Study Protocol with Statistical Analysis Plan

Prospective Randomized Study of the modulating effect of MEXIDOL® as an adjuvant stimulant of the cognitive-emotional component of the rehabilitation treatment in patients with acute cerebral failure

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Study Protocol

The study procedures for the visits are presented in Table 1.

Conditions	Acute Cerebral Failure (Ischemic Stroke, Traumatic Brain Injury)
Study Design	Study Type: Interventional Primary Purpose: Treatment Study Phase: Phase 4 Interventional Study Model: Parallel Assignment Number of Arms: 2 Masking: None (Open Label) Allocation: Randomized (1:1) Enrollment: 60 [Actual] Time Frame: 66 days (I: parenteral therapy 10 days; II: oral therapy 8 weeks)
Arms	1. Mexidol and Standard Therapy 2. Standard Therapy
Method of Application	Mexidol, solution for intravenous (IV) and intramuscular administration, IV 500 mg for 10 days, then Mexidol FORTE 250, film-coated tablets 250 mg, orally 1 tablet 3 times a day for 8 weeks.
Standard and Concomitant therapy	Standard treatment: basic practices of kinesitherapy, occupational therapy, speech therapy, clinical psychology, supplemented by adjuvant procedures of electrotherapy and rehabilitation environment therapy. The patient's rehabilitation load was at least 3 hours a day for 12 days. Patients may continue their pre-study therapy for other chronic conditions if, in the opinion of the investigator, they do not interfere with the results of this study and are administered at a stable dose during the study.
Primary Purpose	To evaluate the effect of pharmacological modulation of the rehabilitation process with the drug Mexidol as an adjuvant component of rehabilitation treatment of emotional and cognitive disorders in patients with Acute Cerebral Failure (Ischemic Stroke, Traumatic Brain Injury).
Secondary Purpose	To establish the possibility of identifying an individual clinical response to Mexidol therapy (responders and non-responders) and to determine indications for including the drug in an individual rehabilitation program.
Exploratory Purpose	• To establish, using neurophysiological methods, the effect of the drug on perfusion-metabolic coupling (TCDG-EEG [transcranial dopplerography and electroencephalography] monitoring at the time of drug infusion) as an indirect indicator of increased metabolic activity of the brain. • To establish, using clinical scales, the presence of a connection between the use of the drug Mexidol and the dynamics of recovery of the emotional-cognitive status of patients with acute cerebral insufficiency, during the period of permanent inpatient-outpatient rehabilitation treatment.
Research objectives (Outcome Measures)	1. Assessment of attentiveness and performance – the presence of the effect of Mexidol infusion on the change in the results of the Schulte test [work efficiency] before the start of the course, at the end of the

	course of infusion therapy and after the course of therapy with the tablet form of Mexidol FORTE 250 2. Dynamics of cognitive status according to the Montreal Cognitive Assessment (MoCA test) 3. Severity of depression according to the Beck Depression Inventory (BDI scale) 4. Reduction in anxiety according to the Hospital Anxiety and Depression Scale (HADS) 5. The degree of severity and dynamics of the Post Intensive Care Syndrome (PICS) according to the PICS-score 6. Dynamics of level of mobility according to the Rivermead index 7. Dynamics of the level of life according to the Rehabilitation Routing Scale (RRS) 8. Severity and dynamics of muscle strength according to the Muscle Strength Quantitative Rating (MRC) Scale 9. Variants of specific dynamics of neurophysiological parameters of perfusion (transcranial dopplerography) and metabolism (electroencephalography) at the time of infusion of Mexidol (event related monitoring)
Safety and Tolerability Criteria:	Incidence of Treatment-Emergent Adverse events related to Mexidol
Inclusion Criteria:	• ≥18 years old • Signed Informed Consent Form • Acute Cerebral Failure (Ischemic Stroke, Traumatic Brain Injury) • Montreal Cognitive Assessment (MoCA test) >15; ≤22
Exclusion Criteria:	• < 18 years old • Epilepsy • Pregnancy • Acute failure of one or more organ systems • Purulent-inflammatory disease of any localization • Participating in any other clinical trial
Ethical and Legal Aspects	This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following: • The ethical principles that have their origin in the Declaration of Helsinki. • International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline. • All applicable laws and regulations, including, without limitation, privacy laws, clinical trial disclosure laws, and regulations.

Table 1. Schedule of study procedures.

