CLINICAL TRIAL PROTOCOL

No. PHS-APIS-004-MEX-SOL-TAB

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

December 14, 2022

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"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)"

Version 1.5 dated 14.12.2022.

This document has been prepared in accordance with the Federal Law of the Russian Federation No. 61-FZ "On Circulation of Medicines" dated 12.04.2010, No. 271-FZ "On Amendments to the Federal Law "On Circulation of Medicines" dated 11.10.2010, Order of the Ministry of Health of the Russian Federation No. 200n dated 01.04.2016. "On Approval of the Rules of Good Clinical Practice, National Standard of the Russian Federation "Good Clinical Practice" GOST R 52379-2005, Rules of Good Clinical Practice of the Eurasian Economic Union.

General information about the clinical trial and signatures of responsible persons

Title of the clinical trial	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 (NIC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) when administered sequentially in patients in the acute and early recovery periods of ischaemic stroke (MIR).	
Protocol	No. PHS-APIS-004-MEX-SOL-TAB version 1.5	dated 14.12.2022
Sponsor	**RPC PHARMASOFT LTD** Legal address: Russia, 115407, Moscow, Sudostroitelnaya str., 41, floor 1, room. 12. Postal address: Russia, 109544, Moscow, Blvd Enthusiastov, 2. Tel/fax +7 (495) 626-47-55	
Name and title of the person authorized to sign the Clinical Trial Protocol and amendments on behalf of the Sponsor	Tatyana Anatolyevna Mityushkina Medical Director	(signed) *signature* 14.12.2022 *Date*
Legal organization engaged by the developer to conduct the clinical trial	**ClinFarmDevelopment LLC** Legal address: 68, Uglichskaya St., 68, office 1, Yaroslavl, 150031. Phone: (4852) 59-38-86	
List of medical organizations where the clinical trial is to be conducted	A list of the investigational sites involved in this clinical trial (name, address and name of the PI) is provided in a separate list of investigational site and principal investigators.	

Investigator's signature page

I, the undersigned, certify that I have read and understood the contents of Protocol No. PHS-APIS-004-MEX- SOL-TAB "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 (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)".

I consent to the procedures described in this Protocol and undertake to conduct this trial in accordance with the requirements of the National Standard of the Russian Federation "Good Clinical Practice" and other applicable regulatory documents of the Russian Federation.

I will not deviate from the Protocol without prior written authorization from the Sponsor and prior review, and written approval of the Ethics Council, except as necessary to prevent immediate danger to the patient.

I have sufficient time, a sufficient number of qualified staff and adequate equipment to carry out all stages of the trial in a quality and safe manner within the timeframe stipulated in the protocol.

I will take all measures to ensure that all personnel involved in the conduct of the trial at my site(s) are sufficiently familiar with the Investigational Product, the Protocol and their functional responsibilities.

I have received and read all information provided to me relevant to the trial. The objectives and contents of this protocol and the results obtained will be considered confidential and will not be made available to third parties without the prior consent of the Sponsor.

Principal Investigator: _____

FULL NAME

_____

Signature Date

Table of contents

List of figures and tables

List of abbreviations

C_{max}	Maximum concentration
CTCAE	Common Toxicity Criteria for Adverse Events, Common Toxicity Criteria for Adverse Events
HADS	Hospital Anxiety and Depression Scale
ITT	ITT (Intent-to-treat) population, includes all randomized patients regardless of investigational product/placebo administration
LD_{50}	Semi-lethal dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	The mITT (modified Intent-to-treat) population, includes patients who have completed the full course of therapy, regardless of the presence of Protocol violations/abnormalities
MoCA	Montreal Cognitive Assessment
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PP	PP population (Per protocol), includes patients who completed the trial according to the protocol
R	Reference
SARS-CoV-2	Severe acute respiratory syndrome-related coronavirus 2, first identified on 31 December 2019 (causes an infectious disease - COVID-19).
T	Test
T_{max}	Time to reach maximum concentration
abs.unit	Absolute units
BD	Blood pressure
ALT	Alanine aminotransferase
AOS	Antioxidant system
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
IV	Intravenous
IM	Intramuscular
ULN	Upper limit of normal
HIV	Human immunodeficiency virus
WMA	World Medical Association
WHO	World Health Organisation
HPLC	High performance liquid chromatography
GABA	Gamma-aminobutyric acid
GGTP	Gamma-glutamyltranspeptidase
DBD	Diastolic blood pressure
CI	Confidence interval
eGFR	Estimated Glomerular Filtration Rate
IS	Ischaemic stroke

IMU	Instructions for medical use
BMI	Body mass index
IP	Investigational Product
CRF	Case Report Form
CIS	Clinically insignificant
CT	Computed tomography
LDL	Low-density lipoproteins
LEC	Local ethics committee
mg	Milligram
MoH RF	Ministry of Health of the Russian Federation
ICD	International Classification of Diseases
ml	Millilitre
mmHg.	Millimetres of mercury column
INN	International non-proprietary name
INR	International normalized ratio
MRI	Magnetic resonance tomography
NADPH	Nicotinamidadenine dinucleotide phosphate
RPC	Research and production company
AE	Adverse event
ACCD	Acute cerebral circulation disorder
LLC	Limited Liability Company
rel. unit	Relative units
SW	Software
LPO	Lipid peroxidation
CP	Comparator product
RAMS	Russian Academy of Medical Sciences
RF	Russian Federation
SBP	Systolic blood pressure
SAE	Serious adverse event
SOP	Standard operating procedure
CNS	Central nervous system
COX	Cyclooxygenase
RR	Respiratory rate
HR	Heart rate
ED	Endothelial dysfunction
eCRF	Electronic Case Report Form
ECG	Electrocardiogram, electrocardiographic trial

1. Synopsis

Title of the clinical trial:	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	PHS-APIS-004-MEX-SOL-TAB
Sponsor:	RPC PHARMASOFT LLC Legal address: Russia, 115407 Moscow, 41, Sudostroitelnaya St., floor 1, room. 12. Postal address: Russia, 109544, Moscow, Enthusiastov Boulevard, 2 Tel/fax +7 (495) 626-47-55
Investigational sites:	It is planned to conduct clinical studies in several investigational sites in Russia, the Republic of Kazakhstan, and the Republic of Uzbekistan.
Trial Phase:	III
Trial purpose:	The purpose of the present trial is a comparative evaluation of safety and efficacy 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 the preparations 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 in comparison with placebo. 2. To carry out a comparative evaluation of the frequency and severity of adverse events of the preparations 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 compared with placebo.
Trial design:	A prospective multicentre, randomized, double-blind, parallel-group comparative clinical trial.
Trial methodology	The trial is carried out during the inpatient follow-up of patients and as part of patients' outpatient visits to the investigational site. The trial will include the following periods: - **Screening** is a preliminary examination of patients**.** The duration of the period should not be more than 24 hours from the time of the informed consent procedure to randomization. Screening, randomization and initiation of therapy can be done on the same day.

	- **Randomization and initiation of therapy** - randomization, initiation of trial therapy. - **Therapy period** (70 days in total), use of investigational product/placebo (10 days - parenteral administration period, 60 days - oral administration), patient assessment, registration of AEs. After screening, patients fulfilling inclusion criteria and those without inclusion criteria were randomly allocated into two groups (1:1 patient-to-patient ratio): Group I - use of 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. Group II - use of 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 a further 60 days. The use of investigational products is carried out against the background of standard therapy of ischaemic stroke prescribed by the patient's attending physician. Patients will be assessed at the following visits. **Screening:** **Visit 0 - patient screening** (Day -1 / Day 1[1]) - screening, preliminary examination of patients. Visit 0 procedures should be carried out within a maximum of 24 hours and may be carried out on the same day as Visit 1 procedures: - Signing an informed consent form; - Collection of demographic and anthropometric data, anamnesis; - Physical examination - Neurological examination; - Assessment of vital signs (BP, HR, RR, body temperature); - Clinical blood test; - Blood chemistry; - Blood tests for HIV, syphilis, hepatitis B and C[2] - SARS-CoV-2 IgM antibody rapid test - Urinalysis; - Pregnancy test for women with preserved reproductive potential; - ECG[3]; - CT/MRI[4];

[1] Visit 0 - patient screening - is conducted on Day 1 if Visit 0 and Visit 1 are conducted on the same day.

[2] Results obtained within 48 hours prior to Screening may be used

[3] If data are available for a patient from instrumental examinations performed within 48 hours prior to inclusion in the trial, they can be used to assess the patient's condition and eligibility for inclusion/non-inclusion. The use of such data shall be permitted only if the data are available in full and for all parameters required by the Protocol.

[4] It is planned to use data from neuroimaging examinations (CT/MRI) performed within 48 hours prior to patient inclusion in the trial to assess patient status and eligibility for inclusion/non-inclusion. A repeat CT/MRI scan is not required if these findings are present.

[1] If the first administration of investigational product (start of parenteral therapy) falls in the afternoon (first

	- Completion of specialized scales (mRS, NIHSS); - Assessment of prior and concomitant therapy; - Assessment of inclusion/non-inclusion criteria **Randomization and initiation of therapy** **Visit 1 (Day 1) - randomization and initiation of therapy** - Randomization - Completion of specialised scales and calculation of indices (HADS, MoCA, Rivermead mobility index); - Prescribing and initiation of investigational therapy; - AE registration **Therapy period:** Includes standard therapy prescribed to the patient depending on the clinical picture of the disease and symptomatology. The investigational therapy is assigned to the patient according to the results of the randomization procedure. **Visit 2** (day 11/12[1] from the start of therapy, Visit procedures are performed at the end of parenteral therapy): Physical examination, neurological examination, assessment of vital signs (BP, HR, RR, body temperature), assessment of concomitant therapy, registration of AE and assessment of exclusion criteria, clinical and biochemical blood tests, general urinalysis, ECG, completion of specialised scales and calculation of indices (mRS, NIHSS, HADS, MoCA, Rivermead mobility index), distribution of the oral medication. **Telephone visit 1** (Day 24±2 from initiation of therapy; Day 14±2 from initiation of oral therapy): assessment of concomitant therapy, recording of AE and assessment of exclusion criteria, assessment of compliance. **Visit 3** (Day 40 (+2) from initiation of therapy; Day 30 (+2) from initiation of oral therapy): physical examination, assessment of vital signs (BP, HR, RR, body temperature), assessment of concomitant therapy, registration of AE and assessment of exclusion criteria, dispensing/recording of oral medication and assessment of compliance. **Telephone visit 2** (Day 55±2 from initiation of therapy; Day 45±2 from initiation of oral therapy): assessment of concomitant therapy, recording of AE and assessment of exclusion criteria, and assessment of compliance. **Visit 4** (day 71(+2) from the start of therapy; end of therapy): physical examination, neurological examination, assessment of vital signs (BP, HR, RR, body temperature), assessment of concomitant therapy, registration of AE and assessment of exclusion criteria, clinical and biochemical blood tests, general urinalysis, pregnancy

day of therapy - one administration), Visit 2 is performed on day 12 in the morning.

	test for women with preserved reproductive potential, ECG, completion of specialised scales and calculation of indices (mRS, NIHSS, HADS, MoCA, Rivermead mobility index), return of the product and assessment of compliance. Additional in-person/out-person (phone calls) visits may be conducted if necessary, in the reasonable judgement of the investigator, particularly to monitor the progression of SAEs. The scope of activities and procedures performed at additional visits will be determined by the investigator on an individual basis, depending on the indications. In case of early withdrawal of a patient from the trial, a Visit to End Patient Participation in the Trial is performed, including activities identical to those of Visit 4.
Trial population and number of patients in the trial:	A **maximum of 336 patients** are planned to be **included in** the trial (obtain approval for a clinical trial involving 336 **patients**), from which **at least 304 patients** with a clinically confirmed diagnosis of hemispheric ischaemic stroke who meet the inclusion criteria and no non-inclusion criteria are planned to be **randomized**.
Criteria for inclusion of patients in the trial:	1. Male and female patients aged 40 to 75 years. 2. Availability of an informed consent form signed by the patient (or his/her legal representative if the patient is not physically able to sign) for participation in the trial. 3. First-time diagnosed hemispheric ischaemic stroke (ICD-10 codes: I63 "cerebral infarction." I63.0 to I63.9) not more than 48 hours old. 4. Presence of neuroimaging (according to computerised tomography (CT) or magnetic resonance imaging (MRI)) signs of ischaemic stroke and/or absence of signs of haemorrhagic stroke, ischaemic stroke with haemorrhagic impregnation, as well as other conditions not related to ischaemic stroke and having a similar clinical picture. 5. The patient's functional status score on the Modified Rankin Scale (mRS) is 3 or more points. 6. Patient's NIHSS score of 9 to 15 points inclusive. 7. Negative pregnancy test in female patients of preserved childbearing potential. 8. Consent to the use of adequate contraceptive methods (contraceptive methods with a reliability of more than 90%: non-hormonal intrauterine device; condom with intravaginal spermicide; neck caps with spermicide; diaphragms with spermicide), or complete abstinence from sexual activity for the period of the trial. 9. Patients who are able to understand the requirements of the Trial Protocol and who have consented to all restrictions in the Trial Protocol.
Criteria for not including patients in the trial:	1. Presence of clinically significant allergic reactions in the history. 2. Hypersensitivity and/or intolerance to any component of the investigational product or placebo. 3. Presence of lactose intolerance/congenital galactose intolerance;

