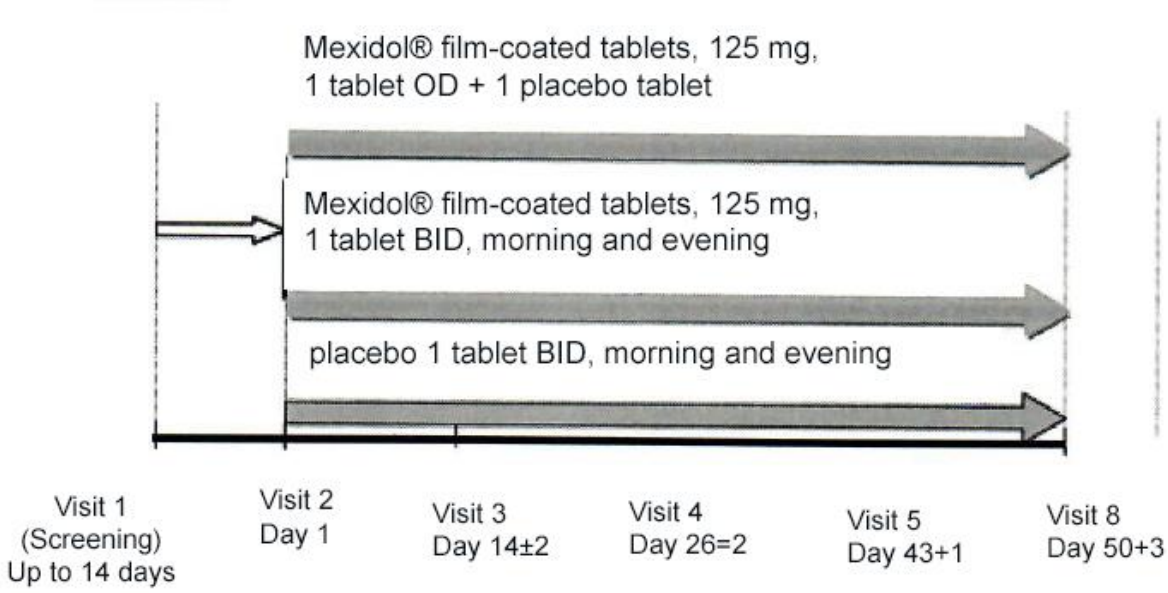
- Clinical Trial Protocol, in strict compliance with the Constitution of the Russian Federation;
- ethical principles of the 1964 Declaration of Helsinki of the World Medical Association, as revised in 2013.
- Federal Law N 61-FZ dated 12 April 2010 "On Circulation of Medicines" (current version);
- 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

Deviations from the protocol in statistical analyses are not planned. However, 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	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
001	1	1	1	**168**	2	28	6
002	3	1	2	**169**	3	29	1
003	2	1	3	**170**	3	29	2
004	3	1	4	**171**	1	29	3
005	2	1	5	**172**	2	29	4
006	1	1	6	**173**	1	29	5
007	3	2	1	**174**	2	29	6

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
008	3	2	2	**175**	2	30	1
009	2	2	3	**176**	1	30	2
010	2	2	4	**177**	3	30	3
011	1	2	5	**178**	3	30	4
012	1	2	6	**179**	2	30	5
013	3	3	1	**180**	1	30	6
014	2	3	2	**181**	2	31	1
015	2	3	3	**182**	3	31	2
016	3	3	4	**183**	3	31	3
017	1	3	5	**184**	1	31	4
018	1	3	6	**185**	1	31	5
019	1	4	1	**186**	2	31	6
020	1	4	2	**187**	3	32	1
021	3	4	3	**188**	2	32	2
022	3	4	4	**189**	1	32	3
023	2	4	5	**190**	2	32	4
024	2	4	6	**191**	3	32	5
025	2	5	1	**192**	1	32	6
026	2	5	2	**193**	2	33	1
027	3	5	3	**194**	3	33	2
028	3	5	4	**195**	2	33	3
029	1	5	5	**196**	3	33	4