The study procedures	Visit				
	Screening				
	Visit 1 Day -5/-1	Visit 2 Day 1	Visit 3 Day 10	Video visit 4 Day 38	Visit 5 Day 66
Obtaining Informed Consent	X				
Checking inclusion/exclusion criteria	X	X			
Collection of anamnesis data	X				
Conducting a physical examination	X	X			
Measurement of BMI	X				
Body temperature	X				
Vital signs of the body's condition (mean BP, HR, RR)	X	X	X		X
Randomization		X			
The Rehabilitation Routing Scale (RRS)	X		X	X	X
The Montreal Cognitive Assessment (MoCA test)	X		X		X
The Beck Depression Inventory (BDI scale)		X	X	X	X
The Hospital Anxiety and Depression Scale (HADS)		X	X	X	X
The Rivermead index		X	X	X	X
The Muscle Strength Quantitative Rating Scale (MRC)		X	X	X	X
The Post Intensive Care Syndrome (PICS) score		X	X	X	X
The Schulte test		X	X		X
Neurophysiological parameters (EEG, TCDG)		X			
Administration of the study drug intravenously		X----------X			
Dispensation of the study drug for oral administration			X		
Return of the drug and assessment of treatment compliance (if the drug is taken orally)					X
Question about the intake of concomitant drugs	X	X	X	X	X
Monitoring of adverse events		X	X	X	X

Statistical Analysis Plan

To create conditions for an independent assessment of the obtained results, statistical data processing at the end of the study will be performed by employees not involved in the management of patients participating in the study. Data processing will be performed in the software environment of the TIBCO® Statistica™ v.13 and R v.4.4.1 and higher packages or similar, corresponding to the tasks of statistical analysis.

For statistical analysis of quantitative features, compliance with the normal distribution law will be preliminarily assessed by one of the generally accepted methods (Shapiro-Wilk criterion). When testing statistical hypotheses for indicators with a normal distribution, parametric criteria will be used, and for indicators whose distribution differs from normal, nonparametric criteria will be used.

The following indicators will be calculated as descriptive statistics parameters for continuous (quantitative) data:

- n – number of valid observations;
- M, Mean – arithmetic mean;
- Me, Median – median;
- Min – minimum value;
- Max – maximum value;
- Q1 – lower quartile;
- Q3 – upper quartile;
- Range – range;
- IQR – interquartile range;
- SD – standard deviation;
- SE – standard error of the mean;
- w – Wilcoxon-Mann-Whitney test for independent groups;
- t – Student's t-test with Welch's correction for independent groups;
- f – Fisher's exact test;
- $\chi 2$ – Chi-square test.

For ordinal, categorical and qualitative variables:

- absolute frequency (number of observations);
- relative frequency (expressed as a percentage).

The results of the assessment of quantitative variables, the distribution of which corresponds to the law of normal distribution, will be presented as M±SD, where M is the mean value, and SD is the standard deviation. The results of the assessment of quantitative variables, the distribution of which does not correspond to the law of normal distribution, will be presented as Me [Q1; Q3], where Me is the median, and Q1 and Q3 are the lower and upper quartiles.

Efficacy and safety indicators, as well as their changes, will be presented using descriptive statistics by visits and therapeutic groups. For study visits, qualitative (dichotomous) indicators will be compared between groups based on the Pearson $\chi 2$ criterion, the Pearson $\chi 2$ criterion with Welch's correction, or the Fisher exact test for tables of arbitrary dimension (if the frequency of the indicator in at least one of the subgroups is 5 or less).

Comparison of groups by quantitative indicators can be carried out using the Student's T-test and the Mann-Whitney test. Comparison of intra-group parameters before and after treatment can be

performed using the T-test for related samples or the Wilcoxon-Mann-Whitney test. Statistically significant values are p-level <0.05.

Safety analysis will be performed for the safety population. The following safety parameters are provided for in this study:

• Total number of AEs, stratified by severity and frequency;

• Frequency of AEs, related, in the opinion of the physician-investigator, to the use of the study drug;

• Frequency of serious adverse events (SAEs), related, in the opinion of the physician-investigator, to the use of the study drug;

• Proportion of patients with at least one AE;

• Proportion of patients with 2 or more AEs.

The dynamics of quantitative safety parameters relative to baseline values will be assessed and compared with each other using ANOVA with repeated measures. This method allows to simultaneously check for statistically significant dynamics (at least one average value at one time point differs from the others), and also to compare the dynamics and ranges of the indicator values when obtaining the compared drugs. In case of inappropriateness of the use of parametric methods, a similar analysis of the change in the distribution of indicators during therapy will be carried out using non-parametric analogues - the Friedman criterion and the Wilcoxon signed rank criterion, and intergroup comparisons of changes - using the Wilcoxon-Mann-Whitney criterion.