	Lapp lactase deficiency or glucose-galactose malabsorption syndrome. 4. BMI value > 35. 5. Recurrent stroke. 6. Haemorrhagic stroke (confirmed by neuroimaging (CT or MRI). 7. Haemorrhagic infarction (ischaemic stroke with haemorrhagic impregnation). 8. Parkinson's disease or parkinsonism. 9. Multiple sclerosis. 10. Uncontrolled epilepsy. 11. Demyelinating diseases of the nervous system. 12. Hereditary degenerative diseases of the CNS. 13. Presence of infectious diseases of the CNS in the anamnesis. 14. Traumatic brain injuries with pronounced neurological symptoms and cognitive impairment. 15. A history of neurodevelopmental anomalies or other neurological disorders seriously affecting motor or cognitive function in the reasonable opinion of the investigator. 16. Patients who have undergone thrombolytic therapy or thrombectomy. 17. Need for surgical intervention. 18. Evidence of a first-diagnosed disease that, in the reasonable opinion of the investigating physician, would preclude the patient's participation in the trial. 19. Evidence of a significant uncontrolled comorbid condition that, in the reasonable opinion of the investigator, would preclude the patient's participation in the trial, including: • Respiratory system disorders; • Cardiovascular disorders including SBP ≥ 200 mmHg, DBP ≥ 100 mmHg at trial entry; • Severe renal impairment (eGFR<30ml/min/1.73 m^2); • Severe liver function impairment (ALT, AST activity> 2 times ULN); • Endocrine disorders; • Gastrointestinal disorders. • Deep vein thrombosis or pulmonary embolism, identification of a flotating thrombus. • The onset of a seizure syndrome. • Occurrence of unrelieved hyperthermia. • Occurrence of unrelieved hyperglycaemia. 20. Endogenous psychiatric disorders according to anamnesis. 21. Anamnestic information about dementia of the Alzheimer type. 22. Systemic autoimmune diseases or vascular collagenosis requiring previous or current treatment with systemic corticosteroid drugs, cytostatics; malignant neoplasms within the last 5 years. 23. A history of alcohol or drug dependence. 24. Pregnancy or lactation period. 25. The need to use medications that are prohibited in this trial. 26. Administration of unauthorized or off-protocol medications

	within 2 weeks prior to trial inclusion (except for a single administration of ethylmethylhydroxypyridine succinate at the emergency medical services stage). 27. Positive result of at least one of the following tests: blood tests for HIV, syphilis, hepatitis B and C (including history). 28. The presence of any significant history of a condition, in the opinion of the investigating physician, that prevents the patient from being included in the trial. 29. Participation in any clinical trial less than 3 months prior to the start of the trial. 30. Positive result of a rapid test for IgM antibodies to SARS-CoV-2 virus.
Criteria for exclusion of patients from the trial:	1. Withdrawal of informed consent by the patient or the patient's legal representative. 2. Need for additional therapy not permitted under this protocol. 3. Serious adverse events or adverse events that do not fulfil the criteria for seriousness and where, in the opinion of the investigator, further participation in the trial would be dangerous to the health or well-being of the patient. 4. Investigator or sponsor's decision to exclude a patient due to a significant protocol deviation/protocol violation. 5. Any patient condition that, in the reasonable judgement of the investigator, requires the patient to be withdrawn from the trial. 6. Positive result of at least one of the following tests: blood tests for HIV, syphilis, hepatitis B and C, if the test results are obtained after the patient's randomization procedure. 7. Allergic reaction to trial medications requiring their cancellation. 8. Loss of contact with the patient followed by failure to attend the visit. 9. Recurrent stroke. 10. A positive result of the rapid test for IgM antibodies to SARS-CoV-2 virus and/or a positive result of laboratory testing for the presence of SARS-CoV-2 RNA using nucleic acid amplification methods, regardless of clinical manifestations. 11. Diseases and/or conditions of the subject detected for the first time during routine medical examinations and procedures that prevent the subject from continuing his/her participation in the trial, and/or indicate that the patient was wrongly included in the trial (failure to meet the selection criteria for the trial at the time of inclusion). Patients who were excluded from the trial during screening prior to the administration of investigational therapy should not be randomized into this trial. Excluded subjects will be monitored for the development of AE/SAE until their resolution or stabilisation of AE/SAE-induced manifestations.
Investigational product (ID):	The trial will evaluate the safety and efficacy parameters 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). 1. Mexidol® solution for intravenous and intramuscular administration 50 mg/ml (RPC PHARMASOFT LLC, Russia). Composition per 1 ml: ***Active ingredient:*** Ethylmethylhydroxypyridine succinate - 50.0 mg. **Excipients:** Sodium metabisulphite (Sodium disulphite) - 0.4 mg; Water for injection up to 1 ml 2. Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia). Composition per 1 tablet: ***Active ingredient:*** Ethylmethylhydroxypyridine succinate as 100 % substance - 250.0 mg **Excipients:** lactose monohydrate, povidone K-30, magnesium stearate. **Film coating:** Opadray II pink 33G240018 (hypromellose, titanium dioxide, lactose monohydrate, macrogol 4000, triacetin, iron oxide dye red, iron oxide dye yellow) In the present trial, IP is used in patients in the acute and early recovery periods of ischaemic stroke: Group I - use of 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.
Comparator product:	The trial involves the use of Placebo 1 and Placebo 2 in patients in the acute and early recovery periods of ischaemic stroke: 1. Placebo 1 (placebo solution) (RPC PHARMASOFT LLC, Russia). Composition per 1 ml: Sodium chloride 9 mg Water for injection up to 1 ml 2. Placebo 2 (placebo film-coated tablets) (RPC PHARMASOFT LLC, Russia). Composition per 1 tablet: Lactose monohydrate - 445.0 mg; Povidone K-30 - 50.0 mg; Magnesium stearate - 5.0 mg. Weight of uncoated tablet is 500.0 mg. **Film coating:** Opadray II pink 33G240018: - 15.0 mg hypromellose; titanium dioxide;

	lactose monohydrate; macrogol 4000; triacetin; red iron oxide colourant; iron oxide yellow colouring agent. Weight of the tablet is 515.0 mg. Group II - use of 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 a further 60 days.
Drugs of standard and concomitant therapy:	Patients will receive standard (baseline) therapy according to the Clinical Guidelines "Ischaemic Stroke and Transient Ischaemic Attack in Adults", 2015. Baseline therapy includes correction of disorders of systemic and cerebral hemodynamics, rheological and coagulation properties of blood, prevention of complications of stroke. However, standard therapy drugs should not be classified as unauthorized in the present trial. If concomitant pathology is not a criterion for exclusion of the patient from the trial, the treatment of concomitant pathology within the framework of this protocol is carried out according to the accepted standard scheme. Concomitant therapy drugs should not be classified as unapproved protocols.
Unapproved or off-protocol medications:	Unapproved or off-protocol drugs include drugs and/or dietary supplements from the following groups: A) preparations containing succinic acid and its salts (including reamberin, remaxol, cytoflavin). B) preparations containing vitamin B6 and/or its derivatives. B) drugs belonging to the groups of antioxidants and antihypoxants (including drugs - derivatives of 3-hydroxypyridine: methyl ethylpyridinol, ethyl methylhydroxypyridine succinate (except for those used in the investigational therapy). D) drugs with nootropic type of action: - citicoline preparations. - choline alphoscerate preparations. nootropic drugs of the pyrrolidine series, including piracetam. - dimethylaminoethanol derivatives: deanol aceglumate, meclofenoxate. - pyridoxine derivatives: pyritinol, pyridoxine+threonine. - GABA derivatives and analogues: γ-aminobutyric acid, nicotinoyl-GABA, γ-amino-P-phenyl-butyric acid hydrochloride, gopanthenic acid, calcium γ-hydroxybutyrate. - ginkgo biloba preparations and its derivatives. - neuropeptides and their analogues with nootropic action. - 2-mercanthobenzimidazole derivatives: ethylthiobenzimidazole. - polypeptides and organic composites: cattle cerebral cortex polypeptides, cerebrolysin. - correctors of cerebral circulation disorders - vinpocetine, xanthinol nicotinate, vincamine, naphthidrofuryl, cinnarizine; combined preparation hexobendine+etamivan+etofylline. general tonic agents and adaptogens of plant origin.

	- preparations containing acetylaminoanthartaric acid. - psychostimulants - salbutiamine.
Trial Schedule:	The trial includes the following stages: - **Screening -** preliminary examination of patients. - **Randomization and initiation of therapy** - randomization, initiation of trial therapy. - **Therapy period -** use of investigational product/placebo + standard therapy, patient assessment, registration of AE.
Trial duration:	The total duration of patient participation in the trial will be no more than 74 days, including the screening period.
Efficacy criteria:	**Primary efficacy criterion:** - The magnitude of change in the patient's **mRS** (Modified Rankin Scale) score at the end of therapy vs. baseline (in points). **Secondary efficacy criteria:** - The magnitude of change in the patient's **mRS** (Modified Rankin Scale) score at the end of parenteral therapy vs. baseline (in points). - Proportion of disabled patients (**mRS** score 3 or more) at the end of therapy; - Proportion of disabled patients (**mRS** score 3 or more) at the end of parenteral therapy; - Proportion of patients with mRS score 0-1 at the end of therapy; - Proportion of patients with mRS score 0-1 at the end of parenteral therapy; - The magnitude of change in the patient's **NIHSS** (National Institutes of Health Stroke Scale) score at the end of therapy vs. baseline (in points). - 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 points). - The magnitude of change in the patient's **MoCA** cognitive status score at the end of therapy vs. baseline (in points). - The magnitude of change in the patient's **MoCA** cognitive status score at the end of parenteral therapy vs. baseline (in points). - The magnitude of change in the patient's **Rivermead** Mobility Index score at the end of therapy vs. baseline (in points). - 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 points). - The magnitude of change in the patient's **HADS** score at the end of therapy vs. baseline (in points). - The magnitude of change in the patient's **HADS** score at the end of parenteral therapy vs. baseline (in points).
Safety Assessment Criteria:	Safety and tolerability will be assessed throughout the trial (from first use of the investigational product/placebo) using the following data: — AE/SAE reports data, — Physical examination data, vital signs (BP, HR, respiratory rate, body temperature), — 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 SAs with at least a possible association with the use of the investigational product.
Statistical methods:	The choice of statistical analysis method will be determined by the type of raw data, type of distribution. 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, it is possible to expand the list of methods used, if necessary for qualitative data processing. Statistical processing of data obtained during the trial will be performed using the R statistical programming language (version 3.4.4 or higher) and/or SAS statistical software (version 9.4 or higher), or other specific applicable software that ensures the appropriate quality of the data obtained. The following population groups will be used for the analyses: 1. The ITT (Intent-to-treat) population will include all randomized patients regardless of investigational product/placebo administration. 2. 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/abnormalities. 3. The PP (Per protocol) population will include patients who completed the trial in accordance with the Protocol. 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. <u>Analysing efficacy data:</u> The primary population for the evaluation of efficacy criteria, proof of the hypothesis of superiority of the trial grug 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. This approach in selecting the population for analysis is based on the design of the planned clinical trial: patients in both the investigational product and placebo groups will receive standard (baseline) therapy (according to the Clinical Guidelines "Ischaemic Stroke and Transient Ischaemic Attack in Adults", 2015) with proven efficacy. In this regard, the use of the ITT population for a more conservative assessment of therapy is inappropriate, as this approach markedly levels the clinical effects of investigational product, therefore, to compensate for the therapeutic effects of baseline therapy and to properly assess the effects of investigational product, as the main population for the analysis of efficacy parameters in the planned

trial PP population is considered.
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 vs. baseline (in points)".
In the case of a superiority trial, the null hypothesis (H_0) and the alternative hypothesis (H_1) are formulated as follows:

$H_0: \varepsilon = \mu_\tau - \mu_{рл} \leq \delta$, $H_1 : \varepsilon > \delta$, $\delta > 0$, 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 the investigational product compared to placebo therapy, the lower bound of the 95% (or 97.06% in the case of a phase II trial) 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 $(\delta, +\infty)$.
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.
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. The test for conformity to the normal law of distribution will be carried out using the Shapiro-Wilk test. Comparisons of frequencies of indicators between treatment groups will be made using Pearson's $\chi 2$ test or Fisher's exact test.

Analysing safety data:

Safety parameters will be analysed in the ITT population.
Safety data will be analysed using the methods outlined for the assessment of
efficacy parameters. Analyses of AEs will be performed based on an assessment of the incidence of adverse events / serious adverse events. Adverse events reported during the course of the trial will be presented by frequency (number of patients with AEs and number of such AEs in the group). AEs will also be presented by severity and relationship to investigational product administration. Comparison of frequencies between therapy groups will be performed using Fisher's exact test or Pearson's $\chi 2$ test.

Ethical and legal aspects:	The trial will be conducted according to the Protocol, in strict compliance with the Constitution of the Russian Federation; the ethical principles of the 1964 Declaration of Helsinki of the World Medical Association, as revised in 2013; and other applicable legal requirements of the Russian Federation: Federal Law of the Russian Federation dated 21 November 2011 No. 323-FZ "On the Fundamentals of Public Health Protection in the Russian Federation"; Federal Law of the Russian Federation dated 27 July 2006 No. 152-FZ "On Personal Data" (as amended by N 261-FZ dated 25.07.2011), Federal Law of the Russian Federation No. 61-FZ "On Circulation of Medicines"; National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice", which meets the standards of the Guidelines for Good Clinical Practice (ICH-GCP) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical Products for Human Use (ICH); Order of the Ministry of Health of the Russian Federation No. 200n of 01.04.2016; Recommendations of FGBU "NCESMP" of the Ministry of Health of Russia when preparing reports on clinical studies and reports on bioequivalence studies of medicinal products (letter dated 26.11.2013, No. 13308); 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 of 13 September 2010 (current version), as well as in accordance with Resolution of the Government of the Russian Federation No. 393 of 18 May 2011 "On Amendments to the Model Rules of Compulsory Life and Health Insurance for Patients Participating in Clinical studies of a Medicinal Product"; Order of the Federal Service for Healthcare Oversight. Life and health insurance for patients is provided by AlfaStrakhovanie JSC.

2. TRIAL RATIONALE

2.1. Relevance of the trial

Acute cerebral circulatory disorders (ACCD) are a problem of great medical and social importance due to the significant frequency of their development, high rate of disability and mortality [Evzelman M. A. and Alexandrova N. A., 2013]. Stroke includes ACCD, characterized by the sudden (within minutes, less often - hours) appearance of focal neurological symptoms (motor, speech, sensory, coordinator, visual and other disorders) and/or general cerebral disorders (changes in consciousness, headache, vomiting, etc.), which persist for more than 24 hours or lead to the death of the patient in a shorter period of time due to the cause of cerebrovascular origin [Vereshchagin N. V. et al., 2002].

The annual stroke mortality rate in Russia is one of the highest in the world (175 cases per 100,000 population per year). According to the National Stroke Association register, 31 per cent of stroke patients require assistance to care for themselves and 20 per cent are unable to walk independently. Residual phenomena after stroke are detected in about 2/3 of patients, of which 50% - cognitive impairment, which limits social adaptation, including labour activity and self-care in the home, even in the absence of significant motor impairment [Evzelman M. A. and Alexandrova N. A., 2013; Stakhovskaya et al., 2012].