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
030	1	5	6	**197**	1	33	5
031	2	6	1	**198**	1	33	6
032	2	6	2	**199**	3	34	1
033	3	6	3	**200**	2	34	2
034	1	6	4	**201**	2	34	3
035	3	6	5	**202**	3	34	4
036	1	6	6	**203**	1	34	5
037	1	7	1	**204**	1	34	6
038	1	7	2	**205**	1	35	1
039	3	7	3	**206**	1	35	2
040	2	7	4	**207**	2	35	3
041	3	7	5	**208**	3	35	4
042	2	7	6	**209**	2	35	5
043	3	8	1	**210**	3	35	6
044	3	8	2	**211**	2	36	1
045	2	8	3	**212**	2	36	2
046	2	8	4	**213**	1	36	3
047	1	8	5	**214**	1	36	4
048	1	8	6	**215**	3	36	5
049	1	9	1	**216**	3	36	6
050	2	9	2	**217**	1	37	1
051	2	9	3	**218**	2	37	2

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
052	1	9	4	**219**	3	37	3
053	3	9	5	**220**	2	37	4
054	3	9	6	**221**	3	37	5
055	1	10	1	**222**	1	37	6
056	3	10	2	**223**	3	38	1
057	1	10	3	**224**	2	38	2
058	2	10	4	**225**	1	38	3
059	2	10	5	**226**	1	38	4
060	3	10	6	**227**	3	38	5
061	3	11	1	**228**	2	38	6
062	2	11	2	**229**	1	39	1
063	1	11	3	**230**	2	39	2
064	2	11	4	**231**	2	39	3
065	3	11	5	**232**	1	39	4
066	1	11	6	**233**	3	39	5
067	3	12	1	**234**	3	39	6
068	2	12	2	**235**	1	40	1
069	1	12	3	**236**	3	40	2
070	3	12	4	**237**	2	40	3
071	1	12	5	**238**	3	40	4
072	2	12	6	**239**	2	40	5
073	2	13	1	**240**	1	40	6

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
074	2	13	2	**241**	3	41	1
075	1	13	3	**242**	3	41	2
076	3	13	4	**243**	2	41	3
077	3	13	5	**244**	1	41	4
078	1	13	6	**245**	1	41	5
079	3	14	1	**246**	2	41	6
080	2	14	2	**247**	3	42	1
081	2	14	3	**248**	1	42	2
082	1	14	4	**249**	1	42	3
083	3	14	5	**250**	2	42	4
084	1	14	6	**251**	3	42	5
085	2	15	1	**252**	2	42	6
086	_ 3	15	2	**253**	2	43	1
087	1	15	3	**254**	3	43	2
088	1	15	4	**255**	2	43	3
089	3	15	5	**256**	1	43	4
090	2	15	6	**257**	1	43	5
091	2	16	1	**258**	3	43	6
092	1	16	2	**259**	1	44	1
093	3	16	3	**260**	2	44	2
094	3	16	4	**261**	1	44	3
095	1	16	5	**262**	3	44	4

Plan for statistical analysis of efficacy and safety parameters

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
096	2	16	6	**263**	2	44	5
097	1	17	1	**264**	3	44	6
098	1	17	2	**265**	1	45	1
099	2	17	3	**266**	1	45	2
100	2	17	4	**267**	2	45	3
101	3	17	5	**268**	3	45	4
102	3	17	6	**269**	3	45	5
103	2	18	1	**270**	2	45	6
104	1	18	2	**271**	3	46	1
105	2	18	3	**272**	2	46	2
106	3	18	4	**273**	1	46	3
107	1	18	5	**274**	1	46	4
108	3	18	6	**275**	3	46	5
109	1	19	1	**276**	2	46	6
110	1	19	2	**277**	1	47	1
111	2	19	3	**278**	3	47	2
112	2	19	4	**279**	2	47	3
113	3	19	5	**280**	3	47	4
114	3	19	6	**281**	2	47	5
115	3	20	1	**282**	I	47	6
116	3	20	2	**283**	2	48	1
117	1	20	3	**284**	1	48	2

