Statistical Analysis Plan

A prospective international multicentre randomized, double-blind, placebo-controlled parallel-group clinical trial to evaluate the safety and efficacy of 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 their sequential use in patients in the acute and early recovery periods of ischaemic stroke (MIR)

NCT Number: NCT06437626

Pharmasoft

November 12, 2021

Plan of statistical analysis of efficacy and safety parameters version 1.0 dated 12.11.2021 based on the results of

"A prospective international multicentre randomized double-blind placebo-controlled parallel-group clinical trial to evaluate the safety and efficacy of 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 their sequential use in patients in the acute and early recovery periods of ischaemic stroke (IS)" under protocol #PHS-APIS-004-MEX-SOL-TAB, version 1.3 dated 07.06.2021.

Plan for statistical analysis of efficacy and safety parameters

Approval sheet for the statistical analysis of efficacy and safety parameters, version 1.0 dated 12.11.2021, in "Prospective international multicentre randomized double-blind placebo-controlled parallel-group clinical trial to evaluate the safety and efficacy of 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 their sequential use in patients in the acute and early recovery periods of ischaemic stroke (IS)", protocol #PHS-APIS-004-MEX-SOL-TAB, version 1.3 dated 07.06.2021.

Project Manager

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History of changes to the document

Version number	Date of issue	Amendments	
		Section	**Modifications made**
1.0	12.11 .2021	New document	

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List of abbreviations

ALT - alanine aminotransferase;
AST - aspartate aminotransferase;
DBP - diastolic blood pressure;
IV - intravenous;
IM - intramuscular;
GGTP - gamma-glutamyl transpeptidase;
CI - confidence interval;
BMI - Body Mass Index;
MP - medicinal product;
AE - Adverse event;
AR - adverse reaction;
SBD - systolic blood pressure;
SAE - serious adverse event;
HR - respiratory rate;
HR - Heart rate;
ALP - alkaline phosphatase;
eCRF - electronic case report form;
ECG - electrocardiography.
ANOVA - Analysis of variance;
CTCAE - Common Toxicity Criteria for Adverse Events;
GCP - Good Clinical Practice;
HADS - Hospital Anxiety and Depression Scale;
ITT - Intent-to-treat population, includes all randomized patients regardless of investigational product/placebo administration
MedDRA - Medical Dictionary for Regulatory Activities;
mITT - modified Intent-to-treat population includes patients who have completed the full course of therapy, regardless of the presence of violations/ deviations from the Protocol;
MoCA - Montreal Cognitive Assessment Scale;
mRS - Modified Rankin Scale;
NIHSS - National Institutes of Health Stroke Scale;
PP - Per protocol population includes patients who completed the trial according to the Protocol.

In the tables of efficacy and safety of the medicinal products Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) vs. placebo the following parameters of descriptive statistics will be given:
N - number of valid observations;
Mean - arithmetic mean;
Median - middle point in a dataset
Min - minimum value;
Max - maximum value;
Q_1 - lower quartile;
Q_3 - upper quartile;

SD - standard deviation;
CV - coefficient of variation.

1. Trial background

Trial title: Prospective international multicentre randomized, double-blind, placebo-controlled, parallel-group clinical trial to evaluate the safety and efficacy of 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 their sequential use in patients in the acute and early recovery periods of ischaemic stroke (MIR).
Protocol No.: PHS-APIS-004-MEX-SOL-TAB, version 1.3 dated 07.06.2021
Sponsor: RPC PHARMASOFT LLC, Russia
Investigational product: Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) 10 ml (500 mg) BID by intravenous drip in 100-200 ml of 0.9% NaCl solution for 10 days and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) 1 tablet TID for the next 60 days.
Comparison product: Placebo 1, solution for intravenous and intramuscular injection, 10 ml BID by intravenous drip in 100-200 ml of 0.9% NaCl solution for 10 days and Placebo 2, film-coated tablets, 1 tablet TID for the next 60 days.
Development Phase: III
Trial design: A prospective multicentre, randomized, double-blind, parallel-group comparative clinical trial.
Number of patients: 304
Purpose of the trial: comparative evaluation of efficacy and safety of 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 comparison with placebo during their sequential use in patients in the acute and early recovery periods of ischaemic stroke.
Trial objectives:

1. To evaluate the efficacy of Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) during their sequential use in patients in the acute and early recovery periods of ischaemic stroke vs. placebo.
2. To carry out a comparative evaluation of the frequency and severity of adverse events of Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) during their sequential use in patients in the acute and early recovery periods of ischaemic stroke vs. placebo.

Additional objective: To carry out a comparative evaluation of pharmacodynamic effects of 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) during their sequential use in patients in the acute and early recovery periods of ischaemic stroke vs. placebo.

Plan for statistical analysis of efficacy and safety parameters

Primary endpoint:

The magnitude of change in the patient's mRS (Modified Rankin Scale) score at the end of therapy vs. baseline (in scores).

Secondary endpoints:

1. The magnitude of change in the patient's mRS (Modified Rankin Scale) score at the end of parenteral therapy vs. baseline (in scores).
2. Proportion of disabled patients (mRS score 3 or more) at the end of therapy vs. baseline;
3. Proportion of disabled patients (mRS score 3 or more) at the end of parenteral therapy vs. baseline;
4. The magnitude of change in the patient's NIHSS (National Institutes of Health Stroke Scale) score at the end of therapy vs. baseline (in scores).
5. The magnitude of change in the patient's NIHSS (National Institutes of Health Stroke Scale) score at the end of parenteral therapy vs. baseline (in scores).
6. The magnitude of change in the patient's MoCA cognitive status score at the end of therapy vs. baseline (in scores).
7. The magnitude of change in the patient's MoCA cognitive status score at the end of parenteral therapy vs. baseline (in scores).
8. The magnitude of change in the patient's Rivermead Mobility Index score at the end of therapy vs. baseline (in scores).
9. The magnitude of change in the results of the patient's state assessment by the Rivermead mobility index at the end of the parenteral course of therapy vs. baseline (in scores).
10. The magnitude of change in the patient's HADS score at the end of therapy vs. baseline (in scores).
11. The magnitude of change in the patient's HADS score at the end of parenteral therapy vs. baseline (in scores).

Criteria for assessing pharmacodynamic effects:

1. The magnitude of change in the results of assessment of LPO activity (malonic dialdehyde) and AOS indicators (superoxide dismutase, Se-dependent glutathione peroxidase) at the end of therapy vs. baseline;
2. The magnitude of change in the results of assessment of LPO activity (malonic dialdehyde) and AOS indicators (superoxide dismutase, Se-dependent glutathione peroxidase) at the end of the parenteral course of therapy vs. baseline;
3. The magnitude of change in the results of evaluation of laboratory parameters reflecting ED (Willebrandt factor, endothelin 1, homocysteine) and antihypoxant effect (hypoxia-inducible factor HIF-Iα, lactate, neuron-specific enolase) at the end of therapy vs. baseline;
4. The magnitude of change in the results of evaluation of laboratory parameters reflecting ED (Willebrandt factor, endothelin 1, homocysteine) and antihypoxant effect (hypoxia-inducible factor HIF-1α, lactate, neuron-specific enolase) at the end of the parenteral course of therapy vs. baseline.

Plan for statistical analysis of efficacy and safety parameters

Safety parameters

Safety and tolerability will be assessed throughout the trial (from first use of the investigational product/placebo) using the following data:

1. AE/SAE reports data,
2. Physical examination data, vital signs (BP, HR, respiratory rate, body temperature),
3. Indicators of laboratory analyses and instrumental methods of examination.

A conclusion on the safety of the investigational product will be made after statistical evaluation of all AEs, including serious SAEs with at least a possible association with the use of the investigational product.

Applicable significance level: probability of a 1st kind of error is set at 5%. As an interim analysis of the primary endpoint data is planned, a genus I error correction approach α (α = 0.0294) will be used to prove the hypothesis of "superiority" of investigational product therapy vs. placebo therapy for the primary efficacy criterion.

2. Purpose of data statistical analysis

The purpose of the development of this Statistical Analysis Plan is to describe the planned analysis of efficacy and safety data in the "Prospective international multicentre randomized double-blind placebo-controlled parallel-group clinical trial to evaluate the efficacy and safety of 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 their sequential use in patients in the acute and early recovery periods of ischaemic stroke (IS)" under protocol #PHS-APIS-004-MEX-SOL-TAB, version 1.3 dated 07.06.2021, 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.