The most common in clinical practice is ischaemic stroke (IS) - ACCD, accompanied by

damage to brain tissue, impairment of its functions due to obstruction or cessation of blood flow to one or another part [Evzelman M. A. and Alexandrova N. A., 2013]. According to the register of brain stroke, conducted by the Research Institute of Neurology RAMS (Scientific Centre of Neurology), by the end of the acute period (3 weeks from the onset of the disease) hemiparesis is observed in 81.2% of surviving patients, including hemiplegia - 11.2%, arthropathy - 15-20%, aphasia - 35.9%, dysarthria - 13% [Fedin A. I. et al., 2009].

The pathomorphological basis of ischaemic strokes is a variety of pathogenetic factors leading to the formation of ischaemic foci in cerebral structures. The pathogenesis of cerebral structures lesions in acute stroke is usually homogeneous, despite the background variety of causes that cause them, and it consists in disorders of energy synthesis [Fedin A. I. et al., 2009]. The accumulated experience has shown that the zone of irreversible changes in the brain during an IS increases gradually, with the development of one or another stage of the ischaemic cascade [Gusev E. Gusev. I. and Skvortsova V. I., 2002].

The main directions of therapy of ischaemic stroke in the acute period are reperfusion (thrombolytic therapy, anticoagulants) and primary neuroprotection aimed at interruption of fast glutamate-calcium channel mechanisms in order to correct the imbalance of excitatory and inhibitory neurotransmitter systems. It is recommended to start this type of neuroprotection from the first minutes of ischaemic stroke and to continue it during the first 3 days, especially actively during the first 12 h of the disease. Secondary neuroprotection is aimed at interrupting the delayed mechanisms of cell death (on the distant consequences of ischaemia) and includes the use of inhibitors of pro-inflammatory cytokines and adhesion molecules, antioxidants, trophic factors, neuropeptides [Novikova L. B. et al., 2013].

Stimulation of the metabolic chain of the Krebs cycle is considered a promising way to improve the energy supply of the cell. This effect can be achieved by using succinate-containing substances, in particular, Mexidol® (2-ethyl-6-methyl-3-hydroxypyridine succinate). Mexidol® exhibits antioxidant and antiradical properties, has a wide range of effects on various mechanisms of regulation and metabolic activity of cells [Fedin A. I. et al., 2009].

In the course of experimental studies, the effect of Mexidol® on the development of excitotoxicity *in vitro* was shown. Mexidol® inhibits the development of glutamate-induced neurotoxicity, ascorbate-dependent (non-enzymatic) and NADPH2-dependent (enzymatic) iron-induced lipid peroxidation, has the ability to bind superoxide anion radical, increases the activity of Se-dependent glutathione peroxidase. These effects underlie its antioxidant and antihypoxant action [Shchulkin A. V., 2013]. The results of chemoreactomic analysis of ethylmethylhydroxypyridine succinate molecule showed that the main targets of its pharmacological action are acetylcholine and GABA-A receptors, COX-2 enzymes, 5-LOG and PPAR-receptor [Torshin I. Yu et al, 2016].

During the trial of efficacy and safety of Mexidol®, its effect on the dynamics of neurological manifestations of the disease, emotional status and quality of life in patients with chronic cerebral ischaemia it was found that by the end of the trial in the patients of the main group significantly decreased the severity of motor activity disorders, normalized quality of life indicators (SF-36 scale), there was a significant improvement in the indicators of cognitive functions. High efficacy and safety of treatment of patients with chronic cerebral ischaemia with Mexidol® has been confirmed [Chukanova E. I. et al., 2015].

Thrombolytic therapy (TLT) in combination with the use of Mexidol® leads to a significantly faster reduction in the severity of neurological deficit and somatic complications. TLT in combination with Mexidol® creates conditions not only for the recovery of neurological functions, but also for the prevention of reactions of secondary brain damage [Chefranova Zh. Yu et al., 2012]. It was found that the inclusion of Mexidol® in the scheme of complex rehabilitation treatment significantly improves the results of rehabilitation of patients, contributing to both an increase in the degree of recovery of neurological functions and an increase in the level of everyday adaptation [Kovalchuk V. V., 2011]. The positive effects of

Mexidol® in patients in the acute period of AI were demonstrated: there was a complete regression of general cerebral symptoms and marked regression of focal deficit, which determined the feasibility of using Mexidol® in complex therapy [Shevchenko L. A. et al., 2006].

In elderly patients in the recovery period of ischaemic stroke, therapy with Mexidol® improved well-being, memory and mnestic functions, reduced the level of depression. The patients had a wider range of social and domestic activity, reduced spasticity, improved cerebral blood circulation and activated the relationship between hemodynamics in the extra- and intracranial vessels of the carotid basin, indicating the activation of metabolic processes in the brain [Kuznetsova S. M. et al., 2009].

The efficacy and safety of long-term sequential therapy with Mexidol® compared to placebo was evaluated in the EPICA clinical trial in patients in the acute and early recovery periods of hemispheric AI. Treatment with Mexidol® showed a significant reduction in symptoms and functional impairment, there was significantly more pronounced compared to placebo improvement in life activity, measured on a modified Rankin scale: 0-2 points on the modified Rankin scale, was observed in 96.7% of patients in the group of Mexidol® and 84.1% in the placebo group*(p=0*.039) [Stakhovskaya L. V. et al., 2017].

At the end of therapy, the neurological deficit was significantly lower in the Mexidol® therapy group when tested by the stroke scale of the
National Institutes of Health vs. placebo. Mexidol® therapy contributed to a significant improvement in the quality of life starting from the 2nd visit. The vast majority of patients in the group of therapy with Mexidol noted that they had no problems with movement, self-care, performance of daily activities, did not experience pain and discomfort, anxiety and depression. In the subpopulation of patients with diabetes mellitus in the group of therapy with Mexidol® the quality of life was significantly higher by the end of therapy [Stakhovskaya L. V. et al., 2017].

Thus, the efficacy and safety of Mexidol® therapy in patients with MI in the acute and early recovery periods have been proved in a number of studies.

2.2. Name and description of the products under investigation

Investigational product (T)

Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml

Trade Name:	Mexidol®
Group name:	Ethylmethylhydroxypyridine succinate
Marketing Authorization Holder/ Claims Receiving Organisation:	**RPC PHARMASOFT LTD** Legal address: Russia, 115407 Moscow, 41, Sudostroitelnaya St., floor 1, room. 12. Postal address: Russia, 109544, Moscow, Enthusiastov Boulevard, 2 Tel/fax +7 (495) 626-47-55
Manufacturer:	Ellara LLC, Russia, 601122, Vladimir region, Petushinsky district, Pokrov, 20 Franz Stolwerk St., p.2, page 2
Dosage form:	solution for intravenous and intramuscular administration
Dosage:	50 mg/ml
Composition per 1 ml:	***Composition per 1 ml:*** *Active ingredient:* Ethylmethylhydroxypyridine succinate - 50.0 mg *Excipients:*

	Sodium metabisulphite (Sodium disulphite)- 0.4 mg Water for injection. - up to 1 ml Ampoules will be used in the trial 5 ml
Description:	Transparent colourless or slightly yellowish liquid
Storage conditions	Store in a dry, light-protected place out of reach of children at temperatures not exceeding 25°C.
Packaging and labelling	In ampoules of colourless or light-protective glass with a blue breakpoint or with a white breakpoint and three marking rings (upper - yellow, middle - white, lower - red). 5 Ampoules each in PVC blister. 1 or 2 or 3 blisters together with instructions for medical use in a pack of cardboard for consumer packaging. 4, 10 or 20 PVC blister together with instructions for medical use in a carton pack (for hospitals). According to the National Standards of the Russian Federation GOST R 52379-2005 dated 27.09.2005 and GOST R 52249-2009 dated 20.05.2009, the labelling of IP packages, in addition to the mandatory information (name, dosage, storage conditions and expiry date, information about the manufacturer, date of issue and batch number), will contain the inscription **"For clinical studies"** and a space for entering information about the investigational site and the surname, name, patronymic of the Principal Investigator. Given the design features of the trial, the trial is planned to be blinded to the packaging of the investigational product and the comparator product (placebo).

Pharmacotherapeutic group Antioxidant agent

ATC code: N07XX

Chemical name:

2-ethyl-6-methyl-3-hydroxypyridine succinate

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

It has antihypoxic, membrane-protective, nootropic, anticonvulsant, anxiolytic effect, increases the body's resistance to stress. The drug increases the body's resistance to the effects of major damaging factors, to oxygen-dependent pathological conditions (shock, hypoxia and ischaemia, impaired cerebral circulation, intoxication with alcohol and antipsychotic drugs (neuroleptics)).

Mexidol® improves cerebral metabolism and blood supply to the brain, improves microcirculation and rheological properties of blood, reduces platelet aggregation.

It stabilizes membrane structures of blood cells (erythrocytes and platelets) during haemolysis. It has a hypolipidaemic effect, reduces the level of total cholesterol and LDL. It reduces enzymatic toxaemia and endogenous intoxication in acute pancreatitis.

The mechanism of action of Mexidol® is due to its antihypoxant, antioxidant and membrane-protective action. It inhibits the processes of lipid peroxidation, increases the activity of superoxide dismutase, increases the lipid-protein ratio, reduces membrane viscosity, and increases membrane fluidity. Modulates the activity of membrane-bound enzymes (calcium-independent phosphodiesterase, adenylate cyclase, acetylcholinesterase), receptor complexes (benzodiazepine, GABA, acetylcholine), which enhances their ability to bind to ligands, helps preserve the structural and functional organisation of biomembranes, transport neurotransmitters and improve synaptic transmission.

Mexidol® increases dopamine levels in the brain. Causes enhancement of compensatory activity of aerobic glycolysis and reduction of the degree of inhibition of oxidative processes in the Krebs cycle under hypoxia, with an increase in the content of ATP, creatine phosphate and activation of energy-synthesising functions of mitochondria, stabilisation of cell membranes. Mexidol® normalises metabolic processes in ischemic myocardium, reduces the necrosis zone, restores and improves myocardial electrical activity and contractility, increases coronary blood flow in the ischemia zone, reduces the consequences of reperfusion syndrome in acute coronary insufficiency. It increases antianginal activity of nitro preparations. Mexidol® promotes preservation of retinal ganglion cells and optic nerve fibres in progressive neuropathy caused by chronic ischemia and hypoxia. It improves functional activity of the retina and optic nerve, increasing visual acuity.

Pharmacokinetics

When administered intravenously, it is determined in blood plasma for 4 h after administration. Time to reach maximum concentration Tmax is 0.45-0.5 h. Cmax at administration of 400-500 mg dose is 3.5-4.0 μg/ml. Mexidol® is rapidly transferred from the bloodstream to organs and tissues and rapidly eliminated from the body. The mean retention time (MRT) is 0.7-1.3 h. The drug is excreted mainly with urine, mainly in glucuron-conjugated form and in insignificant amounts in unchanged form.

Indications for use:

acute cerebral circulatory disorders;
craniocerebral trauma, consequences of craniocerebral injuries;
dyscirculatory encephalopathy;
autonomic dystonia syndrome;
mild cognitive disorders of atherosclerotic genesis;

anxiety disorders in neurotic and neurosis-like states;
acute myocardial infarction (from the first day) as part of complex therapy;
primary open-angle glaucoma of various stages, as part of complex therapy;
management of withdrawal syndrome in alcoholism with predominance of neurosis-like and vegetative-vascular disorders;
acute intoxication with antipsychotic drugs;
acute purulent-inflammatory processes of the abdominal cavity (acute necrotising pancreatitis, peritonitis) as part of complex therapy.

Method of application and doses (according to the IMU):

IM or IV (bolus or drip). In infusion method of administration the drug should be diluted in 0.9% sodium chloride solution.

Mexidol® is administered slowly over 5-7 min, drip - at a rate of 40-60 drops per minute. The maximum daily dose should not exceed 1200 mg.

In acute cerebral circulatory disorders Mexidol® is used in the first 10-14 days - IV drip 200-500 mg 2-4 times a day, then IM 200-250 mg 2-3 times a day for 2 weeks.

In craniocerebral trauma and consequences of craniocerebral traumas Mexidol® is used during 10 - 15 days by IV drip 200 - 500 mg 2 - 4 times a day.

In dyscirculatory encephalopathy in decompensation phase Mexidol® should be administered by IV bolus or drip in a dose of 200 - 500 mg 1 - 2 times a day for 14 days. Then 100 - 250 mg/day IM for the next 2 weeks.

For course prophylaxis of dyscirculatory encephalopathy the drug is administered IM in a dose of 200 - 250 mg BID for 10 - 14 days.

In mild cognitive disorders in elderly patients and in anxiety disorders the drug is administered IM in a daily dose of 100 - 300 mg/day for 14 - 30 days.

In acute myocardial infarction as part of complex therapy Mexidol® is administered IV or IM for 14 days, against the background of conventional therapy of myocardial infarction, including nitrates, beta-adrenoblockers, angiotensin-converting enzyme (ACE) inhibitors, thrombolytics, anticoagulant and antiaggregant agents, as well as symptomatic agents as indicated.

In the first 5 days, to achieve maximum effect, the drug should be administered intravenously, in the following 9 days Mexidol® can be administered intramuscularly.

Intravenous administration of the drug is performed by drip infusion, slowly (to avoid side effects) on 0.9% sodium chloride solution or 5% dextrose (glucose) solution in the volume of 100 - 150 ml within 30 - 90 min. If necessary, slow bolus administration of the drug is possible, lasting at least 5 minutes.

Administration of the drug (intravenous or intramuscular) is carried out TID, every 8 hours. The daily therapeutic dose is 6 - 9 mg/kg body weight per day, single dose - 2 - 3 mg/kg body weight. The maximum daily dose should not exceed 800 mg, single dose - 250 mg.

In open-angle glaucoma of various stages as a part of complex therapy Mexidol® is administered IM 100 - 300 mg/day, 1 - 3 times a day for 14 days.

In withdrawal alcohol syndrome Mexidol® is administered in a dose of 200 - 500 mg by IV drip or IM 2 - 3 times a day for 5 - 7 days.

In acute intoxication with antipsychotic agents, the drug is administered IV at a dose of 200 - 500 mg/day for 7 - 14 days. *In acute purulent-inflammatory processes of the abdominal cavity (acute necrotising pancreatitis, peritonitis)* the drug is administered in the first day in both preoperative and postoperative periods. The administered doses depend on the form and severity of the disease, prevalence of the process, variants of the clinical course. The drug should be withdrawn gradually only after a sustained positive clinical and laboratory effect.

In acute oedema (interstitial) pancreatitis Mexidol® is administered 200 - 500 mg TID, by IV drip (in 0.9% sodium chloride solution) and IM.