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
118	2	20	4	**285**	3	48	3
119	1	20	5	**286**	3	48	4
120	2	20	6	**287**	2	48	5
121	2	21	1	**288**	1	48	6
122	2	21	2	**289**	1	49	1
123	3	21	3	**290**	2	49	2
124	3	21	4	**291**	1	49	3
125	1	21	5	**292**	3	49	4
126	1	21	6	**293**	3	49	5
127	2	22	1	**294**	2	49	6
128	1	22	2	**295**	2	50	1
129	2	22	3	**296**	3	50	2
130	3	22	4	**297**	2	50	3
131	3	22	5	**298**	1	50	4
132	1	22	6	**299**	3	50	5
133	2	23	1	**300**	1	50	6
134	1	23	2	**301**	2	51	1
135	3	23	3	**302**	1	51	2
136	3	23	4	**303**	3	51	3
137	1	23	5	**304**	3	51	4
138	2	23	6	**305**	1	51	5
139	1	24	1	**306**	2	51	6

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
140	2	24	2	**307**	2	52	1
141	1	24	3	**308**	3	52	2
142	3	24	4	**309**	3	52	3
143	2	24	5	**310**	1	52	4
144	3	24	6	**311**	1	52	5
145	3	25	1	**312**	2	52	6
146	3	25	2	**313**	3	53	1
147	2	25	3	**314**	1	53	2
148	2	25	4	**315**	3	53	3
149	1	25	5	**316**	1	53	4
150	1	25	6	**317**	2	53	5
151	1	26	1	**318**	2	53	6
152	2	26	2	**319**	2	54	1
153	1	26	3	**320**	3	54	2
154	2	26	4	**321**	3	54	3
155	3	26	5	**322**	1	54	4
156	3	26	6	**323**	2	54	5
157	2	27	1	**324**	1	54	6
158	3	27	2	**325**	3	55	1
159	3	27	3	**326**	2	55	2
160	2	27	4	**327**	2	55	3
161	1	27	5	**328**	1	55	4

Patient randomization number	Group	Block number	Order number within the block	Patient randomization number	Group	Block number	Order number within the block
162	1	27	6	**329**	1	55	5
163	1	28	1	**330**	3	55	6
164	1	28	2	**331**	1	56	1
165	2	28	3	**332**	3	56	2
166	3	28	4	**333**	2	56	3
167	3	28	5	**-**	-	-	-

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

The FAS and PP populations will be used for efficacy analyses, with the FAS population planned to be used as the main population. The criterion chosen as the primary criterion for efficacy evaluation is:

- Mean change in the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline.

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

As a sensitivity analysis, the analysis of the primary variable in the ITT population will be repeated in the per protocol (PP) population. 95% confidence intervals will also be presented.

The secondary efficacy evaluation criteria chosen are:

- Mean change on the SNAP-IV inattention subscale after 6 weeks of therapy vs. baseline;
- Mean change on SNAP-IV subscale hyperactivity/impulsivity after 6 weeks of therapy vs. baseline;
- Mean change on the SNAP-IV subscale, oppositional defiant disorder, after 6 weeks of therapy vs. baseline;
- Mean change on the SNAP-IV subscale - Conners' clinical index;
- Mean change on the Spence children's anxiety scale (SCAS) after 6 weeks of therapy vs. baseline;

- Mean change on ADHD Rating Scale-IV scores after 6 weeks of therapy vs. baseline;
- Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale score after 6 weeks of therapy vs. baseline;
- Assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores);
- The Clinical Global Impressions Scale - Improvement (CGI-I) score after 6 weeks of therapy vs. baseline.

Two-sided confidence intervals will be used to assess treatment efficacy (primary and secondary efficacy criteria). A conclusion on superiority can be made if the upper bound of the two-sided 95% confidence interval for the difference in mean changes in SNAP-IV scores of Mexidol® vs. placebo is negative.

For primary and secondary efficacy criteria, differences will be considered statistically significant at the p-value level of <0.05.

The χ-square test or Fisher's exact test will be used to assess differences in event rates.

The χ-square test or Fisher's exact test will also be used to assess differences in patient adherence.

Demographic and baseline characteristics will be characterized using descriptive statistical methods for the analysis sample as a whole and for therapeutic subgroups, with testing of the null hypothesis of no differences between the trial groups at baseline. Descriptive statistics for data whose distribution follows the law of normal distribution will be presented using the arithmetic mean and standard deviation. For otherwise distributed data, descriptive statistics will be presented using non-parametric measures (median/mode, quartiles). The assessment of normality of distribution for interval indicators will be determined by the Shapiro-Wilk test.