The trial will be conducted in accordance with the Protocol, in strict compliance with applicable regulatory requirements, including but not limited to:

- Constitution of the Russian Federation;
- Current version of the Federal Law of the Russian Federation dated 21 November 2011 No. 323-FZ "On the Fundamentals of Health Protection of Citizens in the Russian Federation";
- Current version of the Federal Law of the Russian Federation No. 61-FZ "On Circulation of Medicines" dated 12 April 2010;
- Current version of the Federal Law of the Russian Federation dated 27 July 2006 N 152-FZ "On Personal Data"
- Order of the Ministry of Health of the Russian Federation No. 200 n of 01.04.2016. "On Approval of the Rules of Good Clinical Practice";
- Russian National Standard GOST R 52379-2005 "Good Clinical Practice", which complies with the standards of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical Products for Human Use (ICH) Good Clinical Practice Guidelines (ICH-GCP);

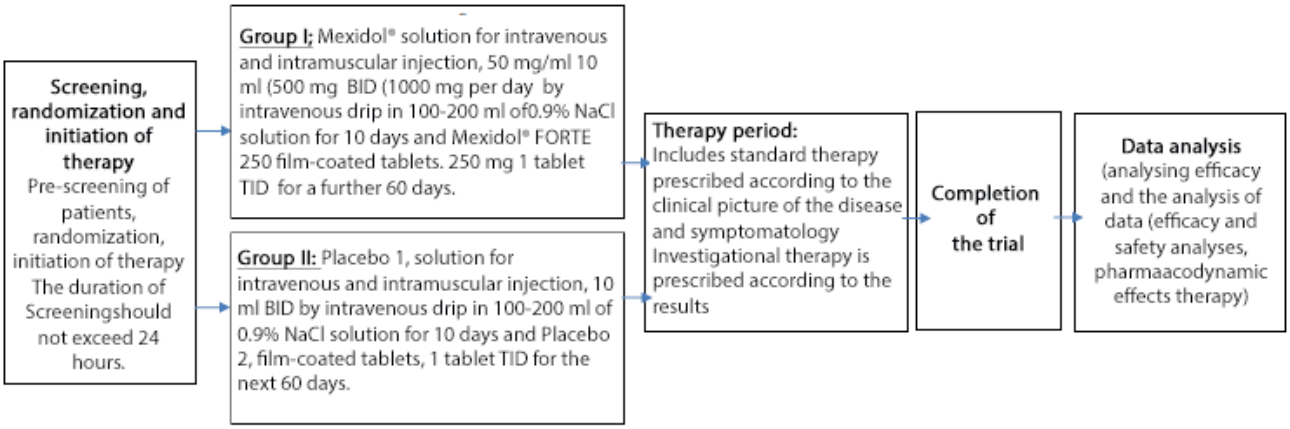
- Rules of Good Clinical Practice of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission dated 3 November 2016 No. 79;
- Rules of Compulsory Life and Health Insurance for Patients Participating in Clinical studies of a Medicinal Product approved by Resolution of the Government of the Russian Federation No. 714 dated 13 September 2010;
- Resolution of the Government of the Russian Federation No. 393 dated 18 May 2011 "On Amendments to the Model Rules for Compulsory Life and Health Insurance for Patients Participating in Clinical studies of a Medicinal Product";
- Rules of the International Conference on Harmonisation of Technical Requirements for Registration of Medicinal Products for Human Use;
- The World Medical Association's 1964 Declaration of Helsinki, most recently revised (Fortaleza, 2013);
- Guidelines for Expertise of Medicinal Products of FGBU NCESMP of the Ministry of Health of Russia (Moscow, 2013)
- Order of the Federal Service for Healthcare Oversight No. 1071 dated 15.02.2017 "On Approval of the Procedure for Pharmacovigilance";
- Order of the Ministry of Health and Social Development of the Russian Federation No. 757n dated 26.08.2010 "On Approval of the Procedure for Monitoring the Safety of Medicinal Products for Medical Use, Registration of Adverse Actions, Serious Adverse Reactions, Unexpected Adverse Reactions in the Use of Medicinal Products for Medical Use";

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).

3. Deviations from protocol

A statistical plan has been prepared and will be agreed prior to the statistical analysis. Statistical analyses were planned according to the Clinical Trial Protocol. Deviations from the protocol in statistical analyses are not planned. Any deviation from the protocol is permitted only in an emergency or after written authorization from the Sponsor. 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. All deviations of the present from the statistical analysis plan with their justification will be reported in the Clinical Trial Report. No changes will be made to the list of parameters to be evaluated. Statistical analysis methods may be changed if this would facilitate a more correct and informative analysis, any changes will be described and justified in the final Clinical Trial Report .

4. Trial procedures



5. Randomization

Table 1. Randomization scheme developed by Smooth Drug Development

Country	Block number	Randomization code	Therapy
Republic of Kazakhstan	001	616	B
Republic of Kazakhstan	001	174	A
Republic of Kazakhstan	001	637	B
Republic of Kazakhstan	001	869	A
Republic of Kazakhstan	2	455	A
Republic of Kazakhstan	2	548	B
Republic of Kazakhstan	2	687	A
Republic of Kazakhstan	2	809	B
Republic of Kazakhstan	3	810	B
Republic of Kazakhstan	3	680	A
Republic of Kazakhstan	3	294	A
Republic of Kazakhstan	3	513	B
Republic of Kazakhstan	4	180	A
Republic of Kazakhstan	4	467	B
Republic of Kazakhstan	4	986	A
Republic of Kazakhstan	4	365	B
Republic of Kazakhstan	5	865	A
Republic of Kazakhstan	5	678	B
Republic of Kazakhstan	5	671	B
Republic of Kazakhstan	5	677	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Republic of Uzbekistan	6	641	B
Republic of Uzbekistan	6	214	A
Republic of Uzbekistan	6	189	A
Republic of Uzbekistan	6	223	B
Republic of Uzbekistan	7	611	A
Republic of Uzbekistan	7	450	B
Republic of Uzbekistan	7	213	B
Republic of Uzbekistan	7	688	A
Republic of Uzbekistan	8	498	B
Republic of Uzbekistan	8	427	A
Republic of Uzbekistan	8	217	B
Republic of Uzbekistan	8	505	A
Republic of Uzbekistan	9	315	B
Republic of Uzbekistan	9	411	A
Republic of Uzbekistan	9	699	B
Republic of Uzbekistan	9	626	A
Republic of Uzbekistan	10	330	A
Republic of Uzbekistan	10	983	B
Republic of Uzbekistan	10	249	B
Republic of Uzbekistan	10	566	A
Russian Federation	11	933	B
Russian Federation	11	393	A
Russian Federation	11	507	B
Russian Federation	11	493	A
Russian Federation	12	524	A
Russian Federation	12	648	B
Russian Federation	12	697	A
Russian Federation	12	912	B
Russian Federation	13	303	A
Russian Federation	13	228	B
Russian Federation	13	802	A
Russian Federation	13	738	B
Russian Federation	14	435	A
Russian Federation	14	732	B
Russian Federation	14	456	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	14	279	B
Russian Federation	15	394	B
Russian Federation	15	804	A
Russian Federation	15	274	A
Russian Federation	15	238	B
Russian Federation	16	285	A
Russian Federation	16	160	B
Russian Federation	16	170	B
Russian Federation	16	876	A
Russian Federation	17	846	B
Russian Federation	017	757	A
Russian Federation	017	555	A
Russian Federation	017	131	B
Russian Federation	018	700	A
Russian Federation	018	154	B
Russian Federation	018	132	B
Russian Federation	018	197	A
Russian Federation	019	235	A
Russian Federation	019	835	B
Russian Federation	019	818	B
Russian Federation	019	656	A
Russian Federation	020	291	B
Russian Federation	020	337	A
Russian Federation	020	151	B
Russian Federation	020	785	A
Russian Federation	21	608	B
Russian Federation	21	344	A
Russian Federation	21	770	B
Russian Federation	21	772	A
Russian Federation	022	936	B
Russian Federation	022	923	A
Russian Federation	022	758	A
Russian Federation	022	705	B
Russian Federation	023	902	A
Russian Federation	023	329	B

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	023	198	A
Russian Federation	023	728	B
Russian Federation	024	156	A
Russian Federation	024	402	B
Russian Federation	024	459	B
Russian Federation	024	193	A
Russian Federation	025	999	B
Russian Federation	025	252	A
Russian Federation	025	900	B
Russian Federation	025	306	A
Russian Federation	026	874	B
Russian Federation	026	305	A
Russian Federation	026	173	B
Russian Federation	026	470	A
Russian Federation	027	251	A
Russian Federation	027	155	B
Russian Federation	027	119	B
Russian Federation	027	652	A
Russian Federation	028	613	B
Russian Federation	028	929	A
Russian Federation	028	896	A
Russian Federation	028	492	B
Russian Federation	029	623	A
Russian Federation	029	984	B
Russian Federation	029	761	A
Russian Federation	029	568	B
Russian Federation	030	917	A
Russian Federation	030	599	B
Russian Federation	030	601	B
Russian Federation	030	488	A
Russian Federation	031	447	B
Russian Federation	031	260	A
Russian Federation	031	750	A
Russian Federation	031	877	B
Russian Federation	032	694	B