Mild severity of necrotising pancreatitis - 100 - 200 mg TID aby IV drip (in 0.9% sodium

chloride solution) and IM.

Medium severity - 200 mg TID, intravenous drip (in 0.9% sodium chloride solution).

Severe course - in pulse dosaging of 800 mg on the first day, with a BID regimen of administration; further on 200 - 500 mg BID with a gradual decrease in the daily dose.

Extremely severe course - in the initial dosage of 800 mg/day until persistent relief of manifestations of pancreatogenic shock, after stabilisation of the condition 300 - 500 mg BID by IV drip (in 0.9% sodium chloride solution) with gradual reduction of daily dosage.

Contraindications

Acute liver and kidney dysfunction, hypersensitivity to the drug. Strictly controlled clinical studies of safety of use of Mexidol in children, during pregnancy and lactation have not been conducted.

Side effects

To avoid side effects, it is recommended to observe the dosing regime and the rate of drug administration.

The frequency of side effects was determined according to the World Health Organisation (WHO) classification:

very frequent (≥10%); frequent (≥1%, but < 10%); infrequent (≥0.1%, but < 1%); rare (≥0.01%, but < 0.1%); very rare (<0.01%); frequency unknown (frequency cannot be determined based on available data).

Immune system disorders: very rare - anaphylactic shock, angioedema, urticaria.

Mental disorders: very rare - somnolence.

Nervous system disorders: very rare - headache, dizziness (may be associated with excessively high rate of administration and is of short-term nature).

Vascular disorders: very rare - decrease in BP, increase in BP (may be associated with excessively high rate of administration and is transient).

Respiratory system, chest and mediastinal organs: very rare - dry cough, sore throat, chest discomfort, breathing difficulties (may be associated with excessively high rate of administration and is of short-term nature).

Gastrointestinal disorders: very rare - dry mouth, nausea, unpleasant odour, metallic taste in the mouth.

Skin and subcutaneous tissue disorders: very rare - pruritus, rash, hyperaemia.

General disorders and administration site reactions: very rare - sensation of warmth.

Interaction

It increases the effect of benzodiazepine anxiolytics, anticonvulsants (carbamazepine), antiparkinsonian agents (levodopa). It reduces the toxic effects of ethyl alcohol.

Special precautions

In individual cases, especially in predisposed patients with bronchial asthma with hypersensitivity to sulfites, the development of severe hypersensitivity reactions and bronchospasm is possible.

Overdose

Symptoms: drowsiness, insomnia.

Treatment: due to low toxicity, overdose is unlikely. Treatment is usually not required - symptoms disappear on their own within 24 hours. In severe manifestations, supportive and symptomatic treatment is carried out.

Use in pregnancy and during breastfeeding:

Mexidol® is contraindicated in pregnancy and during breastfeeding.

Effect of the IP on the ability to drive vehicles or operate mechanisms:

During the period of IP administration, caution should be exercised in work requiring quick psychophysical reactions (driving vehicles, mechanisms, etc.).

Within the framework of the present clinical trial it is planned to use Mexidol® solution for

intravenous and intramuscular administration, 50 mg/ml (Pharmasoft, Russia) 10 ml (500 mg) BID (1000 mg per day) by intravenous drip in 100-200 ml of 0.9% NaCl solution for 10 days in patients in the acute and early recovery periods of ischaemic stroke against the background of standard therapy.

Mexidol® Forte 250 film-coated tablets, 250 mg

Trade Name:	Mexidol® Forte 250
Group name:	Ethylmethylhydroxypyridine succinate
Marketing Authorization Holder/ Claims Receiving Organisation:	**RPC PHARMASOFT LTD** Legal address: Russia, 115407 Moscow, 41, Sudostroitelnaya St., floor 1, room. 12. Postal address: Russia, 109544, Moscow, Enthusiastov Boulevard, 2 Tel/fax +7 (495) 626-47-55
Manufacturer:	ZiO-Zdorovye CJSC, Russia, 142103, Moscow region, Podolsk, Zheleznodorozhnaya street, 2. Tel: +7 (495) 419 20 64 Mobile tel.: +7 (903) 117 09 14
Dosage form:	Film-coated tablets
Dosage:	250 mg
Composition per 1 tablet:	Composition per 1 tablet: ***Active ingredient:*** Ethylmethylhydroxypyridine succinate as 100 % substance - 250.0 mg **Excipients:** lactose monohydrate, povidone K-30, magnesium stearate. **Film coating:** Opadray II pink 33G240018 (hypromellose, titanium dioxide, lactose monohydrate, macrogol 4000, triacetin, iron oxide dye red, iron oxide dye yellow)
Description:	Round biconvex tablets covered with light pink film coating. On a transverse section, the nucleus is almost white.
Storage conditions	Store in a place protected from light, out of reach of children, at temperatures not exceeding 25 °C.
Packaging and labelling	10 Film-coated tablets in a PVC/Alu blister 1, 2, 3, 4, 5, 6 Blisters together with instructions for use in a carton pack. According to the National Standards of the Russian Federation GOST R 52379-2005 dated 27.09.2005 and GOST R 52249-2009 dated 20.05.2009, the labelling of IP packages, in addition to the mandatory information (name, dosage, storage conditions and expiry date, information about the manufacturer, date of issue and batch number), will contain the inscription **"For clinical studies"** and a space for entering information about the investigational site and the surname, name, patronymic of the Principal Investigator. Given the design features of the trial, the trial is planned to be blinded to the packaging of the investigational product and the comparator product (placebo).

Pharmacotherapeutic group

antioxidant agent

ATC code: N07XX

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of action

It belongs to the class of 3-oxypyridines. The mechanism of action of Mexidol® FORTE 250 is due to its antioxidant, antihypoxant and membrane-protective action. It inhibits lipid peroxidation, increases superoxide dismutase activity, increases the lipid-protein ratio, improves cell membrane structure and function. Causes an increase in compensatory activation of aerobic glycolysis and a decrease in the degree of inhibition of oxidative processes in the Krebs cycle under hypoxia with an increase in the content of adenosine triphosphate (ATP) and creatine phosphate, activation of energy-synthesising functions of mitochondria. It supports the activation of aerobic glycolysis that develops during acute ischaemia and promotes the restoration of mitochondrial redox processes under hypoxia conditions, increases ATP and creatine phosphate synthesis. The drug modulates the activity of membrane-bound enzymes (calcium-independent phosphodiesterase, adenylate cyclase, acetylcholinesterase), receptor complexes (benzodiazepine, gamma-aminobutyric acid (GABA), acetylcholine), which enhances their ability to bind to ligands, contributes to the preservation of structural and functional organisation of biomembranes, transport of neurotransmitters and improvement of synaptic transmission. In conditions of critical reduction of coronary blood flow, it promotes preservation of structural and functional organisation of cardiomyocyte membranes, stimulates the activity of membrane enzymes - phosphodiesterase, adenylate cyclase, acetylcholinesterase.

Mexidol® Forte 250 increases the content of dopamine in the brain.

Pharmacodynamic effects

Mexidol FORTE 250 is an inhibitor of free-radical processes, membrane protector with antihypoxic, stress-protective, nootropic, antiepileptic and anxiolytic action. The drug increases the body's resistance to various damaging factors in pathological conditions (hypoxia and ischaemia, impaired cerebral circulation, intoxication with ethanol and antipsychotic drugs). Anti-stressor effect is manifested in normalization of post-stress behaviour, somatovegetative disorders, restoration of sleep-wake cycles, disturbed learning and memory processes, reduction of dystrophic and morphological changes in various brain structures. It has hypolipidemic action, reduces the content of total cholesterol and low-density lipoproteins. Mexidol® FORTE 250 improves the functional state of ischaemic myocardium. It ensures the integrity of morphological structures and physiological functions of ischaemic myocardium. In conditions of coronary insufficiency it increases collateral blood supply of ischemic myocardium, promotes preservation of cardiomyocyte integrity and maintenance of their functional activity. It effectively restores myocardial contractility in reversible cardiac dysfunction. It stabilizes the membrane structures of blood cells (red blood cells and platelets), reducing the likelihood of haemolysis.

Clinical efficacy and safety

It improves metabolism and blood supply to the brain, improves microcirculation and rheological properties of blood, reduces platelet aggregation.

It improves the clinical course of myocardial infarction, increases the efficacy of therapy, and reduces the incidence of arrhythmias and intracardiac conduction disturbances [43]. It normalizes metabolic processes in ischemic myocardium, increases antianginal activity of nitrates, improves blood rheological properties, reduces the effects of reperfusion syndrome in acute coronary insufficiency.

Mexidol® FORTE 250 has a pronounced antitoxic effect in withdrawal syndrome. It

eliminates neurological and neurotoxic manifestations of acute alcohol intoxication, restores behavioural disorders, autonomic functions, and is also able to relieve cognitive impairment caused by long-term ethanol intake and its withdrawal.

It reduces enzymatic toxaemia and endogenous intoxication in acute pancreatitis.

Under the influence of the drug, the effect of tranquilising, neuroleptic, antidepressant, sleeping and anticonvulsant drugs is enhanced, which allows to reduce their doses and side effects.

Pharmacokinetics

Absorption

It is rapidly absorbed when taken orally. The maximum concentration (C_{max}) at doses of 400-500 mg is 3.5-4.0 μg/ml. It is rapidly distributed in organs and tissues.

Distribution

The mean retention time (MRT) of the drug in the body when administered orally is 4.9-5.2 h.

Biotransformation

Metabolised in the liver by glucuronconjugation. Five metabolites have been identified: 3-oxypyridine phosphate - formed in the liver and broken down into phosphoric acid and 3-oxypyridine with the participation of alkaline phosphatase; the 2nd metabolite - pharmacologically active, formed in large quantities and detected in the urine 1-2 days after administration; the 3rd - excreted in large quantities with urine; the 4th and 5th - glucuronconjugates.

Elimination

T1/2 at ingestion is 2.0-2.6 h. It is rapidly excreted with urine mainly in the form of metabolites and in an insignificant amount - in unchanged form. It is most intensively excreted during the first 4 h after drug administration. Urinary excretion rates of unchanged drug and metabolites have individual variability.

Indications for use

consequences of acute cerebral circulatory disorders, including after transient ischaemic attacks, in the phase of subcompensation as prophylactic courses;

mild head injury, consequences of head injuries;

encephalopathies of various genesis (dyscirculatory, dysmetabolic, post-traumatic, mixed);

autonomic dystonia syndrome;

mild cognitive disorders of atherosclerotic genesis;

anxiety disorders in neurotic and neurosis-like states;

ischaemic heart disease as part of complex therapy;

coping with withdrawal syndrome in alcoholism with predominance of neurosis-like and vegetative-vascular disorders, post-abstinence disorders;

condition after acute intoxication with antipsychotic drugs;

asthenic conditions, as well as for the prevention of somatic diseases under the influence of extreme factors and loads;

exposure to extreme (stressor) factors.

Method of administration and doses

250 Mg IV TID.

Initial dose - 250 mg (1 tablet) 1-2 times a day with gradual increase until therapeutic effect. The maximum daily dose is 750 mg (3 tablets).

Duration of treatment 2-6 weeks; for alcohol withdrawal - 5-7 days. Duration of the course of therapy in patients with ischaemic heart disease is not less than 1.5 - 2 months.

Repeated courses (on the doctor's recommendation) should preferably be carried out in the spring and autumn periods.

Special patient groups

Children

Safety and efficacy of Mexidol FORTE 250 in children aged 0 to 18 years have not been established.

Method of administration:

Per os.

Contraindications

- acute liver and kidney dysfunction,
- hypersensitivity to ethylmethylhydroxypyridine succinate or to any of the excipients.
- infancy (due to insufficiently studied effect of the drug);
- pregnancy, breastfeeding (due to insufficient trial of the drug action);
- lactose intolerance, lactase deficiency, glucose-galactose malabsorption.

Special instructions and precautions for use

Patients with rare hereditary fructose intolerance, galactose intolerance, galactosemia or glucose-galactose malabsorption should not take this preparation.

Fertility, pregnancy and lactation

Mexidol FORTE 250 is contraindicated in pregnancy and during breastfeeding.

Side effects

Summary of adverse reactions

The frequency of side effects was determined according to the World Health Organisation (WHO) classification:

very frequent (≥10%); frequent (≥1%, but < 10%); infrequent (≥0.1%, but < 1%); rare (≥0.01%, but < 0.1%); very rare (<0.01%); frequency unknown (frequency cannot be determined based on available data).

Immune system disorders: very rare - angioedema, urticaria.

Mental disorders: very rare - somnolence.

Nervous system disorders: very rare - headache.

Gastrointestinal disorders: very rare - dry mouth, nausea, pain, burning and discomfort in the epigastric region, heartburn, flatulence, diarrhoea.

Skin and subcutaneous tissue disorders: very rare - rash, pruritus, hyperaemia.

Suspected adverse reactions reporting

It is important to report suspected adverse reactions after registration of the medicinal product in order to ensure continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse drug reactions through the national adverse reaction reporting systems of the Eurasian Economic Union member states.

Russian Federation
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Federal Service for Surveillance in Healthcare
Phone: +7 (495) 698-45-38, +7 (499) 578-02-30
Email: pharm@roszdravnadzor.ru
Site http://www.roszdravnadzor.ru/

Overdose

Symptoms

Drowsiness, insomnia.

Treatment

Due to low toxicity, overdose is unlikely. Treatment is usually not required - symptoms disappear on their own within 24 hours. In severe manifestations, supportive and symptomatic treatment is carried out.

Interaction with other medicines

Mexidol® FORTE 250 is combined with all drugs used for the treatment of somatic diseases.

Increases the effect of benzodiazepines, antidepressants, anxiolytics, antiepileptics (carbamazepine) and
antiparkinsonian drugs (levodopa), nitrates. It reduces the toxic effects of ethanol.

Effect of the IP on the ability to drive vehicles or operate mechanisms

During the period of drug administration, caution should be exercised in work requiring quick psychophysical reactions (driving vehicles, mechanisms, etc.).

Within the framework of the present clinical trial it is planned to use Mexidol® FORTE 250, film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) 1 tablet TID for 60 days after a 10-day course of intravenous administration of Mexidol®, solution for
intravenous and intramuscular administration, 50 mg/ml in patients in the acute and early recovery periods of ischaemic stroke against the background of standard therapy.

More detailed information on the pharmacological properties of Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml and Mexidol® FORTE 250, film-coated tablets, 250 mg is available in the Investigator's Brochure.

Comparator product (R)

The trial involves the use of Placebo 1 and Placebo 2 in patients in the acute and early recovery periods of ischaemic stroke.