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

No interim statistical analyses of efficacy are planned as part of this trial. Statistical analysis of the results will be done after the trial is completed.

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 an estimated association of at least "possible") will be presented for system organ classes (SOC - System Organ Class MedDRA - the highest level of classification of AEs, taking into account etiology, localization of manifestations and classification objectives).

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). The protocol provides for the recording of all AEs that occur to the patient after the first administration of the trial therapy and until the end of the patient's participation in the trial. 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-test will be used as the non-paramatric analogue of the t-criterion.

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

To assess the robustness of the trial results, a sensitivity analysis will be performed on the main efficacy parameter: "Mean change in the total score on the inattention, hyperactivity/impulsivity subscale of the SNAP-IV scale after 6 weeks of therapy vs. baseline".

Since sensitivity analysis aims to assess the impact on the trial results of deviations from the methods of analysis used, as well as the impact of missing data values and a priori assumptions in order to identify the results that are most dependent on questionable or untenable assumptions, this trial includes an assessment of the impact of the following factors on the main conclusion of the trial:

- **Investigational site:** planned analysis adjusted for the covariate “Site” using a generalized linear model (GLM) to assess the consistency of the results with the analysis without introducing one;
- **Analysed populations:** in addition to the main analysis in the FAS population, a secondary analysis in the PP population is planned to assess the consistency of the results with the main analysis;
- **Various assessments for treatment success:** secondary efficacy endpoints were planned to support the results of the primary efficacy analysis using the t-test - for data whose distribution conforms to the law of normal distribution, or the Mann-Whitney U-test for data whose distribution does not conform to the law of normal distribution.
- **Missing data:** analyses of full cases and post-hoc analyses using the last observation carry forward method (LOCF) to assess consistency of results are assumed.

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 purpose of the trial, statistical analysis of the results is planned to compare the efficacy of the therapy regimen including Mexidol® in the treatment of attention deficit hyperactivity disorder (ADHD) in children 6-12 years old at different dosing regimens

with the efficacy of the regimen including placebo and a combination of the investigational product and placebo.

The main efficacy criterion is the mean change in the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline. Descriptive statistics for this indicator will be given and the following statistical hypotheses will be tested:

$$H^0: \mu_p=\mu_T;$$
$$H^1: \mu_T<\mu_p$$

μ_T - mean change in SNAP-IV score in the experimental group (group 1 Mexidol®, 125 mg OD, or group 2 (Mexidol®, 125 mg BID);

μ_P - mean change in SNAP-IV score in control group 3 (placebo).

The sign "<" is associated with the fact that the change has a negative value.

Comparison of the values of the two groups of patients will be performed by calculating the 95% confidence interval for the difference of μ1 (μ2) and μ0 values. A conclusion on superiority can be made if the upper bound of the two-sided 95% confidence interval for the difference in mean changes in SNAP-IV scores of Mexidol® vs. placebo is negative.

Testing of the null statistical hypothesis can be done using one-factor analysis of variance with Dunnett's posterior criterion and evaluation of contrasts or similar applicable statistical analysis method.

The χ-square test or Fisher's exact test will be used to assess differences in event rates.

The χ-square test or Fisher's exact test will also be used to assess differences in patient adherence.

8. Estimation of the required sample size

The sample size calculation is based on the guidelines outlined in Chow S, Shao J, Wang H. Sample Size calculation in Clinical Research. 2nd edition. 2008.

The present trial assumes a 1:1:1 distribution of patients into groups ($\mu_1=\mu_2=\mu_0$).