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	032	169	A
Russian Federation	032	509	A
Russian Federation	032	273	B
Russian Federation	033	428	A
Russian Federation	033	144	B
Russian Federation	033	192	B
Russian Federation	033	469	A
Russian Federation	034	922	B
Russian Federation	034	893	A
Russian Federation	034	253	B
Russian Federation	034	817	A
Russian Federation	035	242	B
Russian Federation	035	811	A
Russian Federation	035	130	B
Russian Federation	035	711	A
Russian Federation	036	609	B
Russian Federation	036	476	A
Russian Federation	036	219	B
Russian Federation	036	395	A
Russian Federation	037	484	B
Russian Federation	037	718	A
Russian Federation	037	290	A
Russian Federation	037	152	B
Russian Federation	038	300	A
Russian Federation	038	992	B
Russian Federation	038	840	B
Russian Federation	038	230	A
Russian Federation	039	985	B
Russian Federation	039	946	A
Russian Federation	039	769	A
Russian Federation	039	522	B
Russian Federation	040	736	B
Russian Federation	040	808	A
Russian Federation	040	431	B
Russian Federation	040	495	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	041	137	B
Russian Federation	041	970	A
Russian Federation	041	905	A
Russian Federation	041	715	B
Russian Federation	042	215	A
Russian Federation	042	508	B
Russian Federation	042	774	A
Russian Federation	042	832	B
Russian Federation	043	713	A
Russian Federation	043	782	B
Russian Federation	043	250	B
Russian Federation	043	432	A
Russian Federation	044	501	B
Russian Federation	044	845	A
Russian Federation	044	960	A
Russian Federation	044	667	B
Russian Federation	045	570	B
Russian Federation	045	903	A
Russian Federation	045	257	B
Russian Federation	045	943	A
Russian Federation	046	413	B
Russian Federation	046	857	A
Russian Federation	046	218	A
Russian Federation	046	825	B
Russian Federation	047	500	A
Russian Federation	047	650	B
Russian Federation	047	875	A
Russian Federation	047	849	B
Russian Federation	048	227	B
Russian Federation	048	976	A
Russian Federation	048	220	A
Russian Federation	048	165	B
Russian Federation	049	696	B
Russian Federation	049	379	A
Russian Federation	049	403	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	049	147	B
Russian Federation	050	582	B
Russian Federation	050	157	A
Russian Federation	050	539	B
Russian Federation	050	642	A
Russian Federation	051	831	B
Russian Federation	051	884	A
Russian Federation	051	504	B
Russian Federation	051	727	A
Russian Federation	052	270	A
Russian Federation	052	210	B
Russian Federation	052	895	A
Russian Federation	052	120	B
Russian Federation	053	102	A
Russian Federation	053	380	B
Russian Federation	053	239	A
Russian Federation	053	466	B
Russian Federation	054	624	A
Russian Federation	054	229	B
Russian Federation	054	996	A
Russian Federation	054	768	B
Russian Federation	055	815	A
Russian Federation	055	640	B
Russian Federation	055	339	B
Russian Federation	055	562	A
Russian Federation	056	887	B
Russian Federation	056	338	A
Russian Federation	056	378	B
Russian Federation	056	942	A
Russian Federation	057	867	B
Russian Federation	057	837	A
Russian Federation	057	918	A
Russian Federation	057	264	B
Russian Federation	058	232	B
Russian Federation	058	945	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	058	363	B
Russian Federation	058	627	A
Russian Federation	059	981	A
Russian Federation	059	353	B
Russian Federation	059	209	B
Russian Federation	059	112	A
Russian Federation	060	765	B
Russian Federation	060	256	A
Russian Federation	060	904	B
Russian Federation	060	163	A
Russian Federation	061	162	A
Russian Federation	061	779	B
Russian Federation	061	776	A
Russian Federation	061	939	B
Russian Federation	062	991	B
Russian Federation	062	263	A
Russian Federation	062	520	A
Russian Federation	062	325	B
Russian Federation	063	899	A
Russian Federation	063	590	B
Russian Federation	063	533	B
Russian Federation	063	327	A
Russian Federation	064	222	A
Russian Federation	064	592	B
Russian Federation	064	871	B
Russian Federation	064	168	A
Russian Federation	065	979	B
Russian Federation	065	659	A
Russian Federation	065	474	A
Russian Federation	065	299	B
Russian Federation	066	308	A
Russian Federation	066	587	B
Russian Federation	066	318	B
Russian Federation	066	407	A
Russian Federation	067	494	B

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	067	527	A
Russian Federation	067	645	B
Russian Federation	067	212	A
Russian Federation	068	878	B
Russian Federation	068	658	A
Russian Federation	068	702	B
Russian Federation	068	812	A
Russian Federation	069	345	B
Russian Federation	069	361	A
Russian Federation	069	775	B
Russian Federation	069	201	A
Russian Federation	070	657	A
Russian Federation	070	397	B
Russian Federation	070	543	A
Russian Federation	070	401	B
Russian Federation	071	730	B
Russian Federation	071	343	A
Russian Federation	071	559	A
Russian Federation	071	980	B
Russian Federation	072	646	A
Russian Federation	072	418	B
Russian Federation	072	851	B
Russian Federation	072	261	A
Russian Federation	073	585	B
Russian Federation	073	506	A
Russian Federation	073	490	A
Russian Federation	073	692	B
Russian Federation	074	799	B
Russian Federation	074	489	A
Russian Federation	074	178	B
Russian Federation	074	243	A
Russian Federation	075	967	B
Russian Federation	075	673	A
Russian Federation	075	862	B
Russian Federation	075	346	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	076	630	B
Russian Federation	076	644	A
Russian Federation	076	436	A
Russian Federation	076	792	B
Russian Federation	077	963	B
Russian Federation	077	240	A
Russian Federation	077	689	A
Russian Federation	077	150	B
Russian Federation	078	265	B
Russian Federation	078	433	A
Russian Federation	078	451	B
Russian Federation	078	534	A
Russian Federation	079	948	B
Russian Federation	079	940	A
Russian Federation	079	564	B
Russian Federation	079	858	A
Russian Federation	080	183	A
Russian Federation	080	479	B
Russian Federation	080	485	B
Russian Federation	080	748	A
Russian Federation	081	384	A
Russian Federation	081	586	B
Russian Federation	081	575	A
Russian Federation	081	368	B
Russian Federation	082	593	B
Russian Federation	082	883	A
Russian Federation	082	916	A
Russian Federation	082	224	B
Russian Federation	083	944	B
Russian Federation	083	990	A
Russian Federation	083	625	A
Russian Federation	083	952	B
Russian Federation	084	499	A
Russian Federation	084	108	B
Russian Federation	084	698	B

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Country	Block number	Randomization code	Therapy
Russian Federation	084	607	A
Russian Federation	085	675	A
Russian Federation	085	733	B
Russian Federation	085	669	A
Russian Federation	085	783	B
Russian Federation	086	679	A
Russian Federation	086	472	B
Russian Federation	086	115	A
Russian Federation	086	597	B
Russian Federation	087	289	B
Russian Federation	087	726	A
Russian Federation	087	594	A
Russian Federation	087	313	B
Russian Federation	088	563	A
Russian Federation	088	268	B
Russian Federation	088	710	B
Russian Federation	088	124	A
Russian Federation	089	158	B
Russian Federation	089	376	A
Russian Federation	089	387	B
Russian Federation	089	388	A
Russian Federation	090	856	A
Russian Federation	090	237	B
Russian Federation	090	879	A
Russian Federation	090	236	B
Russian Federation	091	182	A
Russian Federation	091	629	B
Russian Federation	091	889	B
Russian Federation	091	558	A
Russian Federation	092	719	A
Russian Federation	092	553	B
Russian Federation	092	245	B
Russian Federation	092	292	A
Russian Federation	093	414	B
Russian Federation	093	618	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	093	516	A
Russian Federation	093	781	B
Russian Federation	094	544	B
Russian Federation	094	880	A
Russian Federation	094	763	B
Russian Federation	094	475	A
Russian Federation	095	331	B
Russian Federation	095	614	A
Russian Federation	095	722	A
Russian Federation	095	478	B
Russian Federation	096	739	B
Russian Federation	096	833	A
Russian Federation	096	755	A
Russian Federation	096	271	B
Russian Federation	097	389	A
Russian Federation	097	668	B
Russian Federation	097	525	A
Russian Federation	097	752	B
Russian Federation	098	842	A
Russian Federation	098	284	B
Russian Federation	098	660	B
Russian Federation	098	826	A
Russian Federation	099	352	A
Russian Federation	099	794	B
Russian Federation	099	143	B
Russian Federation	099	532	A
Russian Federation	100	246	B
Russian Federation	100	135	A
Russian Federation	100	589	B
Russian Federation	100	443	A
Russian Federation	101	211	A
Russian Federation	101	322	B
Russian Federation	101	834	B
Russian Federation	101	446	A
Russian Federation	102	805	A