Placebo 1.

Manufacturer:	Ellara LLC, Russia 601122, Vladimir region, Petushinsky district, Pokrov, Franz Stolwerk str. 20, p.2
Dosage form:	intravenous and intramuscular solution
Composition per 1 ml:	Composition per 1 ml: Sodium chloride 9 mg Water for injection up to 1 ml 5 ml ampoules will be used in the trial
Description:	Placebo appearance corresponds to the appearance of the investigational product Mexidol® solution for intravenous and intramuscular administration
Storage conditions	Store at a temperature not exceeding 25°C.
Packaging and labelling	5 ampoules in a blister package. 1 or 2 blisters together with instructions for medical use in a carton pack. 4, 10 or 20 blisters together with instructions for medical use in a carton pack (for hospitals). According to the National Standards of the Russian Federation GOST R 523792005 dated 27.09.2005 and GOST R 52249-2009 dated 20.05.2009, the labelling of IP packages, in addition to the mandatory information (name, dosage, storage conditions and expiry date, information about the manufacturer, date of issue and batch number), will contain the inscription **"For clinical studies"** and a space for entering information about the investigational site and the surname, name, patronymic of the Principal Investigator. Given the design features of the trial, the trial is planned to be blinded to the packaging of the investigational product and the

	comparator product (placebo).

In the framework of the present clinical trial it is planned to use Placebo 1, solution for intravenous and intramuscular administration, BID by intravenous drip in 100-200 ml of 0.9% NaCl solution for 10 days in patients in the acute and early recovery periods of ischaemic stroke on the background of standard therapy.

Placebo 2.

Manufacturer:	ZiO-Zdorovye CJSC, Russia, 142103, Moscow region, Podolsk, Zheleznodorozhnaya street, 2. Tel: +7 (495) Tel: +7 (495) 419 20 64 Mobile tel.: +7 (903) 117 09 14
Dosage form:	Film-coated tablets
Composition per 1 tablet:	Composition per 1 tablet: Lactose monohydrate - 445.0 mg; Povidone K-30 - 50.0 mg; Magnesium stearate - 5.0 mg. Weight of uncoated tablet is 500.0 mg. **Film coating:** Opadray II pink 33G240018: - 15.0 mg hypromellose; titanium dioxide; lactose monohydrate; macrogol 4000; triacetin; red iron oxide colourant; iron oxide yellow colouring agent. Weight of the tablet is 515.0 mg.
Description:	The appearance of the placebo corresponds to the appearance of the investigational product Mexidol® FORTE 250 film-coated tablets
Storage conditions	Store at a temperature not exceeding 25°C.
Packaging and labelling	10 film-coated tablets in a PVC/Alu blister. 1, 2, 3, 4, 5, 6 blisters together with the instructions for use in the carton pack. According to the National Standards of the Russian Federation GOST R 52379- 2005 dated 27.09.2005 and GOST R 52249-2009 dated 20.05.2009, the labelling of IP packages, in addition to the mandatory information (name, dosage, storage conditions and expiry date, information about the manufacturer, date of issue and batch number), will contain the inscription **"For clinical studies"** and a space for entering information about the investigational site and the surname, name, patronymic of the Principal Investigator. Given the design features of the trial, the trial is planned to be blinded to the packaging of the investigational product and the comparator product (placebo).

In the framework of the present clinical trial it is planned to use Placebo 2, film-coated tablets, 1 tablet TID for 60 days after a 10-day course of intravenous administration of Placebo

1, solution for intravenous and intramuscular administration, in patients in the acute and early recovery periods of ischaemic stroke on the background of standard therapy.

2.3. Results of preclinical and clinical studies

2.3.1. Results of preclinical studies

Pharmacokinetics

Studies have established that ethylmethylhydroxypyridine succinate has high bioavailability. When parenterally administered to rats, it was rapidly absorbed from the abdominal cavity with a half-absorption period of 0.94 hours; maximum concentrations in plasma were reached in 3 hours, and in the brain and liver of animals - in 2-3 hours [Voronina T.A., 2003].

In experiments conducted on mongrel rats, it was found that when administered orally, the elimination stage of the drug has a clear biphasic character [Miroshnichenko I.I. et al., 1994].

In the trial of pharmacokinetics and biotransformation of ethylmethylhydroxypyridine succinate in mice, the concentration of the drug was determined by high-performance liquid chromatography (HPLC) in blood plasma in the interval from 1 to 90 min; in urine - 24 h after administration of ethylmethylhydroxypyridine succinate [Kravtsova O.Yu., 2005].

In the trial of biotransformation features of ethylmethylhydroxypyridine succinate, 5 metabolites represented by dealkylated and conjugated transformation products were isolated and identified: (1) 2,6-dimethyl-3- oxipyridine; (2) 6-methyl-3-oxypyridine; (3) phosphate conjugate 2-ethyl,6-methyl-3- oxipyridine; (4) glucuron conjugate 2-ethyl-6-methyl-3-oxypyridine; (5) phosphate-glucuron conjugate 2-ethyl-6-methyl-3-oxypyridine. The first metabolite was found to have the same anxiolytic activity as the parent substance, and even surpasses it in antihypoxic and sedative effects. The third metabolite plays an important role in the membranotropic action and pharmacological activity of ethylmethylhydroxypyridine succinate, prolonging the effect of the original drug due to the formation of hepatic depot [Kravtsova O.Yu. et al., 2003].

Toxicity

Acute toxicity

Determination of acute toxicity of tablet form of Mexidol® preparation was carried out on two species of animals (mice, rats) at two routes of administration (intraperitoneally and orally). After administration of the drug, animal behaviour, appearance, reactions to external stimuli were observed for 14 days and in case of death, the number of deaths and clinical picture of death were noted. It was found that at intraperitoneal administration of Mexidol® in experiments on mice LD50 was 430 (310-602) mg/kg. When the drug was administered orally to mice, the LD50 was 2000 mg/kg. When Mexidol® was administered intraperitoneally to rats, the LD50 was 820 (700.8-959) mg/kg. When the drug was administered orally to rats LD50 was 3000 mg/kg [Seredenin S.B. et al., 1994].

The trial of acute toxicity of the injectable form of Mexidol® was carried out on mongrel rats during 14 days by intramuscular injections - in the thigh, and intravenous injections - in the tail vein. When administering the technically maximum possible volume (dose 2500 mg/kg, volume 10 ml), no lethal effects were observed [Kosmachev A.B., 2004].

The results of toxicometry, data of observations of experimental animals in the postintoxication period of acute poisoning, as well as necropsy data allow us to assign the drug Mexidol® to the following classes of toxicity: tablet form - class 4 (low toxicity), solution for IV and IM administration - class 5 (practically non-toxic drug substances). [Hodge H. et al., 1975].

Subacute toxicity

Subacute toxicity of the preparation Mexidol® solution for intravenous and intravenous administration was studied on 150 mongrel rats, of which 30 animals constituted the control

group for each route of administration. The drug was administered once daily for 14 days. Two administration techniques were investigated: intramuscularly (into the thigh muscle) and intravenously (into the tail vein). Two doses, 10 mg/kg and 500 mg/kg (50 times higher), were studied. After the end of administration, animals of all groups were slaughtered and sent for autopsy and pathomorphological examination. Pathomorphological trial showed that intramuscular and intravenous administration of the tested drug Mexidol® at doses of 10 mg/kg and 500 mg/kg does not cause pathological morphological changes in internal organs, including the brain and does not have an irritating effect at the injection sites [Kosmachev A.B., 2004].

Chronic toxicity

Experiments to trial the general toxic effect of the tablet form of Mexidol® were conducted on 48 mongrel white rats of both sexes. Rats were administered Mexidol® as a suspension of crushed tablets on distilled water per os (via a probe into the stomach) once a day for 6 months at the following dosages: 25 mg/kg (therapeutic dose) and 250 mg/kg, ten times the therapeutic dose. As a result of experiments it was found that the drug does not cause pathological changes in vital organs and systems of the animal body, even applied in a dose that is ten times higher than the therapeutic dose. At histological trial it was found that preparation Mexidol® does not cause pathological changes of internal organs, and also does not have local irritant effect [Seredenin S.B. et al., 1994].

Specific toxicity

As a result of the conducted studies it was found that Mexidol® when administered during pregnancy at a dose of 250 mg/kg intragastrically has no embryotoxic and teratogenic effect. When trialing allergic properties of the oral dosage form of Mexidol®, the data of reactions of general and active cutaneous anaphylaxis indicate the presence of sensitising properties when the drug is administered at a dose of 25 mg/kg, which can be considered as a manifestation of individual sensitivity, since the number of animals with positive reactions did not exceed 50%. The trial of mutagenic activity was carried out on mice. Testing has not revealed in the oral dosage form of Mexidol® mutagenic activity at any stage of the spermatogenesis cycle [Seredenin S.B. et al., 1994].

Pharmacological effects

The effect of Mexidol® on the process of Fe^{2+}-induced LPO of apo-B-containing serum lipoproteins was studied by recording chemiluminescence kinetics. Mexidol® in different concentrations was found to inhibit the LPO process of apo-B lipoproteins isolated from blood serum of healthy donors by precipitation method. The established mechanism of inhibition is due to the effect of the drug on the state of Fe^{2+} ions and/or the efficiency of their interaction with lipoproteins. The detected antioxidant effect of Mexidol® may be an important link in the general mechanism of its antioxidant action. [Teselkin Y.O., Davydov B.V., 2006].

The lipid spectrum in the brain tissue in different terms of post-resuscitation period with subcutaneous administration of Mexidol® at a dose of 50 mg/kg was studied in rats in the experiment when modelling clinical death by cardiovascular bundle constriction according to V.G. Korpachev. The administration of the drug increased the phosphatidylserine content, normalised the relative amounts of phosphatidylethanolamine and cholesterol, free fatty acids and the absence of lysophosphatidylserine in the remote post-resuscitation period. Mexidol® promoted the formation of protective-adaptive reactions at the level of lipid component of brain cell membranes in the early reperfusion period, preventing the development of irreversible damage to the phospholipid metabolism of the brain in the remote postreanimation period. [Andreeva N.N., Mukhina I.V., 2005].

The effect of Mexidol® and its structural components on carbohydrate content and lipid peroxidation in the liver of white mice under acute stress when administered at a dose of 100 mg/kg intraperitoneally was studied. Mexidol® inhibited the increase of glycogen content in liver tissue without affecting the content of free glucose in it. At the same time, the drug inhibited LPO processes. Protective effect of Mexidol® in the liver can be explained by its

membrane-stabilising effect, which is manifested by inhibition of membrane LPO and changes in their phospholipid composition, as well as normalization of the functioning of membrane-bound enzymes [Devyatkina T.A. et al., 1999].

The trial of the use of Mexidol® on the model of intracerebral posttraumatic haematoma (haemorrhagic stroke) in rats showed its efficacy at a dose of 100 mg/kg when administered for 7 days. In the experiment the drug significantly reduced the frequency of neurological disorders (paresis, manoeuvres), increased the survival rate of animals. Mexidol® improved learning and memory processes in rats with haemorrhagic stroke (HS) in the test of conditioned passive avoidance reflex, influenced motor activity in the open field test. The author emphasised that a particularly important consequence of the drug's action is its ability to exert a complex effect on the different disorders occurring after HS. Mexidol® reduces the mortality of animals after stroke, improves neurological status, eliminates post-stroke memory disorders, has anxiolytic effect, improves orientation-research behaviour [Kraineva V.A., 2006].

Mexidol® prevented the development of amnesia in mice induced by complex extreme exposure, attenuating this type of amnesia in mice with bilateral ligation of the common carotid arteries. Mexidol® induced a pronounced anti-amnesic effect in models of amnesia induced by maximal electroshock, scopolamine and acute normobaric hypoxia with hypercapnia. Mexidol® at microelectrophoretic administration at a dose of 100 mg/kg depressed the spontaneous activity of neurons of different brain structures 4.2-7.4 times more often than stimulated. [Soloviev N.A., Yasnetsov V.V., 2006].

In another trial on the model of local cerebral ischaemia (LCI) of rabbits, an experimental evaluation of neuroprotective efficacy of Mexidol® at a dosage of 5 mg/kg intramuscularly was carried out with the trial of cerebral and skin microhemodynamics, lipid peroxidation (LPO), oxygen transport function and blood COS, O2 mass transfer parameters in brain tissues. Administration of Mexidol® in the early post-ischaemic period in rabbits with LCI caused a decrease in primary and secondary LPO products with an increase in the activity of the enzymatic link of the antioxidant system, improving the supply of brain tissues with O2, and enhancing the processes of cerebral and intradermal haemodynamics . The use of Mexidol leads to normalization or improvement of a number of homeostatic constants of the organism, changes in which play an important role in the structure of the pathogenesis of cerebral ischemia, which, according to the authors, can serve as a pathogenetic justification for its use in the complex neuroprotective pharmacotherapy of patients with cerebrovascular pathology of ischemic genesis. [Nechipurenko N.I. et al., 2006].

The neuroprotective activity of Mexidol® during gravitational overload in craniocaudal position was studied on the model of total brain ischaemia in rats. It was found that intraperitoneal administration of Mexidol® at doses of 5, 10 and 100 mg/kg increased the survival rate of laboratory animals in hypergravity. The effectiveness of prophylactic use of this drug is due to the limitation of hyperglycaemia and lactate acidosis, LPO processes in the brain and in erythrocytes, reducing the permeability of erythrocyte membranes for calcium ions, maintaining the autoregulation reaction of cerebral vessels. [Makarova L.M., 2006].

Mexidol® in the experiment at a dose of 20 mg/kg at intraperitoneal administration had a favourable effect on blood supply of the myocardial ischemia zone after coronary occlusion in rats. The drug reduced the decrease in left ventricular pressure and velocity characteristics of contraction of the left ventricle of the heart with local ischaemia, as well as in the acute period of myocardial infarction led to a decrease in lactacidaemia, glucose extraction and reduction of the electronegative shift of the redox potential of the system lactate/pyruvate [Gatsura V.V., 1996].

2.3.2. Results of clinical studies

Mexidol® is rapidly absorbed when taken orally, at doses of 400-500 mg Cmax is 3.5-4 mcg/ml. The drug is rapidly distributed in organs and tissues. The average retention time of

ethylmethylhydroxypyridine succinate in the body when administered orally is 4.9-5.2 h; T1/2 is 2-2.6 h. [IMU].