The following input data are used in the calculations:

1. The significance level is 95% (respectively, the I error is 0.05). Since the boundaries of the 95% confidence interval must be two-sided and testing of the superiority hypothesis is one-sided, a one-sided error I of 0.025 will be applied to test the hypothesis, which is equivalent to an error of 0.05 for a two-sided test.
2. Acceptable trial power is at least 80 per cent;
3. The mean change in SNAP-IV score in the placebo group is -2.0 points, and the standard deviation for the change is 4.70 points.
4. The mean change in SNAP-IV score in the Mexidol® group is -4.5 points, and the standard deviation for the change is 7.515 points.
5. The modulus of the difference in mean SNAP-IV scores between the Mexidol and placebo groups is 2.5 points

Thus, based on the calculations based on the data above, the number of patients to complete the trial according to the protocol was at least 100 in each group or a total of at least

300. Assuming a 10% drop-out rate during follow-up, the trial is planned to include 333 patients (111 in each group).

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:

for quantitative data:

- arithmetic mean (M);
- standard deviation (SD);
- median (Me);
- interquartile range (QRange);
- minimum (Min);
- maximum (Max);

for ordinal data:

- median (Me);
- 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) and range 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 survey as well as their causes will be detailed in the statistical report.

10. Safety analysis

The protocol provides for the recording of all AEs that occur to the patient after the first administration of the trial therapy and until the end of the patient's participation in the trial. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). 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 an estimated association of at least "possible") will be presented for system organ classes (SOC - System Organ Class MedDRA - the highest level of classification of AEs, taking into account 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.

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.

The following safety assessment parameters will be analysed: the number of adverse events (AEs) and serious AEs (SAEs) and the incidence of AEs/SAEs associated with the investigational product/placebo.

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 (i.e., with an estimated association of at least "possible"), will be summarized for body systems. Data on patient dropouts from the trial due to the development of AEs (if any) will be tabulated.

The trial will record all AEs that occur in a patient after a single dose of investigational products in the specified dose.

Adverse event (AE) - an 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 events develop, 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 investigational product is administered to the patient in the trial until completion of the trial.

The severity of AEs is assessed as follows:

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 choose the closest description of the severity of the adverse event from those given in the classification based on personal clinical experience:

Degree of severity	Category	Definition/Description
1	Mild	No symptoms or mild symptoms, only clinical or diagnostic follow-up is required; no intervention is indicated
2	Moderate	Only minimal, localised or non-invasive interventions are indicated; limitation of daily living activities
3	Severe	Severe or clinically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disability; limitation of self-care in activities of daily living
4	Life-threatening/ Disability to work	Life-threatening consequences, urgent intervention required
5	Fatal	Death associated with an adverse event

"Severe" adverse event will not necessarily be “serious" in nature, “serious" adverse event will not necessarily be "severe" by definition.

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 adverse reaction regress after drug withdrawal and occur with repeated administration.
- *Probable.* Clinical manifestations of an AE that include changes in laboratory values that are temporally related to the use of the investigational product, that are unlikely to be related to comorbidities or other factors, and that 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 involving abnormalities of laboratory indications categorised as 'adverse reactions' that need further data (for accurate assessment) or these obtained data are currently being analysed.
- *Unclassifiable.* Reports of a suspected adverse reaction cannot be evaluated because there is insufficient or conflicting information.

The occurrence of an adverse event will be considered to be related to the investigational product if the relationship is considered by the investigator as definite, probable, possible.
Serious adverse event (SAE) - "Serious" adverse event is defined as any adverse medical event that, regardless of the dose of the medicinal product:

- resulted in death;
- was life-threatening;
- has caused severe or permanent disability or incapacity for work;
- required an inpatient admission (other than a previously planned admission) or causes an extension of the current hospitalization;
- resulted in a congenital anomaly/developmental defect;
- required medical intervention to prevent the above conditions;
- there has been transmission of an infectious agent through a medicinal product.

In addition, a serious adverse event includes any event that does not formally fit the above criteria but is a significant medical event from the investigator's point of view.

"Serious" adverse reaction is a serious adverse event with a causal relationship (possible, probable, or credible) to the use of the investigational product;

All other AEs that do not meet these criteria will be considered as “non-serious".

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 presented with 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 survey 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.

Data harmonisation, if possible, will be done by converting values to commonly used or most common units of measurement in the dataset. In case the units of measurement cannot be harmonised, the data will be presented as tables without further statistical treatment.

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

11. Patient populations to be analysed

The following groups will be used for the analysis:

1. **Safety population** - will include all patients who have taken at least one dose of the investigational product;
2. **Full analysis set (FAS) population -** will include all randomized patients who have taken at least one dose of the investigational product and who have an assessed response to therapy after 6 weeks of therapy. This will be the main population for efficacy analyses;
3. **Per protocol population (PP)** is a subgroup of the FAS population that will include patients in the absence of significant protocol deviations regarding inclusion/non-inclusion criteria, adherence to therapy, and use of concomitant therapy. This will be an additional population used for efficacy analyses.