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	102	312	B
Russian Federation	102	966	A
Russian Federation	102	604	B
Russian Federation	103	277	A
Russian Federation	103	511	B
Russian Federation	103	176	A
Russian Federation	103	114	B
Russian Federation	104	915	B
Russian Federation	104	423	A
Russian Federation	104	647	A
Russian Federation	104	550	B
Russian Federation	105	753	B
Russian Federation	105	571	A
Russian Federation	105	634	A
Russian Federation	105	914	B
Russian Federation	106	686	A
Russian Federation	106	113	B
Russian Federation	106	369	A
Russian Federation	106	159	B
Russian Federation	107	852	B
Russian Federation	107	684	A
Russian Federation	107	390	A
Russian Federation	107	622	B
Russian Federation	108	674	B
Russian Federation	108	778	A
Russian Federation	108	947	A
Russian Federation	108	969	B
Russian Federation	109	596	B
Russian Federation	109	751	A
Russian Federation	109	438	A
Russian Federation	109	591	B
Russian Federation	110	666	B
Russian Federation	110	541	A
Russian Federation	110	295	A
Russian Federation	110	106	B

Plan for statistical analysis of efficacy and safety parameters

Country	Block number	Randomization code	Therapy
Russian Federation	111	123	B
Russian Federation	111	100	A
Russian Federation	111	139	A
Russian Federation	111	631	B
Russian Federation	112	302	A
Russian Federation	112	206	B
Russian Federation	112	349	A
Russian Federation	112	420	B
Russian Federation	113	359	B
Russian Federation	113	430	A
Russian Federation	113	797	B
Russian Federation	113	780	A
Russian Federation	114	740	A
Russian Federation	114	457	B
Russian Federation	114	860	A
Russian Federation	114	577	B
Russian Federation	115	606	B
Russian Federation	115	122	A
Russian Federation	115	549	A
Russian Federation	115	288	B

Therapy A - Investigational product solution for intravenous and intravenous administration and investigational product film-coated tablets;
Therapy B - Placebo 1 solution for intravenous and intravenous administration and Placebo 2 film-coated tablets.

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

The ITT, mITT and PP populations will be used for efficacy analyses, with the PP population planned to be used as the main population.

The following indicator has been chosen as the **primary efficacy criterion**:

The magnitude of change in the patient's mRS (Modified Rankin Scale) score at the end of therapy vs. baseline (in scores).

The following indicators were selected as **secondary** endpoints:

- The magnitude of change in the patient's mRS (Modified Rankin Scale) score at the end of parenteral therapy vs. baseline (in scores).
- Proportion of disabled patients (mRS score 3 or more) at the end of therapy vs. baseline;
- Proportion of disabled patients (mRS score 3 or more) at the end of parenteral therapy vs. baseline;

- The magnitude of change in the patient's NIHSS (National Institutes of Health Stroke Scale) score at the end of therapy vs. baseline (in scores).
- The magnitude of change in the patient's NIHSS (National Institutes of Health Stroke Scale) score at the end of parenteral therapy vs. baseline (in scores).
- The magnitude of change in the patient's MoCA cognitive status score at the end of therapy vs. baseline (in scores).
- The magnitude of change in the patient's MoCA cognitive status score at the end of parenteral therapy vs. baseline (in scores).
- The magnitude of change in the patient's Rivermead Mobility Index score at the end of therapy vs. baseline (in scores).
- The magnitude of change in the results of the patient's state assessment by the Rivermead mobility index at the end of the parenteral course of therapy vs. baseline (in scores).
- The magnitude of change in the patient's HADS score at the end of therapy vs. baseline (in scores).
- The magnitude of change in the patient's HADS score at the end of parenteral therapy vs. baseline (in scores).

The **criteria for assessing pharmacodynamic effects** are listed below:

- The magnitude of change in the results of assessment of LPO activity (malonic dialdehyde) and AOS indicators (superoxide dismutase, Se-dependent glutathione peroxidase) at the end of therapy vs. baseline;
- The magnitude of change in the results of assessment of LPO activity (malonic dialdehyde) and AOS indicators (superoxide dismutase, Se-dependent glutathione peroxidase) at the end of the parenteral course of therapy vs. baseline;
- The magnitude of change in the results of evaluation of laboratory parameters reflecting ED (Willebrandt factor, endothelin 1, homocysteine) and antihypoxant effect (hypoxia-inducible factor HIF-Iα, lactate, neuron-specific enolase) at the end of therapy vs. baseline;
- The magnitude of change in the results of evaluation of laboratory parameters reflecting ED (Willebrandt factor, endothelin 1, homocysteine) and antihypoxant effect (hypoxia-inducible factor HIF-1α, lactate, neuron-specific enolase) at the end of the parenteral course of therapy vs. baseline.

Safety and tolerability will be assessed throughout the trial (from first use of the investigational product/placebo) using the following data:

1. AE/SAE reports data,
2. Physical examination data, vital signs (BP, HR, respiratory rate, body temperature),
3. Indicators of laboratory analyses and instrumental methods of examination.

A conclusion on the safety of the investigational product will be made after statistical evaluation of all AEs, including serious SAEs with at least a possible association with the use of the investigational product.

7. Statistical hypothesis

The trial plans to test the hypothesis of "superiority" of therapy with the investigational product vs. placebo therapy. The following indicator was chosen as the primary efficacy criterion: "The magnitude of change in the patient's mRS (Modified Rankin Scale) score at the

end of therapy (Day 71) vs. baseline (in scores)"

In the case of a superiority trial, the null hypothesis (H0) and the alternative hypothesis (H1) are formulated as follows:

$$H_0: \varepsilon = \mu_T - \mu_p \leq \delta,$$
$$H_1: \varepsilon > \delta, \delta > 0, \text{ where}$$

- ε - true difference between the value of the primary efficacy index (μ_τ) in the group of patients taking the investigational product (T) and the value of the primary efficacy index (μ_p) in the group of patients taking placebo,
- δ - the boundary of "superiority" of therapy with the investigational product compared to placebo therapy by the primary efficacy indicator.

To prove superiority of therapy with an investigational product compared with placebo therapy, the lower bound of the 95% one-sided confidence interval (CI) for the difference in values of the primary efficacy criterion ($\mu_\tau - \mu_p$) must be greater than δ, where $\delta > 0$, i.e. CI must fall within the interval $(\delta, +\infty)$.

8. Estimation of the required sample size

The sample size calculation was based on the results of the Phase III clinical trial of Mexidol® [Multicentre randomized double-blind placebo-controlled parallel-group clinical trial of the safety and efficacy of MEXIDOL® (solution for intravenous and intravenous administration / coated tablets) in long-term sequential therapy in patients with hemispheric ischaemic stroke in the acute and early recovery periods - (EPICA)] dated 30.09.2016.

To calculate the sample size, data from the EPICA clinical trial were used for the ITT population (patients who received the investigational product or placebo at least once), as this population allows us to draw conclusions about the efficacy of the investigational therapy on the population closest to the patient population in real clinical practice.

According to the results of the EPICA clinical trial, the mean value of the change in the mRS score at the end of the course of therapy relative to the baseline level in the group of therapy with the investigational product was (mean (SD)) 278 (0.755) scores, in the placebo group - 1.986 (0.847) scores 2.278 (0.755) scores, in the group of placebo therapy - 1.986 (0.847) scores, the difference (Mexidol® - placebo) is 0.292 scores, 95% confidence interval for the difference (Mexidol® - placebo) is (0.027, 0.556). The "superiority" boundary (δ) was chosen as the lower boundary of the confidence interval constructed for the difference (Mexidol® - placebo). Thus, $\delta = 0.027$ scores.

To test the hypothesis of "superiority" of therapy with the investigational product compared with placebo therapy at a significance level of $\alpha = 0.05$ (5%) to ensure power1-$\beta = 0.8$ (80%) , the sample size was calculated for the primary efficacy criterion given the parallel design, a 1:1 randomization scheme (i.e., k= 1 - the ratio of sample sizes of the groups nT/ ppl.i.e. k = 1 - the ratio of sample sizes in the groups n_T/n_p), the expected difference in efficacy between the compared drugs $\varepsilon = 0.292$ and with a mixed standard deviation (SD) of the in-group efficacy $\sigma = 0.802$ scores.

The formula [Chow Sh.-Ch., Shao J., Wang H., 2008] was used in the calculation:

$$n_T = n_R = \frac{(1 + 1/k) \times (z_a + z_\beta) \times \sigma^2}{(\varepsilon - \delta)^2}$$

where z_α and z_β - quantiles of the normal distribution N (0,1) (mean: 0, standard deviation: 1).