Use of Mexidol® at the pre-hospital stage in the complex therapy of acute cerebral circulatory disorders

The use of Mexidol® at the pre-hospital stage with its subsequent administration in hospital allowed to significantly reduce mortality of patients with various types of ACCD, including hemorrhagic, to achieve faster and more stable regression of neurological symptoms, to improve the subsequent quality of life of patients and the level of their social adaptation. The drug was well tolerated by patients, did not cause significant changes in BP, HR and respiratory rate, no side effects were observed during therapy with Mexidol®. The obtained results allowed to recommend Mexidol® for use at the pre-hospital stage as a means of urgent undifferentiated therapy in emergency conditions in patients with all types of acute disorders of cerebral circulation with subsequent continuation of the drug in hospital [Sidorov A.M. Borisova V.A., 2005].

Use of Mexidol® at the hospital stage in the complex therapy of cerebral circulatory disorders

By improving and stabilising cerebral metabolism, Mexidol® corrects microcirculation disorders, improves blood rheology, inhibits platelet aggregation, improves the immune system, activates intracellular synthesis of protein and nucleic acids, which stimulates reparative processes and limits the zone of ischemic damage in hemispheric stroke. It is in patients with hemispheric lesions by the end of the first day of the disease often revealed hyperoxia, resulting from hyperventilation syndrome. At the same time, the concentrations of components of antioxidant systems are significantly reduced in patients. In acute ischemic stroke, taking into account pharmacokinetic peculiarities of the drug, it is recommended to administer Mexidol® BID at 300 mg with an interval of 12 h (intravenous drip in dilution on physiological solution); daily dose of Mexidol®, which is 600 mg, is recommended to be used for 5 days. The dose is then reduced to 200 mg BID intravenously (400 mg daily) for the next 6-8 days. Then the drug is administered intramuscularly once in a dose of 100 mg per day for 2 more subsequent weeks, and then switch to long-term administration of oral forms of the drug in a dose of 125 mg 2-3 times per day. The duration of oral administration is at least 2 months. In this regimen of Mexidol® administration, more pronounced positive dynamics of neurological status was observed in comparison with patients who were administered the drug according to the standard scheme - 300 mg OD for 10 days. Such a scheme of prescribing Mexidol® allows not only to fully realise antioxidant and energy-correcting effects of the drug, but also gradually activate, "train" own antioxidant systems of the body, as evidenced by the increase in their activity, revealed by the dynamics of laboratory parameters [Rumyantseva S.A. et al., 2011]

Use of Mexidol® in acute cerebral ischaemia (intravenous drip in a dose of 250 mg for 7 days, followed by transfer to intramuscular administration of the drug in a dose of 100 mg once a day for 15 days, and long-term oral administration of the drug: 125 mg TID for 2 months with a break for 1 month and a repeated two-month course) demonstrated its high efficiency due to its multifunctional capabilities with simultaneous effect on different links of the ischaemic cascade [Ivanova N.E. et al., 2010].

On the basis of complex clinical and radiological trial of 272 patients with ischaemic disorders of cerebral circulation with pathology of extracranial sections of carotid and vertebral arteries the main pathogenetic factors in four groups were identified. In the clinical picture of cerebrovascular disease in patients who underwent surgical treatment for extracranial arterial pathology (group 4), low-symptomatic course of chronic CCD was noted in 19 (15.8 %), transient ischaemic attacks - in 73 (60.8 %), consequences of MI - in 28 (23.3 %) cases. A thorough clinical, neurological and radiological examination revealed the most significant pathogenetic factors of cerebral ischaemia.

The positive effect of Mexidol® in complex conservative and surgical treatment of

ischaemic CCD of extracranial genesis, especially in the group of elderly and elderly patients, is confirmed by positive dynamics of Dopplerography, computer stabilography, cognitive evoked potentials of the brain P-300.

Significant improvement in the quality of life was observed for the following indicators: "physical activity", "role of physical problems in limitation of life activity", "general health", mental health". In elderly and senile patients on the background of treatment with Mexidol® in combination with intravenous laser irradiation of blood such indicators as "social activity", "mental health", "the role of emotional problems in the limitation of life activity" improved. This indicates anxiolytic, redynamising and anti-stress effects of Mexidol® in patients, which is very important because due to frequent dizziness, fainting, impaired walking function they become socially and physically limited. Chronic paroxysmal course of VBI in pathology of extracranial VA leads to an increase in the level of situational and reactive anxiety in patients according to the Spielberger test. After complex treatment with Mexidol® signs of asthenisation, depression and anxiety decreased. In terms of correction of these disorders, the combination of parenteral administration of Mexidol® with its long-term (2-3 months) oral administration was particularly effective.

On the basis of dynamic neurophysiological examination and comparison with control groups it has been proved that the use of Mexidol® in pre- and postoperative periods during angio-surgical treatment of ischaemic cerebral circulatory disorders increases the safety and efficiency of surgical treatment. In this case, the adaptation and compensatory capabilities of the organism, brain resistance to chronic ischaemia and sharp changes in cerebral blood flow [Kandyba D.V. et al., 2006] are improved.

The trial of Mexidol® in 30 patients 48-75 years old with the consequences of acute cerebral circulatory failure (duration of the disease up to 1 year) revealed a pronounced therapeutic effect of the drug on cognitive disorders. The drug contributed to the improvement of social adaptation of patients and their psycho-emotional state, which was expressed in the improvement of memory, motor activity, cerebral haemodynamics, bioenergetic activity of the brain, reduction of total cholesterol and low-protein lipoproteins. All trial participants were prescribed Mexidol® 4 ml (200mg) intravenous drip in 100 ml NaCl solution in the morning for 10 days and 2 ml (100mg) intramuscularly in the afternoon for 10 days. Then Mexidol® was administered "per os" (125 mg TID for 1 month). Almost 80-82% of patients had normalized sleep and improved mood. Improvement in memory for current events was noted in 30% of patients. Changes in the motor domain were observed: the index of daily activity increased from 75.14+3.65 to 82.21+4.31.

Overall, the neurological status improved in 50% of patients. Changes in cerebral haemodynamics were recorded under the influence of Mexidol®. According to EEG data, nootropic and neurotropic effects of Mexidol® were noted, increases in the power spectrum and activity of fast-wave rhythmics were registered [Kadin I.M., 2006].

In order to expand the indication for human use, a randomized double-blind multicentre placebo-controlled parallel-group phase III trial of the efficacy and safety of Mexidol® in long-term sequential therapy in patients in the acute and early recovery periods of hemispheric ischaemic stroke (EPICA) was conducted [Stakhovskaya L. V. et al, 2017].

Patients with primary hemispheric ischaemic stroke confirmed by computed tomography (CT)/magnetic resonance imaging (MRI) between 40 and 80 years of age, hospitalized within 72 hours of the onset of IS, were included in the trial. The modified Rankin Scale score at the time of inclusion in the trial had to be 3 points or more; National Institutes of Health Stroke Scale score of 5 to 20 points; Beck Depression Scale score of less than 19 points.

Patients were randomized into two groups: patients of the first group received Mexidol® for 10 days at 500 mg/day intravenous drip followed by tablets (125 mg) 1 tablet TID for 8 weeks, patients of the second group received placebo according to the similar scheme. All patients received basic IS therapy in accordance with the standards of medical care and clinical

guidelines.

A total of 151 patients were included in the trial, of which 150 patients (62 males and 88 females) aged between 40 and 79 years were randomized. 141 patients completed the trial, 9 patients dropped out early. Data from 124 patients who completed the trial according to the protocol were included in the efficacy analysis. Data from 150 patients were included in the safety analysis.

Both groups showed a decrease in mean values when assessed with the modified Rankin Scale. At the end of therapy there was a statistically significant difference between groups (p=0.04): in group 1 - 1.1±0.8 points, in group 2 - 1.5±1.0 points. When assessing the changes vs. baseline, statistically significant differences (p=0.023) were found between the groups: in group 1 the change was 2.3±0.7, in group 2 - 2.0±0.8 points. There was a significant difference in the proportion of patients who achieved recovery of 0-2 points on the Rankin scale at the end of the course of therapy (59 (96.7%) patients in the Mexidol® group and 53 (84.1%) patients in the placebo group) (p=0.039).

According to the National Institutes of Health Stroke Scale at the end of therapy, there was a statistically significant difference between the groups in terms of the sum of scores: group 1 had a lower mean of 1.7±1.4 points and group 2 had a mean of 2.2±1.4 points (p=0.035). There were also statistically significant differences in the change in value relative to baseline between groups of patients with diabetes mellitus: in group 1 (n=11) 5.4±2.3 points, in group 2 4.0±1.4 points (p=0.038).

Tolerability of therapy with Mexidol® and placebo was considered as satisfactory; 41 adverse events (AEs) were registered in 32 patients. There were 37 cases of AEs in 28 patients and 4 cases of severe AEs (SAEs). In the majority of cases the association of AE with the investigational products was determined as absent, in 3 cases - as possible. These abnormalities were random in nature and could develop, including against the background of the underlying and concomitant diseases. No deaths have been reported.

Thus, Mexidol® improves metabolism and blood supply to the brain, has hypolipidemic action, improves energy metabolism of the cell, affects the content of biogenic amines, inhibits free radical oxidation of lipids, increases the activity of antiradical defence enzymes. The result of realisation of the above properties is improvement of memory, learning, preservation of the memory trace and, as a consequence, counteraction to the process of fading of the instilled skills and reflexes, which ultimately contributes to the recovery of motor functions of stroke patients.

Further details of the experimental and clinical results are presented in the Investigator's Brochure.

2.4. Risk/benefit ratio for trial subjects

2.4.1. Possible benefits for patients

Aspects of benefit to the patients participating in this clinical trial consist of the free provision of the investigational product and a set of diagnostic procedures outside the scope of routine clinical practice, also offered free of charge within the framework of this protocol to the trial subjects.

It is assumed that patients in the acute and early recovery periods of ischaemic stroke in the groups of sequential administration of Mexidol® and Mexidol® FORTE 250 will achieve a faster and more significant recovery of body functions, reduction in the probability of disability compared to placebo. The benefit of prescribing Mexidol® and Mexidol® FORTE 250 is the expected reduction in the severity of neurological deficit (motor and cognitive impairments), improvement of patients' quality of life due to earlier and fuller social adaptation during long-term sequential therapy in patients with hemispheric ischaemic stroke.

The prospect of successful therapy (including with standard therapy drugs) for the symptoms of the patients' underlying disease may also be considered an aspect of the benefit of

participation in this clinical trial.

2.4.2. Known risks

The risks assumed by the research subject in connection with participation in this trial should include risks associated with the use of the IP, risks associated with the trial procedures, and risks determined by the experimental nature of the trial.

Risks associated with the use of the investigational product/comparator product

Patients receiving the investigational product

According to the instructions for medical use of Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml, the side effects described in section 2.2 may occur when using the drug.

According to the instructions for medical use of Mexidol® FORTE 250 film-coated tablets, 250 mg, the side effects described in section 2.2 may occur when using the drug.

For the safety of patients, the Protocol provides additional safety measures for the selection of trial subjects. The protocol provides for ongoing medical follow-up of patients, including the recording and assessment of adverse events, which will minimise the risk to patients from participation in this trial.

If known adverse reactions to the drug develop, appropriate action will be taken by the investigator, up to and including discontinuation of the drug.

In addition, there is the possibility of unknown and unforeseen side effects to the drugs used in the trial.

In this trial, Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) 10 ml (500 mg) BID (1000 mg per day) 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) 10 ml (500 mg) BID (1000 mg per day).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. The use of investigational products will be carried out against the background of baseline therapy. It is expected that such a therapy regimen for patients with ischaemic stroke will be characterized by a low probability of side effects.

Based on the above, it can be concluded that for patients in the active treatment group, the benefits of participation in the trial outweigh the possible risks.

Patients receiving placebo

Patients in the placebo group fared less favourably than patients in the active treatment group in terms of the benefit of trial participation.

According to modern recommendations, treatment of patients who have suffered an ischaemic stroke in the early recovery period should be aimed both at elimination of the existing neurological deficit and prevention of neurological deficits
of a recurrent stroke. Therefore, all patients in the trial, including the placebo group, will receive ischaemic stroke therapy according to the Clinical Guidelines for Ischaemic Stroke and Transient Ischaemic Attack in Adults, 2015.

In this clinical trial, patients receive therapy adequate to their status, including their primary and possible comorbidities, in full, with the exception of some drugs prohibited by this protocol.

At the same time, patients in the placebo group do not carry the risks associated with receiving the investigational therapy because the components of the two placebo forms used are inert and their administration (excluding the performance of intravenous injections) is not an invasive procedure.

Thus, for patients in the placebo group, the risk-benefit ratios are balanced and the prescribed therapy is within the limits of available medical care, so the use of placebo in the present trial is ethically acceptable.

Risks associated with diagnostic procedures

The risks associated with diagnostic procedures do not exceed those for routine medical practice.

Other risks taken by patients in connection with participation in a clinical trial are determined by the **experimental nature of the trial**, as the exact outcome is not known.

During the course of the trial, all treatment and diagnostic measures according to the Protocol will be performed at the Sponsor's expense; qualified personnel will participate in the diagnostic examinations. As a result of the examination, patients will receive reliable information about their health status.

Based on the above, it can be concluded that the benefits of patient participation in this clinical trial exceed the risks taken by patients in both groups, which characterises the risk/benefit ratio as ethically acceptable.

2.5. Description and justification of the method of administration, dosage and dosing regimen of investigational products

In accordance with the legal and regulatory framework, the trial will be performed with samples of the investigational product and comparator product provided by the Sponsor.

The trial will evaluate the efficacy and safety parameters 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) vs. placebo on the background of standard therapy.

In the present trial, IP is used in patients in the acute and early recovery periods of ischaemic stroke:

Group I - use of preparations Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) 10 ml (500 mg) BID (1000 mg per day) intravenous drip in 100-200 ml 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.

The trial involves the use of Placebo 1 and Placebo 2 in patients in the acute and early recovery periods of ischaemic stroke:

Group II - use of 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.

According to the instructions for medical use (IMU) of the investigated preparations, one of the indications for use is ACCD and their consequences, and the following dosage regimen is recommended for the dosage form of Mexidol® in the form of solution for intravenous and intravenous administration: for the first 10-14 days - intravenous drip of 200-500 mg 2-4 times a day.

Previous clinical studies have demonstrated the efficacy of sequential use of solution for infusion and tablets in patients with ischaemic stroke (according to routine clinical practice, patients with such pathology (without impairment of vital functions) stay in hospital, after which they are transferred to long-term outpatient observation).