Efficacy analyses will be performed on the FAS population as well as on the PP population of all patients who completed the trial according to the protocol in order to validate the results obtained.

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.

In general, any deviation from the protocol may be accepted only in an urgent case or after obtaining written agreement from the Sponsor and subject to approval by the Ethics Committee. Any deviation from the protocol should be clearly explained in the source documentation and in the eCRF. Classification of protocol deviations will be made by the Sponsor's medical expert before the database lock. Deviations from the protocol will be considered significant in the following cases (the list may be expanded in a subsequent evaluation of protocol deviations):

- skip of visit 4;
- violation of inclusion / non-inclusion criteria;
- violation of the exclusion criteria;
- taking the investigational product/placebo <80% or >120% of the total number of tablets prescribed;
- administration of prohibited drugs.

In the absence of data at Visit 4 when data are available at Visit 5, these patients will not be included in the FAS and PP populations, but will be analysed in the safety population.

In the presence of data at Visit 4 and the presence of the other listed significant protocol deviations, these patients will be included in the full analysis population, safety population, but excluded from the protocol population.

12. Table templates

Table 2. Results of assessment of normality of distribution of indicators (template)

Indicators	Stage	Investigational products								
		Mexidol®			Placebo			Mexidol®+ Placebo		
		W	p	Distribution	W	p	Distribution	W	p	Distribution
Age	Visit 1 (Day-14-1)			normal/other than normal			normal/other than normal			normal/other than normal
Height	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
Body weight	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
BMI	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
HR	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 5 (Day 50+3)			normal/other than normal			normal/other than normal			normal/other than normal
CHD	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 5 (Day 50+3)			normal/other than normal			normal/other than normal			normal/other than normal
Systolic BP	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 5 (Day 50+3)			normal/other than normal			normal/other than normal			normal/other than normal
Diastolic BP	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than
	Visit 5 (Day 50+3)			normal/other than normal			normal/other than normal			normal/other than normal
Haemoglobin	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational products								
		Mexidol®			Placebo			Mexidol®+ Placebo		
		W	p	Distribution	W	p	Distribution	W	p	Distribution
Haematocrit	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Erythrocyte count	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Platelet count	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
White blood cell count	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Eosinophils	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Basophils	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Stab neutrophils	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Segmented neutrophils	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Lymphocytes	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Monocytes	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
ESR	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Total protein	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational products								
		Mexidol®			Placebo			Mexidol®+ Placebo		
		W	p	Distribution	W	p	Distribution	W	p	Distribution
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Albumin	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Glucose	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
ALT	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
AST	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Total bilirubin	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Alkaline phosphatase (ALP)	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Amylase	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Creatinine	Visit 1 (Day -14-1)			normal/other than normal			normal/other than normal			normal/other than normal
	Visit 4 (Day 43+1)			normal/other than normal			normal/other than normal			normal/other than normal
Urine pH	20 weeks			normal/other than normal			normal/other than normal			normal/other than normal
	24 weeks			normal/other than normal			normal/other than normal			normal/other than normal
Urine specific gravity	28 weeks			normal/other than normal			normal/other than normal			normal/other than normal
	32 weeks			normal/other than normal			normal/other than normal			normal/other than normal

Table 3. Statistical analysis of the primary endpoint (template)

Total score on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP IV scale	**Mexidol®**				**Placebo**				**Mexidol®+ Placebo**			
	Visit 2 (Day 1)	**Visit 5 (Day 43+1)**	**Dynamics**		**Visit 2 (Day 1)**	**Visit 5 (Day 43+1)**	**Dynamics**		**Visit 2 (Day 1)**	**Visit 5 (Day 43+1)**	**Dynamics**	
			Abs.	%			**Abs.**	%			**Abs.**	%
N												
Mean												
95% CI, L												
95% CI, U												
Median												
Min												
Max												
Q_1												
Q_3												
Range												
Q Range												
SD												
CV												
Intragroup comparison: comparison of data at the end of therapy with data at the start of therapy (statistical criterion"[1]) (p-level value)												
Comparison of drugs (statistical test[2]) (p-value)												
Indicator span diagram/ indicator scatter diagram												