The minimum number of patients completing the trial according to the protocol must be at least N=2x 114=228 patients (114 patients per group).

Given the possible attrition of patients in the trial, it is planned to **randomize 304 patients**, of whom **at least 228 should complete the trial according to the Protocol**.

The trial plans to conduct an interim analysis of the data, based on which a decision will be made whether to end the trial (if the trial objective is met) or to enroll the additional number of patients needed to confirm the efficacy of the drug, followed by pooling of all data for the final analysis.

9. Statistical evaluation of efficacy parameters and pharmacodynamic effects

Statistical processing of the data (case report forms of all sites) at the end of the trial will be carried out by staff not involved in the management of the patients participating in the trial, in order to create conditions for independent evaluation of the results obtained. The data will be processed in an electronic database using statistical programmes with the necessary functions (TIBCO® Statistica™ v.13 or higher and R v.3.6.2 or higher or other specialised software that determines the appropriate quality of the results obtained).

Descriptive statistics are provided for demographics, baseline values of indices, and values of efficacy and safety indicators at trial visits for the drugs being compared.

Interval (quantitative) data will be described using: arithmetic mean, standard deviation, median, lower (25%) and upper (75%) quartiles, minimum, maximum and coefficient of variation. Categorical (qualitative) data will be described using frequencies, percentages and/or fractions.

The results of quantitative variables evaluation whose distribution follows the law of normal distribution will be presented as M±SD, where M - mean and SD - standard deviation. The results of quantitative variables evaluation whose distribution does not follow the law of normal distribution will be presented as Me [Q_1; Q_3], where Me - median and Q_1 and Q_3 - lower and upper quartiles.

The Shapiro-Wilk criterion will be applied to select parametric or non-parametric methods of analysis. When testing statistical hypotheses, parametric criteria will be used for indicators that have a normal distribution, and non-parametric criteria will be used for indicators with distribution other than normal. Demographic characteristics and descriptive statistics for baseline indicator values will be presented for the population of all randomized patients.

The primary efficacy variable will be analysed in the PP population (main), and in the ITT and mITT populations (additional). Confirmation of superiority of therapy with Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) over placebo therapy will be based on the magnitude of change in the patient's mRS (Modified Rankin Scale) scores at the end of the therapy (Day 71) vs. baseline (in scores).

Secondary efficacy and safety endpoints and their changes will be presented using descriptive statistics by visit and therapy group. On trial visits, qualitative (dichotomous) measures will be compared between groups on the basis of Pearson 's $\chi 2$ testor, if the frequency

of a feature in at least one subgroup is 5 or less, Fisher's exact test (or Fisher-Freeman-Galton test for tables of arbitrary dimensionality). Differences with p values of<0.05 will be considered statistically significant.

To compare quantitative data distributed according to the normal distribution law, it is planned to use standard parametric criteria: Student's t-test for dependent/independent samples, analysis of variance (ANOVA) for repeated measures.

It is planned to use standard nonparametric criteria to compare quantitative data distributed according to a law other than normal: Mann-Whitney U-test, Wilcoxon T-test, Friedman's test.

Benjamini-Yekutili correction will be used for multiple statistical hypothesis testing.

A one-sided test will be applied to analyse the primary endpoint and two-sided statistical tests will be applied to analyse all secondary endpoints.

Scatter plots (boxplots) will be presented for all quantitative measures of efficacy and safety. Data whose distribution differs from normal at least at one visit in one of the groups will be presented as median and interquartile range; data whose distribution is normal at all visits will be presented as mean ± standard deviation.

Pharmacodynamic effects will be analysed in a subpopulation of patients participating in the evaluation of the pharmacodynamic effects of the investigational therapy.

The resulting data will be analysed using the methods outlined for the application of the efficacy data assessment.

The p-level values <0.05 will be considered statistically significant.

The trial did not include interim statistical analyses.

The application of methods of statistical analysis of the obtained data will be determined by their nature, type and features of their distribution. The feasibility of using a number of statistical methods will be assessed after the completion of the data set, due to the unknown nature of their distribution, sample homogeneity, etc. During the course of the analysis, it is possible to expand the list of methods used if it is necessary for qualitative data processing.

All data obtained from the trial are subject to analysis. The final analysis of efficacy parameters will be performed after the clinical part of the trial is completed and the electronic database is finalised. If errors are identified in the electronic database prior to finalisation that cannot be resolved after the completion of patient participation in the trial, the statistical analysis of the data will include an analysis of the sensitivity of the resulting parameters to the presence of questionable data.

10. Safety analysis

Safety indicators as well as their changes will be presented using descriptive statistics by visit and therapy group. On trial visits, qualitative (dichotomous) measures will be compared between groups on the basis of Pearson 's $\chi 2$ testor, if the frequency of a feature in at least one subgroup is 5 or less, Fisher's exact test (or Fisher-Freeman-Galton test for tables of arbitrary dimensionality).

The dynamics of quantitative safety indicators relative to baseline values will be evaluated and compared with each other using ANOVA analysis of variance with repeated measures. This method allows to simultaneously check the presence of statistically significant dynamics (at least one mean value in one time point differs from the rest), as well as to compare the dynamics and ranges of values of the indicator when receiving the compared preparations. In case of inappropriate use of parametric methods, similar analysis of changes in the distributions of

indicators during therapy will be carried out using non-parametric analogues - Friedman test and Wilcoxon sign rank test, and intergroup comparisons of changes - using the Wilcoxon-Mann-Whitney test.

The number and proportion of patients with reported adverse events after the first dose of the investigational product will be tabulated by therapeutic group. Descriptive statistics for adverse events will also be tabulated, taking into account severity, action taken and outcome.

The safety analyses will descriptively present the values of laboratory parameters as well as their changes from baseline values. In addition, clinically significant and nonsignificant deviations of laboratory values by visit will be tabulated by therapeutic group.

Safety assessment will be carried out based on the analysis of the frequency of occurrence of all adverse events, dynamics of laboratory and instrumental parameters.

AEs are recorded after the first use of the drug until the patient completes the trial and are tracked throughout the trial until they are resolved/stabilised.

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

Pre- and post-trial data will be compared to assess safety parameters.

All data will be analyzed on the safety population. Regardless of the reason for trial termination, data from all included patients will be included in the safety analyses of the trial therapy.

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.

Serious adverse event (SAE) - any adverse medical event that, regardless of the dose of the medicinal product, has resulted in death, is life threatening, requires hospitalization or its prolongation, has resulted in permanent or significant disability or impairment, is a congenital anomaly or birth defect or other medically significant event.

Adverse reaction (AR) - unintentional adverse body reaction associated with the use of a medicinal product/investigational product, suggesting at least a possible relationship with the use of a suspected medicinal product/investigational product.

Unexpected adverse reaction (UAE) - an adverse reaction, the nature, severity or outcome of which does not correspond to the information in the current instructions for medical use of the medicinal product or in the investigator's leaflet for an unregistered medicinal product.

Serious unexpected adverse reaction (SUAR) - an unexpected adverse reaction that is characterized by features of a SAE.

The parameters of the AE/SAE will be estimated as follows:

Severity of AEs:

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 follow-up is required; no intervention is indicated;
2. Moderate - only minimal, localised or non-invasive interventions are indicated; limitation of activities of daily living;

3. Severe - severe or clinically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation is indicated; loss of ability to work; limitation of self-care in activities of daily living;
4. Life-threatening / Disability - life-threatening consequences, urgent intervention required;
5. Fatal - death associated with an undesirable event.

Determination of the relationship of AE to the investigational product:

The investigator should assess the association of the adverse event with the investigational product:

- No - clearly and unequivocally related to extraneous causes only, and does not meet the criteria for an unclassifiable, conditional, doubtful, possible, probable or certain relationship.
- Yes - there is a reliable temporal relationship with the use of the medicinal product.

Criteria:

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

The degree of certainty of causality with the investigational product will be assessed using the WHO scale, taking into account the trial design (multiple administration):

Definite. Clinical manifestations of AEs, abnormalities of laboratory parameters occur during the period of drug administration, cannot be explained by the presence of existing diseases and the influence of other factors.

Probable. Clinical manifestations of AEs, abnormalities of laboratory parameters are related in time to the use of the drug, unlikely to be related to concomitant diseases or other factors.

Possible. Clinical manifestations of AEs, changes in laboratory parameters are related in time to the drug intake, but they can be explained by the presence of concomitant diseases or taking other drugs and the influence of chemical compounds.

Doubtful. Clinical manifestations of AEs, changes in laboratory parameters occur in the absence of a clear temporal relationship with the use of the drug; there are other factors (drugs, diseases, chemicals) that may be the cause of 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.