Thus, a randomized double-blind multicentre placebo-controlled parallel-group phase III trial of the efficacy and safety of Mexidol® in long-term sequential therapy in patients in the acute and early recovery periods of hemispheric ischaemic stroke (EPICA) was conducted. Patients with primary hemispheric ischaemic stroke confirmed by computed tomography (CT)/ magnetic resonance imaging (MRI) aged 40 to 80 years, hospitalized no later than 72 hours from the onset of IS. Patients were distributed by randomization into two groups: patients of the first group received Mexidol® 500 mg/day intravenous drip for 10 days followed by tablets (125 mg) 1 tablet TID for 8 weeks, patients of the second group received placebo according to the similar scheme. All patients received basic IS therapy in accordance with the standards of

medical care and clinical guidelines. In both groups there was a decrease in the mean values when assessed by the modified Rankin scale; by the National Institute of Health Stroke Scale at the end of therapy there was a statistically significant difference between the groups in terms of the sum of scores: in group 1 the mean value was lower and was 1.7±1.4 points, in group 2 - 2.2±1.4 points (p=0.035). which allows us to conclude that it is reasonable to include Mexidol® in the therapy of patients in the acute and early recovery periods of IS.

The planned trial involves the administration of Mexidol® for 10 days at 10 ml (500 mg) BID (1000 mg per day) by intravenous drip followed by a higher dose of tablets (250 mg) at 1 tablet TID for 60 days, which is expected to achieve a more pronounced effect in terms of regression of neurological deficit, reduction in the severity of general cerebral symptoms, motor dysfunction and cognitive impairment.

Thus, the present clinical trial refines the recommended dosing regimen with regard to real medical practice, providing for long-term sequential administration of ethylmethylhydroxypyridine succinate preparations in two dosage forms as described above.

Oral administration of Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) is carried out by patients based on the investigator's decision to transfer the patient to the next stage of therapy. The protocol regulates the possibility to start oral administration of the investigational product with the permission of the investigator only after completion of a full ten-day course of intravenous therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia).

On the basis of previously conducted clinical studies it is possible to conclude about possible efficacy and safety of sequential application of dosage forms and routes of administration of Mexidol® and Mexidol® FORTE 250, in the treatment of patients with ischaemic stroke, the total duration of use of different dosage forms of the investigational product (70 days) is aimed at reducing neurological symptoms both in the acute and acute periods of ischaemic stroke, and at early recovery of functions in the early recovery period.

The proposed placebo-controlled trial design, as well as blindedness, will allow to evaluate the efficacy of sequential therapy with Mexidol® in patients with ischaemic stroke, providing the highest level of evidence for the trial of the trial, while minimising the majority of subjective factors on the part of both the patient and the physician.

Treatment of patients with ischaemic stroke based on evidence-based medicine includes the following items: general monitoring (control of blood pressure and temperature, glycaemia and blood ionic composition), specific treatment in the acute phase (intravenous or intra-arterial thrombolysis), preventive therapy (anticoagulants, antiplatelet drugs, surgery on carotid vessels). Currently, among the strategies that reliably improve the results of treatment and outcomes of acute stroke, the level of evidence A is: interventions aimed at maintaining the functioning of important organs and systems, earlier administration of acetylsalicylic acid, thrombolysis, hemicraniectomy, and treatment of the patient in a specialised stroke unit [Stroke: Manual for doctors / Edited by L.V. Stakhovskaya, S.V. Kotov. - M.: LLC "Medical Information Agency", 2013. - 400 p.: ill].

The use of placebo in the control group is primarily due to masking therapy and blinding, which increases the reliability of the findings. According to modern recommendations, treatment of patients with ischaemic stroke in the early recovery period should be aimed at both elimination of the existing neurological deficit and prevention of recurrent stroke. All patients in the trial, including the placebo group, will receive ischaemic stroke therapy according to the Clinical Guidelines for Ischaemic Stroke and Transient Ischaemic Attack in Adults, 2015. It will be prohibited to take drugs that are not authorized/prohibited by this Protocol (drugs positioned by manufacturers as neuroprotectors and proposed for the treatment and prevention of stroke, but have not demonstrated convincing benefits in large and well-designed studies and do not have a convincing evidence base in the therapy of ischemic stroke) [Domashenko M.A., Piradov M.A., 2013]. In view of the above, all patients participating in the trial will fully receive

the recommended therapy for ischaemic stroke with proven efficacy. Thus, the use of placebo on the background of standard therapy is ethically justified.

2.6. Trial quality statement

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 03 November 2016 No. 79;
- The 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 Human Use, Registration of Adverse Actions, Serious Adverse Reactions, Unexpected Adverse Reactions in the Use of Medicinal Products for Human Use";

The clinical trial will be conducted in accordance with the current version of the Trial Protocol. The Protocol and any amendments to the Protocol and the Patient Information Sheet with the Informed Consent Form must be approved/endorsed by the regulatory authorities, the Ethics Council and the Local Ethics Committee.

2.7. Description of the trial population

The calculation of the required sample size for this trial is scientifically and statistically sound and meets the requirements for efficacy and safety studies in the Russian Federation.

The inclusion criteria for volunteers are scientifically justified. It is planned to include in

the trial patients differing in the degree of severity of neurological deficit (Functional Status Score on the modified Rankin Scale (mRS) of 3 and more points, NIHSS score from 9 to 15 points inclusive), which will bring the results obtained in the clinical trial closer to real clinical practice and will allow to assess efficacy of the investigational therapy in the population of patients with severe neurological deficit.

A maximum of 336 patients with diagnosed hemispheric ischaemic stroke are planned to be included in the trial (obtain approval for a clinical trial involving 336 **patients**), from which **at least 304 patients** with a clinically confirmed diagnosis of hemispheric ischaemic stroke meeting the inclusion criteria and no non-inclusion criteria are planned to be **randomized**.

The selection criteria for this trial were carefully considered to ensure patient safety and the validity of the results of this trial.

2.8. References to literature sources essential to the trial

1. Hodge H. et al. Clinical Toxicology of Commercial Products. Acute Poisoning. Ed. IV, Baltimore, 1975. - 427 p.
2. Andreeva N.N., Mukhina I.V. Correction by mexidol of postreanimation changes in brain lipid metabolism. // Experimental and Clinical Pharmacology, 2005. - №3. - P.37-41.
3. Andreeva N.N., Mukhina I.V. Correction by mexidol of postreanimation changes in brain lipid metabolism. Experimental and Clinical Pharmacology., 2005(3): p. 37-39.
4. Vereshchagin N. V., Suslina Z. A., Piradov M. A. Principles of diagnosis and treatment of patients with acute disorders of cerebral circulation // Nervous Diseases. - 2002. - №. 1.
5. Voronina T.A. Domestic drug of new generation Mexidol: main effects, mechanism of action, use // Methodical recommendations, Research Institute of Pharmacology RAMS, - Moscow, 2003.
6. Gatsura VV, Pichugin VV, Sernov LN Anti-ischaemic cardioprotective effect of mexidol // Cardiology, 1996. - №11. - C.59-62.
7. Gusev E. I., Skvortsova V. I. Neuroprotective therapy of ischaemic stroke // Nervous Diseases. - 2002. - №. 1.
8. Devyatkina T.A. et al. Effect of mexidol and its structural components on the content of carbohydrates and lipid peroxidation in acute stress / T.A. Devyatkina, R.V. Lutsenko, E.M. Vazhnichaya, L.D. Smirnov // Voprosy Medovykh Chem. Smirnov // Voprosy med. chemii. 1999. - V. 45, № 3. - P. 12-18.
9. Achievements in the treatment of ischaemic stroke: yesterday, today, tomorrow /Domashenko M.A., Piradov M.A. //Neurology. Psychiatry RMJ, no. 30, 2013. P.1514-1517.
10. Euselman M. A., Alexandrova NA Cognitive disorders in patients with ischaemic stroke and their correction //Journal of Neurology and Psychiatry. SS Korsakov. - 2013. - V. 113. - №. 10. - P. 36-39.
11. Ivanova N.E. Effectiveness of the use of Mexidol in constrictive stenotic arteriopathy // Standards of treatment, 2010. - №3.
12. Instructions for the medical use of the drug Mexidol® FORTE 250. State Register of Medicines.
13. Stroke: Manual for doctors / Edited by L.V. Stakhovskaya, S.V. Kotov. - M.: "Medical Information Agency" LLC, 2013. - 400 p.: ill.
14. Kandyba D.V., Zhulyov N.M., Sokurenko G.Y., Markova O.S., Nikolaeva O.Y., Zueva O.N. Application of Mexidol® in complex conservative and angiosurgical treatment of ischaemic cerebral circulatory disorders of extracranial genesis angiosurgical treatment of ischaemic cerebral circulation disorders of extracranial genesis. // Journal Pharmateca.,2006- № 7,-Clinical studies,- P.1-5.
15. Kovalchuk V. V. Effect of mexidol on neurological deficit, social adaptation and syndromes of neglect and repulsion in patients after stroke // Zhurn nevrol i psikhiat. -

2011. - V. 112. - P. 2.
16. Kravtsova O.Yu. Rationale for the use of mexidol for phenotyping of glucuronoconjugation in animals and humans/Autoref. dissertation for the thesis of Candidate of Biological Sciences, M., 2005.
17. Kravtsova OY, Sariev AK, Zherdev VP Biotransformation of mexidol (experimental and clinical data) // Collection of abstracts of the 2nd Congress of the Russian scientific community pharmacologists. - M., 2003. - P.271.
18. Kraineva V.A. Features and mechanism of neuroprotective effect of mexidol in haemorrhagic stroke in experiment // Stroke, 2006. - № 17. - P. 3-7.
19. Kuznetsova S. M., Kuznetsov V. V., Yurchenko F. V. Mexidol in the rehabilitation of elderly patients with ischaemic stroke //Pharmateka. - 2009. - №. 15. - P. 111-114.
20. Makarova L.M. Neuroprotective effect of the drug Mexidol in total brain ischaemia (to the question of the expediency of the use of this drug in gravitational overload) // Bulletin of Experimental Biology and Medicine, 2006, Supplement No. 1.
21. Miroshnichenko I.I., Kuzmina S.Yu., Voronin A.E. Trial of pharmacokinetics and biodistribution of mexidol in experiment. // Bulletin. VNTS BAV, 1994. - №2. - P.4954.
22. Nechipurenko N.I. et al. Effectiveness of the drug Mexidol® at experimental cerebral ischaemia. / N.I. Nechipurenko, L.A. Vasilevskaya, T.V. Griboedova, N.Y. Shcherbina, Y.I. Musienko // Bulletin of Experimental Biology and Medicine, 2006. - Appendix 1. - C. 224 - 229.
23. Novikova L. B., Sharafutdinova L. R., Sharapova K. M. The use of mexidol in the acute period of ischaemic stroke //Journal of Neurology and Psychiatry. SS Korsakov. - 2013. - V. 113. - №. 9. - P. 83-85.
24. Report on implementation of the research work "Preclinical trial of mexidol safety". S.B. Seredenin, B.I. Lyubimov, A.N. Yavorsky. Moscow. Research Institute of Pharmacology of the Russian Academy of Medical Sciences, 1994.
25. Report on experimental comparative trial of toxicity and pyrogenicity of the drug "Mexifin" produced by "Brand Pharma" and the registered analogue drug St. Petersburg. A.B. Kosmachev. Research Institute of Toxicology of the Ministry of Health of the Russian Federation, 2004.
26. Rumyantseva SA, Fedin AI, Sokhova ON, Antioxidant therapy of ischaemic lesions of the brain. // Journal of Neurology and Psychiatry,- 2011, issue 2, - № 4 p. 28-31.
27. Sidorov A.M. Borisova V.A. Clinical efficacy of the drug Mexidol® in the therapy of cerebrovascular pathology: method. recommendations. M., 2005. - 12 p.
28. Soloviev N.A., Yasnetsov V.V. Experimental-clinical trial of the action of Mexidol® in some pathology. Elucidation of possible localisation and mechanism of action // Bulletin of Experimental Biology and Medicine, 2006 - Supplement No. 1. - P.230-241.
29. Stakhovskaya L. V. et al. Multicentre randomized prospective double-blind placebo-controlled trial of safety and efficacy of Cortexin in the acute and early recovery period of hemispheric ischemic stroke //Vestnik of the Russian Military Medical Academy. - 2012. - V. 1. - №. 37. - P. 238-44.
30. Stakhovskaya L. V. et al. Results of a randomized double-blind multicentre placebo-controlled parallel-group trial of the efficacy and safety of mexidol in long-term sequential therapy in patients in the acute and early recovery periods of hemispheric ischemic stroke (EPICA) //Journal of Neurology and Psychiatry. SS Korsakov. Special Issues. - 2017. - V. 117. - №. 3. - P. 55-65.
31. Teselkin Yu.O., Davydov B.V. Inhibition of serum lipoprotein peroxidation by mexidol // Bulletin of Experimental Biology and Medicine, 2006. - Appendix 1. - P.138-141.
32. Torshin I. Yu et al. Comparative chemoreactome analysis of mexidol //Pharmacokinetics and pharmacodynamics. - 2016. - №. 4.
33. Fedin A. I. et al. Antioxidant therapy for ischaemic stroke. Clinico-electrophysiological

correlations //RMZh. - 2009. - V. 17. - №. 5. - P. 332-334.
34. Chefranova Zh. Yu et al. Evaluation of the effectiveness of mexidol in combination with thrombolytic therapy in patients with ischaemic stroke //Journal of Neurology and Psychiatry. SS Korsakov. - 2012. - V. 112. - №. 4. - P. 49-52.
35. Chukanova E. I., Chukanova A. S., Mamaeva H. I. Results of the trial of the effectiveness and safety of mexidol in patients with chronic cerebral ischaemia // Journal of Neurology and Psychiatry. SS Korsakov. - 2015. - T. 115. - №. 2. - P. 71-4.
36. Shevchenko L.A., Krivosheev R.V., Evdokimov V.A. To the question of therapeutic efficacy of Mexidol in the complex treatment of patients suffering from cerebral strokes. International Journal of Neuroscience. 2006;2(6):88-92.
37. Shchulkin A. B. Effect of mexidol on the development of the phenomenon of neuronal excitotoxicity in vitro // Journal of Neurology and Psychiatry. SS Korsakov. - 2012. - V. 112. - №. 2. - P. 35-39.

3. Purpose and objectives of the trial

3.1. Trial purpose:

The aim of the present trial was to compare the efficacy and safety of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) compared with placebo during their sequential administration in patients in the acute and early recovery periods of ischaemic stroke.