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

Table 4. Statistical analysis of secondary, endpoints (SNAP-GU, CGI-ADHD-S, SCAS, PedMIDAS and ADHD Rating Scale IV) (template)

Indicator[3]	Mexidol®				Placebo				Mexidol®+ Placebo			
	Visit 2 (Day 1)	Visit 5 (Day 43+1)	Dynamics		Visit 2 (Day 1)	Visit 5 (Day 43+1)	Dynamics		Visit 2 (Day 1)	Visit 5 (Day 43+1)	Dynamics	
			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												

[3] - SNAP-IV subscale score - "inattention."
- SNAP-IV subscale score - "hyperactivity/impulsivity."
- SNAP-IV subscale score - oppositional defiant disorder;
- SNAP-IV subscale score - Conners index;
Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S).
- Spence children's anxiety scale (SCAS) scores after 6 weeks of therapy compared to baseline;
PedMIDAS questionnaire score
- ADHD Rating Scale-IV score after 6 weeks of therapy compared with baseline.

[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

Table 5. Statistical analysis of secondary endpoints (CGI-I scale) (template)

The Clinical Global Impressions Scale - Improvement (CGI-I) score.	**Investigational products**		
	Mexidol®	**Placebo**	**Mexidol®+ Placebo**
N			
Mean			
95% CI, L			
95% CI, U			
Median			
Min			
Max			
Q_1			
Q_3			
Range			
Q Range			
SD			
CV			
Comparison of drugs (statistical test[6]) (p-value)			
Indicator span diagram/ indicator scatter diagram			

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

Table 6. Outcomes of the primary endpoint analysis

Total score on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP-IV scale	**Inter-group differences**			
	Mexidol® vs. Mexidol®+Placebo		**Mexidol® vs. Placebo**	
Statistical criterion				
p-level				
CI for difference in variances				
Superiority is proven (Yes/No)				

Table 7. Baseline anthropometric indices (template)

Indicator	**Mexidol®**				**Placebo**				**Mexidol® + 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**	**Age, years**	**Body weight, kg**	**Height, cm**	**BMI**
N																
Mean																
95% CI, L																
95% CI, U																
Median																
Min																
Max																
Q_1																
Q_3																
Range																
QRange																
SD																
CV																

Table 8. Urinalysis values during the trial[7] (template)

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

Table 9. Results of the medical examination during the trial (template)

Indicator[8]		Investigational product		
		Visit 1 (Day -14 -1)	Visit 5 (Day 43+1)	Visit 6 (Day 50+3)
Normal	Abs.			
	%			
Deviations from normal (clinically insignificant)	Abs.			
	%			
Deviations from normal (clinically significant)	Abs.			
	%			
Comparison of drugs (statistical test[9]) (p-value)				

Table 10. Comparison of vital signs when taking the investigational product and the comparator product (template)

Indicator[10]	Investigational product		
	Visit 1 (Day -14 -1)	Visit 5 (Day 43+1)	Visit 6 (Day 50+3)
N			

[7] Applicable for categorical indicators
[8] General condition
- Skin condition
- Musculoskeletal system
- Lymph nodes
- Thyroid gland
- Upper respiratory tract and lungs
- Heart, blood vessels
- Abdominal organs, kidneys
- Neuropsychiatric status

[9] Pearson's $\chi 2$ test/Fisher's exact test
[10] BP, HR, RR.

Indicator[10]	Investigational product		
	Visit 1 (Day -14 -1)	Visit 5 (Day 43+1)	Visit 6 (Day 50+3)
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"[11]) (p-level value)			
Comparison of drugs (statistical test[12]) (p-value)			
Indicator span diagram/ indicator scatter diagram			

Table 11. Results of statistical analysis of blood and urine test results (template)

Indicator[13]	Investigational product	
	Visit 1 (Day -14 -1)	Visit 5 (Day 43+1)
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"[14]) (p-level value)		
Comparison of drugs (statistical test[15]) (p-value)		
Indicator span diagram/ indicator scatter diagram		

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

Table 12. Summary table of the incidence of reported AEs in the group taking Mexidol by severity with randomization numbers of patients (N=)[16]

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
Eyes													
Cataract/10007739 Cataracta			1[3]/6116[17]								1		1
Vascular system													
Hypertensive crisis/10020802						1/7938[18]						1	1
...													