Foreseeability: assessed only for AEs considered to be an adverse reaction. An unexpected adverse reaction is an adverse reaction, the nature, severity or outcome of which does not correspond to the information in the current instructions for medical use of the medicinal product or in the investigator's leaflet for an unregistered medicinal product.

The outcome of an AE is assessed as follows:

- Transition to SAE - AE resulted in a condition that meets the criteria of seriousness (resulted in death, was life-threatening, required hospitalization of the patient or its prolongation, resulted in permanent or pronounced disability or incapacity, congenital anomalies or malformations, required medical intervention to prevent the development of these conditions. In case of any unexpected suspected transmission of an infectious agent through a medicinal product has occurred);
- Stabilization of the condition (unchanged condition) - the AE has not resolved;
- Recovery with consequences - resolution of an AE has occurred, but the patient still has some residual effects;
- Recovery / cessation of an AE without consequences - AE has completely resolved with no observable residual effects;
- Improvement of the condition is a reduction in the severity of an AE;
- Unknown - the outcome of an AE is unknown because the patient did not show up for the follow-up examination and attempts to obtain follow-up information were unsuccessful (lost for follow-up).

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.

Based on the results of the trial, after the final statistical analysis, a conclusion will be made about the efficacy and safety of different dosages in 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), vs. placebo. Table templates are provided in the annexes to this statistical plan.

11. Patient populations to be analysed

The following population groups will be used for the analyses:

- The ITT (Intent-to-treat) population will include all randomized patients regardless of investigational drug/placebo administration.
- The mITT (modified Intent-to-treat) population will include patients who have completed the full course of therapy, regardless of the presence of Protocol violations/ deviations.
- The PP (Per protocol) population will include patients who completed the trial in accordance with the Protocol.
- **Subpopulation of patients involved in the evaluation of the pharmacodynamic effects of the investigational therapy:** this population will include PP patients with relevant blood test results.

The primary population for the evaluation of efficacy criteria, proof of the hypothesis of

superiority of the investigational product therapy over placebo based on the primary efficacy criterion score, will be the PP population. Additionally, efficacy criteria will be analysed in the ITT and mITT populations. Safety parameters will be analysed in the ITT population.

At the stage of statistical data processing, additional analyses of the efficacy and/or safety of investigational product/placebo in subpopulations of patients of different age groups can be performed.

The final report will include data on all patients included in the trial, including those who dropped out at any time without explanation. No missing data will be supplemented.

12. Interim analysis

The trial plans to conduct an interim analysis of the data, based on which a decision will be made whether to end the trial (if the trial objective is met) or to enroll the additional number of patients needed to confirm the efficacy of the drug, followed by pooling of all data for the final analysis. The choice of this approach is due to the change in the design of the planned clinical trial, duration of use and dosages of the investigational product compared to the previously conducted clinical trial (EPICA).

In the first phase, an interim analysis of the primary endpoint data will be performed on all randomized patients (304 patients) at the end of the trial:

• If the required power ≥ 80% is achieved, a 95% one-sided confidence interval for the difference in values of the primary efficacy criterion (μ_τ - μ_p) will be used to prove the hypothesis of 'superiority'; the results obtained will be analysed and used to write the final clinical trial report.

If the calculated power is less than 80 per cent, the sample size will be recalculated based on the data obtained after the first stage to achieve a trial power of 80 per cent, using a correction for genus I error α (α = 0.0294). A protocol amendment will then be submitted to the Ministry of Health and, once approval is granted, the necessary additional number of patients will be enrolled, followed by pooling of all data for final analysis and writing of the final clinical trial report. A 97.06% one-sided confidence interval for the difference in values of the primary efficacy criterion (μ_τ - μ_p) constructed from pooled patient data, i.e. obtained from the first and second stage results, using α = 0.0294, will be used to prove the hypothesis of 'superiority'. The final clinical trial report will be written using data from all patients.

13. Table templates

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

Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
Anthropometric parameters							
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

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
BMI	Visit 0			normal/other than normal			normal/other than normal
Efficacy indicators							
mRS	Visit 0			normal/other than normal			normal/other than normal
mRS	Visit 2			normal/other than normal			normal/other than normal
mRS	Visit 4			normal/other than normal			normal/other than normal
NIHSS	Visit 0			normal/other than normal			normal/other than normal
NIHSS	Visit 2			normal/other than normal			normal/other than normal
NIHSS	Visit 4			normal/other than normal			normal/other than normal
MoCA	Visit 1			normal/other than normal			normal/other than normal
MoCA	Visit 2			normal/other than normal			normal/other than normal
MoCA	Visit 4			normal/other than normal			normal/other than normal
Rivermead	Visit 1			normal/other than normal			normal/other than normal
Rivermead	Visit 2			normal/other than normal			normal/other than normal
Rivermead	Visit 4			normal/other than normal			normal/other than normal
HADS	Visit 1			normal/other than normal			normal/other than normal
HADS	Visit 2			normal/other than normal			normal/other than normal
HADS	Visit 4			normal/other than normal			normal/other than normal
Indicators of pharmacodynamic effects							
Malonic dialdehyde	Visit 1			normal/other than normal			normal/other than normal
Malonic dialdehyde	Visit 2			normal/other than normal			normal/other than normal
Malonic dialdehyde	Visit 4			normal/other than normal			normal/other than normal
Superoxide dismutase	Visit 1			normal/other than normal			normal/other than normal
Superoxide dismutase	Visit 2			normal/other			normal/other

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
				than normal			than normal
Superoxide dismutase	Visit 4			normal/other than normal			normal/other than normal
Se-dependent glutathione peroxidase	Visit 1			normal/other than normal			normal/other than normal
Se-dependent glutathione peroxidase	Visit 2			normal/other than normal			normal/other than normal
Se-dependent glutathione peroxidase	Visit 4			normal/other than normal			normal/other than normal
Willebrandt factor	Visit 1			normal/other than normal			normal/other than normal
Willebrandt factor	Visit 2			normal/other than normal			normal/other than normal
Willebrandt factor	Visit 4			normal/other than normal			normal/other than normal
Endothelin 1	Visit 1			normal/other than normal			normal/other than normal
Endothelin 1	Visit 2			normal/other than normal			normal/other than normal
Endothelin 1	Visit 4			normal/other than normal			normal/other than normal
Homocysteine	Visit 1			normal/other than normal			normal/other than normal
Homocysteine	Visit 2			normal/other than normal			normal/other than normal
Homocysteine	Visit 4			normal/other than normal			normal/other than normal
Hypoxia-inducible factor HIF-1α	Visit 1			normal/other than normal			normal/other than normal
Hypoxia-inducible factor HIF-1α	Visit 2			normal/other than normal			normal/other than normal
Hypoxia-inducible factor HIF-Iα	Visit 4			normal/other than normal			normal/other than normal
Lactate	Visit 1			normal/other than normal			normal/other than normal
Lactate	Visit 2			normal/other than normal			normal/other than normal
Lactate	Visit 4			normal/other than normal			normal/other than normal
Neuron-specific enolase	Visit 1			normal/other than normal			normal/other than normal
Neuron-specific enolase	Visit 2			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
Neuron-specific enolase	Visit 4			normal/other than normal			normal/other than normal
Complete blood count							
Red blood cells	Visit 0			normal/other than normal			normal/other than normal
Red blood cells	Visit 2			normal/other than normal			normal/other than normal
Red blood cells	Visit 4			normal/other than normal			normal/other than normal
Haemoglobin	Visit 0			normal/other than normal			normal/other than normal
Haemoglobin	Visit 2			normal/other than normal			normal/other than normal
Haemoglobin	Visit 4			normal/other than normal			normal/other than normal
Haematocrit	Visit 0			normal/other than normal			normal/other than normal
Haematocrit	Visit 2			normal/other than normal			normal/other than normal
Haematocrit	Visit 4			normal/other than normal			normal/other than normal
Platelets	Visit 0			normal/other than normal			normal/other than normal
Platelets	Visit 2			normal/other than normal			normal/other than normal
Platelets	Visit 4			normal/other than normal			normal/other than normal
White blood cells	Visit 0			normal/other than normal			normal/other than normal
White blood cells	Visit 2			normal/other than normal			normal/other than normal
White blood cells	Visit 4			normal/other than normal			normal/other than normal
Platelets	Visit 0			normal/other than normal			normal/other than normal
Platelets	Visit 2			normal/other than normal			normal/other than normal
Platelets	Visit 4			normal/other than normal			normal/other than normal
Eosinophils (abs.)	Visit 0			normal/other than normal			normal/other than normal
Eosinophils (abs.)	Visit 2			normal/other than normal			normal/other than normal

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Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
Eosinophils (abs.)	Visit 4			normal/other than normal			normal/other than normal
Eosinophils (relative)	Visit 0			normal/other than normal			normal/other than normal
Eosinophils (relative)	Visit 2			normal/other than normal			normal/other than normal
Eosinophils (relative)	Visit 4			normal/other than normal			normal/other than normal
Basophils (abs.)	Visit 0			normal/other than normal			normal/other than normal
Basophils (abs.)	Visit 2			normal/other than normal			normal/other than normal
Basophils (abs.)	Visit 4			normal/other than normal			normal/other than normal
Basophils (relative)	Visit 0			normal/other than normal			normal/other than normal
Basophils (relative)	Visit 2			normal/other than normal			normal/other than normal
Basophils (relative)	Visit 4			normal/other than normal			normal/other than normal
Bacillary neutrophils (abs.)	Visit 0			normal/other than normal			normal/other than normal
Bacillary neutrophils (abs.)	Visit 2			normal/other than normal			normal/other than normal
Bacillary neutrophils (abs.)	Visit 4			normal/other than normal			normal/other than normal
Bacillary neutrophils (relative)	Visit 0			normal/other than normal			normal/other than normal
Bacillary neutrophils (relative)	Visit 2			normal/other than normal			normal/other than normal
Bacillary neutrophils (relative)	Visit 4			normal/other than normal			normal/other than normal
Segmented neutrophils (abs.)	Visit 0			normal/other than normal			normal/other than normal
Segmented neutrophils (abs.)	Visit 2			normal/other than normal			normal/other than normal
Segmented neutrophils (abs.)	Visit 4			normal/other than normal			normal/other than normal
Segmented neutrophils (relative)	Visit 0			normal/other than normal			normal/other than normal
Segmented neutrophils (relative)	Visit 2			normal/other than normal			normal/other than normal
Segmented neutrophils (relative)	Visit 4			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
Lymphocytes (abs.)	Visit 0			normal/other than normal			normal/other than normal
Lymphocytes (abs.)	Visit 2			normal/other than normal			normal/other than normal
Lymphocytes (abs.)	Visit 4			normal/other than normal			normal/other than normal
Lymphocytes (relative)	Visit 0			normal/other than normal			normal/other than normal
Lymphocytes (relative)	Visit 2			normal/other than normal			normal/other than normal
Lymphocytes (relative)	Visit 4			normal/other than normal			normal/other than normal
Monocytes (abs.)	Visit 0			normal/other than normal			normal/other than normal
Monocytes (abs.)	Visit 2			normal/other than normal			normal/other than normal
Monocytes (abs.)	Visit 4			normal/other than normal			normal/other than normal
Monocytes (relative)	Visit 0			normal/other than normal			normal/other than normal
Monocytes (relative)	Visit 2			normal/other than normal			normal/other than normal
Monocytes (relative)	Visit 4			normal/other than normal			normal/other than normal
ESR	Visit 0			normal/other than normal			normal/other than normal
ESR	Visit 2			normal/other than normal			normal/other than normal
ESR	Visit 4			normal/other than normal			normal/other than normal
Biochemical blood counts							
Urea	Visit 0			normal/other than normal			normal/other than normal
Urea	Visit 2			normal/other than normal			normal/other than normal
Urea	Visit 4			normal/other than normal			normal/other than normal
Creatinine	Visit 0			normal/other than normal			normal/other than normal
Creatinine	Visit 2			normal/other than normal			normal/other than normal
Creatinine	Visit 4			normal/other than normal			normal/other than normal

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Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
Glucose	Visit 0			normal/other than normal			normal/other than normal
Glucose	Visit 2			normal/other than normal			normal/other than normal
Glucose	Visit 4			normal/other than normal			normal/other than normal
AST	Visit 0			normal/other than normal			normal/other than normal
AST	Visit 2			normal/other than normal			normal/other than normal
AST	Visit 4			normal/other than normal			normal/other than normal
ALT	Visit 0			normal/other than normal			normal/other than normal
ALT	Visit 2			normal/other than normal			normal/other than normal
ALT	Visit 4			normal/other than normal			normal/other than normal
Total protein	Visit 0			normal/other than normal			normal/other than normal
Total protein	Visit 2			normal/other than normal			normal/other than normal
Total protein	Visit 4			normal/other than normal			normal/other than normal
Total cholesterol	Visit 0			normal/other than normal			normal/other than normal
Total cholesterol	Visit 2			normal/other than normal			normal/other than normal
Total cholesterol	Visit 4			normal/other than normal			normal/other than normal
Triglycerides	Visit 0			normal/other than normal			normal/other than normal
Triglycerides	Visit 2			normal/other than normal			normal/other than normal
Triglycerides	Visit 4			normal/other than normal			normal/other than normal
Vital signs							
SBP	Visit 0			normal/other than normal			normal/other than normal
SBP	Visit 2			normal/other than normal			normal/other than normal
SBP	Visit 3			normal/other than normal			normal/other than normal

Plan for statistical analysis of efficacy and safety parameters

Indicators	Stage	Investigational Products					
		Mexidol®			Placebo		
		W	P	Distribution	W	P	Distribution
SBP	Visit 4			normal/other than normal			normal/other than normal
DBD	Visit 0			normal/other than normal			normal/other than normal
DBD	Visit 2			normal/other than normal			normal/other than normal
DBD	Visit 3			normal/other than normal			normal/other than normal
DBD	Visit 4			normal/other than normal			normal/other than normal
HR	Visit 0			normal/other than normal			normal/other than normal
HR	Visit 2			normal/other than normal			normal/other than normal
HR	Visit 3			normal/other than normal			normal/other than normal
HR	Visit 4			normal/other than normal			normal/other than normal
RR	Visit 0			normal/other than normal			normal/other than normal
RR	Visit 2			normal/other than normal			normal/other than normal
RR	Visit 3			normal/other than normal			normal/other than normal
RR	Visit 4			normal/other than normal			normal/other than normal
Body temperature	Visit 0			normal/other than normal			normal/other than normal
Body temperature	Visit 2			normal/other than normal			normal/other than normal
Body temperature	Visit 3			normal/other than normal			normal/other than normal
Body temperature	Visit 4			normal/other than normal			normal/other than normal

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

MRS scale scores	Mexidol®							Placebo						
	Visit 0	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0		Visit 0	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0	
			Abs.	%		Abs.	%			Abs.	%		Abs.	%
N														
Mean														
Median														
Min														
Max														
Qi														
Q3														
SD														
CV														
Comparison of drugs (statistical test[1]) (p-value)														
Indicator span diagram/ indicator scatter diagram or indicator trend diagram														

Table 4. Outcome of primary endpoint analysis (template)

Primary endpoint	Mexidol® vs. Placebo

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

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	Difference in means	95% CI[2] lower limit	95% CI, upper limit	Power, %[3]	Superiority is confirmed[4]
The magnitude of change in the patient's mRS (Modified Rankin Scale) score at the end of therapy vs. baseline (in scores).					

Table 5. Statistical analysis of the NIHSS scale (template)

NIHSS scores	Mexidol®						Placebo					
	Visit 0	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0		Visit 0	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0	
			Abs.	%		Abs.	%			Abs.	%		Abs.	%
N														
Mean														
Median														
Min														
Max														
Qi														
Q3														
SD														
CV														

[2] Or "97.06% CI" for Stage 2
[3] Applicable for Stage 1 only
[4] According to the Clinical Trial Protocol, a conclusion of superiority can be made if the upper bound of the two-sided 95% confidence interval for the difference in mean changes in the mean deviation (MD) of Mexidol® compared to placebo is greater than the margin of superiority of investigational product therapy vs. placebo therapy.

Comparison of drugs (statistical test[5]) (p-value)
Indicator span diagram/ indicator scatter diagram or indicator trend diagram

Table 6. Statistical analysis of secondary endpoints (quantitative data, template)

Indicator[6]	**Mexidol®**							**Placebo**						
	Visit1	**Visit 2**	**Dynamics to Visit 0**		**Visit 4**	**Dynamics to Visit 0**		**Visit 1**	**Visit 2**	**Dynamics to Visit 0**		**Visit 4**	**Dynamics to Visit 0**	
			Abs.	**%**		**Abs.**	**%**			**Abs.**	**%**		**Abs.**	**%**
N														
Mean														
Median														
Min														
Max														
Qi														
Q3														
SD														
CV														
Comparison of drugs (statistical test[7]) (p-value)														
Indicator span diagram/ indicator scatter diagram or indicator trend diagram														

[5] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator
[6] MoCA and HADS scales, Rivermead index scores
[7] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

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Table 7. Statistical analysis of pharmacodynamic effect indicators (template)

Indicator[8]	Mexidol®							Placebo						
	Visit 1	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0		Visit 1	Visit 2	Dynamics to Visit 0		Visit 4	Dynamics to Visit 0	
			Abs.	%		Abs.	%			Abs.	%		Abs.	%
N														
Mean														
Median														
Min														
Max														
Qi														
Q3														
SD														
CV														
Comparison of drugs (statistical test[9]) (p-value)														
Indicator span diagram/ indicator scatter diagram or indicator trend diagram														

[8] Indicators of LPO activity (malonic dialdehyde) and AOS indicators (superoxide dismutase, Se-dependent glutathione peroxidase), as well as indicators reflecting ED (Willebrandt factor, endothelin 1, homocysteine) and antihypoxant action (hypoxia-inducible factor HIF-1α, lactate, neuron-specific enolase).