Table 13. Summary table of the incidence of reported AEs in the group taking placebo by severity with randomization numbers of patients (N=)[19]

Adverse eventcode 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
Eyes													
Vascular system													
...													

[16] R - AE related to the investigational product: UR - AE unrelated to the investigational product; R+UR - sum of related and unrelated AEs; nm - degree of relationship, where n is the number of AEs; m 1 - definite relationship; m 2 - probable relationship; m 3 - possible relationship

[17] 13/6116 means - one AE with a degree of possible relationship; 6116 - the patient's randomisation number

[18] 1/7938 means - one unrelated AE, 7938 - randomization number of the patient

[19] R - AE related to the investigational product: UR - AE unrelated to the investigational product; R+UR - sum of related and unrelated AEs; nm - degree of relationship, where n is the number of AEs; m 1 - definite relationship; m 2 - probable relationship; m 3 - possible relationship; for an example of filling in, see Table 12

Table 14. Summary table of the incidence of reported AEs in the group taking Mexidol = placebo by severity with randomization numbers of patients (N=)[20]

Adverse eventcode 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
Eyes													
Vascular system													
...													

Table 15. Summary table of the incidence of AEs after taking each investigational product

Adverse eventcode PT level according to MedDRA version	Mexidol N=		Mexidol+placebo N=		Placebo N=		P-value (Statistical criterion)
	n	%	n	%	n	%	
Eyes							
Vascular system							

Table 16. 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 product	Concomitant therapy	Date the AE resolved	Outcome
		Age, y											
		gender											

[20] A - AE associated with the investigational product: UR - AE unrelated to the investigational product; R+UR - sum of related and unrelated AEs; nm - degree of relationship, where n is the number of AEs; m 1 - definite relationship; m 2 - probable relationship; m 3 - possible relationship; for an example of filling in, see Table 12

		Weight, kg											
		Height, cm											
		race											

Table 17. 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

Table 18. Summary table of the incidence of reported SAEs in the group taking Mexidol by severity with randomization numbers of patients (N=)[21]

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
Eyes													
Vascular system													

Table 19. Summary table of the incidence of reported SAEs in the group taking placebo by severity with randomization numbers of patients (N=)[22]

Adverse event/code PT level according to MedDRA version	Mexidol N=		Mexidol+placebo N=		Placebo N=		P-value (Statistical criterion)
	n	%	n	%	n	%	

[21] A - SAE associated with the investigational product: UR - SAE unrelated to the investigational product; R+UR - sum of related and unrelated SAEs; nm - degree of relationship, where n is the number of AEs; m 1 - definite relationship; m 2 - probable relationship; m 3 - possible relationship; for an example of filling in, see Table 12

Eyes							
Vascular system							
...							

Table 20. Summary table of the incidence of reported SAEs in the group taking Mexidol+placebo by severity with randomization numbers of patients (N=)[23]

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
Eyes													
Vascular system													
...													

Table 21. Summary table of the incidence of SAEs after taking each investigational product

Adverse event/code PT level according to MedDRA version	Mexidol N=		Placebo N=		P-value (Statistical criterion)
	n	%	η	%	
Eyes					
Vascular system					
...					

Table 22. A list of all serious adverse events for each patient

Site number	Randomization number, full name	Demographic data	SAE/code, PT according	AE onset	Severity	Seriousness	Relationship	Actions taken in relation	Actions taken in relation to	Concomitant therapy	Date the AE resolved	Outcome

[23] A - SAE associated with the investigational product: UR - SAE unrelated to the investigational product; R+UR - sum of related and unrelated SAEs; nm - degree of relationship, where n is the number of AEs; m 1 - definite relationship; m 2 - probable relationship; m 3 - possible relationship; for an example of filling in, see Table 12

				to MedDRA version					to the patient	the investigational product			
		Age, y											
		gender											
		Weight, kg											
		Height, cm											
		race											

Table 23. Classification of SAEs according to MedDRA version

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