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

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Table 8. Statistical analysis of the proportion of disabled patients (template)

Percentage of disabled patients		Visit 2		Visit 4	
		Mexidol®	Placebo	Mexidol®	Placebo
Observed	Abs.				
	%				
Not observed	Abs.				
	%				
	%				
Comparison of groups (statistical criterion[10])					
p-level					

Table 9. Statistical analysis of safety indicators (quantitative data, template)

Safety indicator[11]	Mexidol®						Placebo			
	Visit 0	Visit 2	Visit 4	Dynamics to Visit 0		Visit 0	Visit 2	Visit 4	Dynamics to Visit 0	
				Abs.	%				Abs.	%
N										
Mean										
Median										
Min										
Max										
Qi										
Q3										
SD										
CV										
Comparison of drugs (statistical test[12]) (p-value)										
Indicator span diagram/ indicator scatter diagram or indicator trend diagram										

Table 10. Statistical analysis of vital signs (quantitative data, template)

Safety	Mexidol®	Placebo

[10] Pearson 's χ2 criterion or Fisher's exact test
[11] Clinical and biochemical blood counts.
[12] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

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indicator[13]	**Visit 0**	**Visit 2**	**Visit 3**	**Visit 4**	**Dynamics to Visit 0**		**Visit 0**	**Visit 2**	**Visit 3**	**Visit 4**	**Dynamics to Visit 0**	
					Abs.	**%**					**Abs.**	**%**
N												
Mean												
Median												
Min												
Max												
Qi												
Q3												
SD												
CV												
Comparison of drugs (statistical test[14]) (p-value)												
Indicator span diagram/ indicator scatter diagram or indicator trend diagram												

Table 11. Safety performance assessment results: repeated measures analysis of variance (template)

Safety Indicator/Investigational Product	**SS**	**DF**	**MS**	**F**	**p**
Intercept					
Investigational Product					
Error					
Visit					
Visit*Dru					
Error					

Table 12.Results of safety indicators assessment: non-parametric repeated measures analysis of variance (Friedman test, template)

Investigational Product					
Indicator					
Visit	**Average rank**	**Sum of ranks**	**Mean**	**SD**	**p**
Visit 1					
...					

[13] SBP, DBP, HR, RR, body temperature.
[14] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Table 13. Frequency analysis of safety performance outcome assessment (template)

Investigational Product		**Mexidol®**			**Placebo**		
		Visit 0	**Visit 2**	**Visit 4**	**Visit 0**	**Visit 2**	**Visit 4**
Indicator 1							
Normal	Abs.						
	%						
Deviation	Abs.						
	%						
	%						
Comparison of groups (statistical criterion[15])							
p-level							
Indicator 2							
...							

Table 14. Frequency analysis of the safety outcome measure score (clinical significance, template)

Investigational Product		**Mexidol®**			**Placebo**		
		Visit 0	**Visit 2**	**Visit 4**	**Visit 0**	**Visit 2**	**Visit 4**
Indicator 1							
Deviation is clinically significant	Abs.						
	%						
Deviation is clinically insignificant	Abs.						
	%						
	%						
Comparison of groups (statistical criterion[16])							
p-level							
Indicator 2							

[15] Pearson 's $\chi 2$ criterion or Fisher's exact test
[16] Pearson 's $\chi 2$ criterion or Fisher's exact test

Table 15. Statistical analysis of ECG (template)

Investigational Product		Mexidol®			Placebo		
		Visit 0	Visit 2	Visit 4	Visit 0	Visit 2	Visit 4
Normal	Abs.						
	%						
Deviation	Abs.						
	%						
	%						
Comparison of groups (statistical criterion[17])							
p-level							

Table 16. Statistical analysis of physical examination parameters (outcome measure, template)

Investigational Product		Mexidol®				Placebo			
		Visit 0	Visit 2	Visit 3	Visit 4	Visit 0	Visit 2	Visit 3	Visit 4
Indicator 1									
Normal	Abs.								
	%								
Deviation	Abs.								
	%								
	%								
Comparison of groups (statistical criterion[18])									
p-level									
Indicator 2									
...									

Table 17. Distribution of patients by ender (template)

Gender		Mexidol®	Placebo
Female	Abs.		
	%		
Male	Abs.		

[17] Pearson 's χ2 criterion or Fisher's exact test
[18] Pearson 's χ2 criterion or Fisher's exact test

	%		
Differences between		Pearson 's χ2 criterion	
groups			

Table 18. Baseline patient characteristics (template)

Indicator[19]	Mexidol®	Placebo
N		
Mean		
Median		
Min		
Max		
Qi		
Q3		
SD		
CV		
Comparison of groups	Statistical criterion[20], p-value	
Range diagram		**Scatter diagram**

Table 19. Total number of AEs (template)

AE		After administration of	
		Mexidol®	Placebo
Total number of AEs	Abs.		
Number of patients with detected AEs	Abs.		
	%		

Table 20. Relative risk of AEs (template)

Presence of adverse events in patients		Investigational Product	
		Mexidol®	Placebo
Identified	Abs.		
	%		
Not identified	Abs.		
	%		
Differences between preparations		Pearson 's χ2 criterion or Fisher's exact test	
Relative risk of AEs [95% CI]			

[19] Age, height, body weight or BMI
[20] T-test for independent samples or Mann-Whitney test depending on the type of distribution of the indicator

Table 21. Analysing the distribution of AEs by severity (template)

Severity		**Investigational Product**	
		Mexidol®	**Placebo**
Mild	Abs.		
	%		
Moderate	Abs.		
	%		
Severe	Abs.		
	%		
Life-threatening/ Disability to work	Abs.		
	%		
Fatal	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 22. Relationship of AEs to investigational product (template)

The association of the adverse event with the investigational drug		**Investigational Product**	
		Mexidol®	**Placebo**
Yes	Abs.		
	%		
No	Abs.		
	%		
Differences between preparations		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 23: Analysis of the distribution of AEs by administration of the Investigational Product (template)

Relationship to Investigational Product administration		**Investigational Product**	
		Mexidol®	**Placebo**
Definite.	Abs.		
	%		
Probable.	Abs.		
	%		
Possible.	Abs.		
	%		
Doubtful.	Abs.		

	%		
Conditional.	Abs.		
	%		
Unclassifiable.	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 24. Analysis of the distribution of AEs by foreseeability (template)

Expectancy		**Investigational Product**	
		Mexidol®	**Placebo**
Expected	Abs.		
	%		
Unexpected	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 25. Analysis of AR distribution (template)

AE		**Investigational Product**	
		Mexidol®	**Placebo**
AR	Abs.		
	%		
Not an AR	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 26. Analysis of the distribution of AEs by seriousness (template)

Seriousness		**Investigational Product**	
		Mexidol®	**Placebo**
Serious	Abs.		
	%		
Nonserious	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 27. Analysing the distribution of AEs by actions taken (template)

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Actions taken		**Investigational Product**	
		Mexidol®	**Placebo**
No action was taken	Abs.		
	%		
Other (specific actions taken will be indicated)	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

Table 28. Analysis of the distribution of AEs by outcome (template)

Outcome		**Investigational Product**	
		Mexidol®	**Placebo**
Transition to SAE	Abs.		
	%		
Stabilization of the condition (no change in condition):	Abs.		
	%		
Recovery with consequences	Abs.		
	%		
Recovery/termination of an AE without consequences:	Abs.		
	%		
Improved condition	Abs.		
	%		
Unknown:	Abs.		
	%		
Inter-group differences		Pearson 's χ2 criterion or Fisher's exact test	p-value

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Table 29. Summary table of the incidence of reported AEs in the group taking Mexidol by severity with randomization numbers of patients (N=) (*template)*

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

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 31. Summary table of the incidence of AEs after taking each Investigational Product (template)

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

Table 32. List of all adverse events for each patient (template)

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, years											
		gender											
		Weight, kg											
		Height, cm											
		race											

Table 33. MedDRA version classification of AEs (template)

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 34. Summary table of the incidence of reported SAEs in the group taking Mexidol by severity with randomization numbers of patients (N=) (template)

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

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 36. Summary table of the incidence of SAEs after taking each investigational product (template)

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

Table 37. List of all serious adverse events for each patient (template)

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, years											
		gender											
		Weight, kg											
		Height, cm											
		race											

Table 38. MedDRA version classification of SAEs (template)

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