3.2. Trial objectives:

1. To evaluate the efficacy of the preparations 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 the preparations 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.

4. Trial design

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

In accordance with the purpose and objectives of the trial, this clinical trial will determine the parameters of comparative 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) vs. placebo when used in patients in the acute and early recovery periods of ischaemic stroke.

The efficacy of the investigational therapy will be assessed by the following parameters:

Primary efficacy criterion:

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

Secondary efficacy criteria:

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

- Proportion of patients with mRS score 0-1 at the end of therapy;
- Proportion of patients with mRS score 0-1 at the end of parenteral therapy;
- The magnitude of change in the patient's **NIHSS** (National Institutes of Health Stroke Scale) score at the end of therapy vs. baseline (in points).
- 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 points).
- The magnitude of change in the patient's **MoCA** cognitive status score at the end of therapy vs. baseline (in points).
- The magnitude of change in the patient's **MoCA** cognitive status score at the end of parenteral therapy vs. baseline (in points).
- The magnitude of change in the patient's **Rivermead** Mobility Index score at the end of therapy vs. baseline (in points).
- 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 points).
- The magnitude of change in the patient's **HADS** score at the end of therapy vs. baseline (in points).
- The magnitude of change in the patient's **HADS** score at the end of parenteral therapy vs. baseline (in points).

Safety and tolerability will be assessed throughout the trial (from first use of the investigational product/placebo) using the following data:
- AE/SAE reports data,
- Physical examination data, vital signs (BP, HR, respiratory rate, body temperature),
- 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 SAs with at least a possible association with the use of the investigational product.

4.2. Description of the type/design of the trial

This trial is a prospective multicentre, randomized, double-blind, parallel-group comparative trial of 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) when administered sequentially in patients in the acute and early recovery periods of ischaemic stroke vs. placebo.

The trial is carried out during the inpatient follow-up of patients and as part of patients' outpatient visits to the investigational site.

After screening, patients fulfilling inclusion criteria and those without inclusion criteria were randomly allocated into two groups (1:1 patient-to-patient ratio):

Group I - use of preparations Mexidol® solution for intravenous and intramuscular injection, 50 mg/ml (RPC PHARMASOFT LLC, Russia) 10 ml (500 mg) BID (1000 mg per day) intravenous drip in 100-200 ml 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.

Group II - use of 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.

The use of investigational products is carried out against the background of standard therapy of ischaemic stroke prescribed by the patient's attending physician.

The trial will include the following periods:

- Screening - preliminary examination of patients. The duration of the period should not be

more than 24 hours. Screening, randomization and initiation of therapy can be done on the same day.

- **Randomization and initiation of therapy** - randomization, initiation of trial therapy.
- **Therapy period** (70 days in total), use of investigational product/placebo (10 days - parenteral administration period, 60 days - oral administration), patient assessment, registration of AEs.

The graphical scheme of the trial is shown in Figure 4.1.

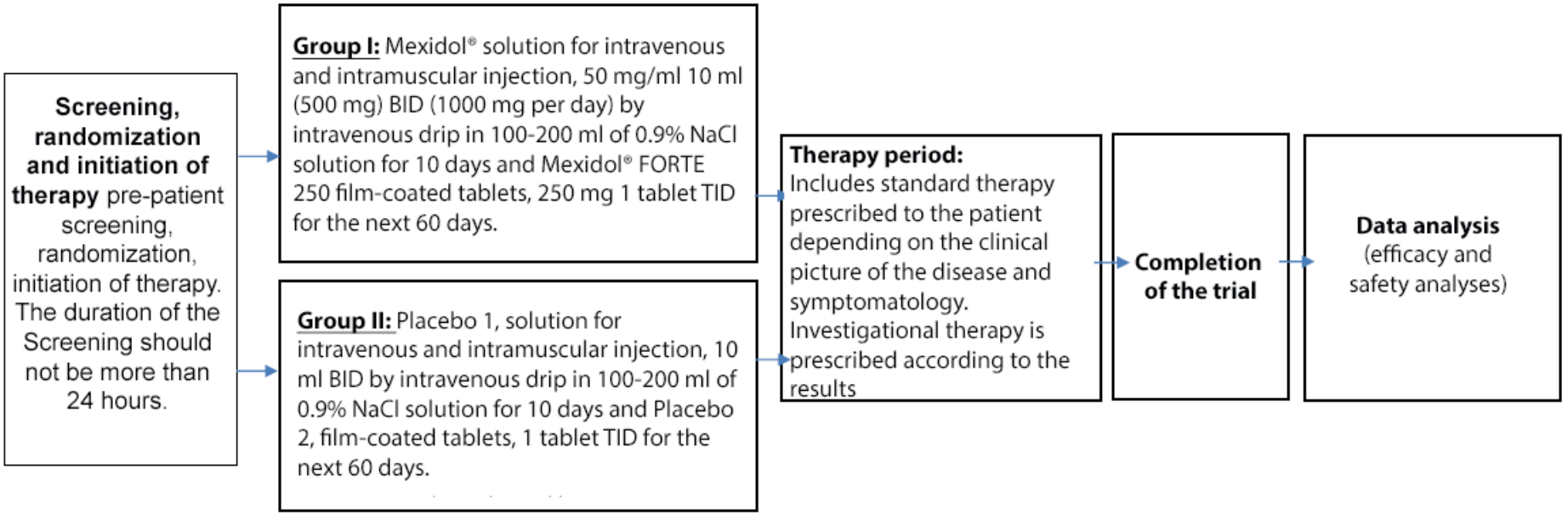

Figure 4.1. Graphical design of the trial

4.3. Measures to minimise/eliminate subjectivity in the conduct of the trial

4.3.1. Blinding

The present trial is a double-blind trial. The double-blind method avoids bias, subjectivity in the evaluation of treatment results. The patient participating in this trial, the Investigator, and the clinical diagnostic laboratory staff will not be aware of which of the medicinal products the patient is taking. In this regard, blinded primary and secondary investigational product/placebo packaging is provided.

4.3.2. Randomization

After the patient (his/her legal representative) signs the Informed Consent Form at the screening stage, he/she is assigned a screening number of the form XXXYYYY, where XX is the number of the investigational site (e.g. 01, 02, 03), YYY is the patient's serial number (starting from 001), according to the order of inclusion (3 digits). If, after all the procedures planned as part of the screening, the investigator decides that the patient can take part in the trial, the patient is randomized.

randomization (an allocation method according to probability theory) is necessary to minimise subjectivity in assigning patients to therapy groups.

The randomization code will be presented in a three-digit format of the form RRR and will be assigned to each screened patient who meets the inclusion/non-inclusion criteria.

Allocation of patients to therapy groups will be done in a 1:1 ratio.

The randomization procedure, assigning a randomization number to the patient will be done after all screening procedures have been carried out before prescribing the IP.

The randomization code of each patient must be compulsorily recorded in the patient's source documentation and CRF.

If a patient early terminates the trial (is excluded from the trial for any reason), his/her randomization code will not be reused.

Randomization will be carried out centrally. For the implementation of centralized randomiztion (electronic randomization system) it is planned to use an automated communication system over the Internet - Interactive Web Response System (IWRS). Once the Investigator enters the patient data, the number will be generated automatically by the system.

4.4. Expected duration of patient participation in the trial

The total duration of patient participation in the trial will be no more than 74 days, including the screening period.

The trial will include the following periods and visits:

- **Screening** (Visit 0) - **pre-screening** of patients.

The duration of the period should not be more than 24 hours from the time of the informed consent procedure to randomization. Screening, randomization and initiation of therapy can be done on the same day.

- **Randomization and initiation of therapy** (Visit 1) - randomization of patients, initiation of trial therapy.
- **Therapy period** (Visits 2-4, Phone calls), use of investigational product/placebo (Duration of therapy - 70 days: 10 days - period of parenteral administration, 60 days - oral administration), assessment of the patient's condition, registration of AE. The total patient period, including scheduled procedures, is 71 (+2) days.

4.5. Suspension, termination of the trial, termination of participation in the trial by individual subjects

The sponsor has the right to temporarily suspend the trial at any time for reasons including, but not limited to, safety, ethical, or administrative issues.

The sponsor has the right to terminate the trial at any time if the goals and objectives of the trial are not being met.

In doing so, the Sponsor must notify the Investigator or the management of the investigational site of the temporary suspension or early termination of the trial in writing.

If the trial is suspended or terminated for safety reasons, the Sponsor will immediately inform the Investigator, as well as regulatory authorities and ethics committees.

The Investigator has the right to terminate participation in the trial (withdraw from the trial) of individual subjects when exclusion criteria are found.

4.6. Investigational product/comparator product record-keeping procedures

The Investigator is responsible for following certain rules for handling investigational products:

- Maintains records of receipt of investigational product/comparator product.
- Maintains records of investigational product/comparator product consumption at the investigational site using the investigational site's drug record form. The investigational product/comparator product should only be given to those members of the investigational site team whose responsibility it is to keep track of the medicines. The allocation of responsibilities is recorded on a special form before the trial begins.
- Ensures that the investigational product/comparator product is administered in strict accordance with the Protocol, i.e. only to those patients who are included in the trial and randomized.
- Ensures that preparations are stored in accordance with the Protocol or other supplemental instruction that includes information on storage conditions of the preparation. The Investigator should regularly record the temperature readings in the room where the preparations are stored, except on weekends and public holidays, and record them in a special logbook of the storage temperature of the preparations.
- Records the IP returned to the Sponsor by completing designated documentation. Unused IP, as well as packaging from used IP, will be returned to Sponsor for destruction.
- All unused medications as well as packs of used medications should be collected for compliance assessment. Compliance will be assessed by the Investigator. The reasons why compliance was not observed should be ascertained by the Investigator wherever possible.

4.7. Storage and disclosure of randomization /screening numbers

The double-blinding condition is observed throughout the trial. The randomization code for a particular patient should be prematurely disclosed in the following cases:

- occurrence of an insured event, if the qualification of the event requires information about the type of prescribed therapy;
- sponsor's decision;
- written request from the local ethics committee supervising the trial;
- decision of regulatory authorities (Ministry of Health, Ethics Council under the Ministry of Health of the Russian Federation, Federal Service for Surveillance in Healthcare, other regulatory body authorized in accordance with the established procedure to control the conduct of clinical studies).

If it is necessary to disclose the code, the investigator performs the unblinding procedure according to the instructions received prior to the trial.

A complete list of all screening/randomization numbers used in the trial and their corresponding therapy is a confidential document, kept by the authorized representative and used to monitor the conduct of the trial.

The Investigator should ensure that the anonymity of the patients is respected. In the CRF, patients are identified only by assigned numbers.

The Investigator must maintain documentation containing patient number information, stored in accordance with the rules applicable to confidential documents.

The Investigator must also maintain in strict confidence documents not intended to be handed over to the Sponsor, particularly signed Patient Information Sheets with the Informed Consent Forms.

4.8. A list of all data recorded directly in the CRF and considered as source data

This trial does not contain data to be entered directly into the CRF without initially recording such information in source documentation.

All information that is recorded in the CRF is previously entered into the patient's source medical documentation - the patient's medical record, blood and urine laboratory test forms, ECG forms, etc. An electronic data collection system can also be used to collect source data (e.g. results of specialized scales).

5. Selection and exclusion of trial participants

5.1. Criteria for inclusion of subjects

1. Male and female patients aged 40 to 75 years.
2. Availability of the Informed Consent Form signed by the patient (or his/her legal representative if the patient is not physically able to sign) for participation in the trial.
3. First-time diagnosed hemispheric ischaemic stroke (ICD-10 codes: I63 "cerebral infarction." I63.0 to I63.9) not more than 48 hours old.
4. Presence of neuroimaging (according to computerised tomography (CT) or magnetic resonance imaging (MRI)) signs of ischaemic stroke and/or absence of signs of haemorrhagic stroke, ischaemic stroke with haemorrhagic impregnation, as well as other conditions not related to ischaemic stroke and having a similar clinical picture.
5. Assessment of the patient's functional status using the Modified Rankin Scale (mRS) 3 or more points).
6. Patient's NIHSS score of 9 to 15 points inclusive.
7. Negative pregnancy test in female patients of preserved childbearing potential.
8. Consent to the use of adequate contraceptive methods (contraceptive methods with a reliability of more than 90%: non-hormonal intrauterine device; condom with intravaginal spermicide; neck caps with spermicide; diaphragms with spermicide), or complete abstinence from sexual activity for the period of the trial.
9. Patients who are able to understand the requirements of the Trial Protocol and who have consented to all restrictions in the Trial Protocol.

5.2. Criteria for non-inclusion of subjects

1. Presence of clinically significant allergic reactions in the history.
2. Hypersensitivity and/or intolerance to any component of the investigational product or placebo.
3. Presence of lactose intolerance/congenital galactose intolerance; Lapp lactase deficiency or glucose-galactose malabsorption syndrome.
4. BMI value > 35.
5. Recurrent stroke.
6. Haemorrhagic stroke (confirmed by neuroimaging (CT or MRI).
7. Haemorrhagic infarction (ischaemic stroke with haemorrhagic impregnation).
8. Parkinson's disease or parkinsonism.
9. Multiple sclerosis.
10. Uncontrolled epilepsy.

11. Demyelinating diseases of the nervous system.
12. Hereditary degenerative diseases of the CNS.
13. Presence of infectious diseases of the CNS in the anamnesis.
14. Traumatic brain injuries with pronounced neurological symptoms and cognitive impairment.
15. A history of neurodevelopmental anomalies or other neurological disorders seriously affecting motor or cognitive function in the reasonable opinion of the investigator.
16. Patients who have undergone thrombolytic therapy or thrombectomy.
17. Need for surgical intervention.
18. Evidence of a first-diagnosed disease that, in the reasonable opinion of the investigating physician, would preclude the patient's participation in the trial.
19. Evidence of a significant uncontrolled comorbid condition that, in the reasonable opinion of the investigator, would preclude the patient's participation in the trial, including:
    - Respiratory system disorders;
    - Cardiovascular disorders including SBP ≥ 200 mmHg, DBP ≥ 100 mmHg at trial entry;
    - Severe renal impairment (eGFR<30ml/min/1.73 m2);
    - Severe liver function impairment (ALT, AST activity> 2 times ULN);
    - Endocrine disorders;
    - Gastrointestinal disorders.
    - Deep vein thrombosis or pulmonary embolism, identification of a flotating thrombus.
    - The onset of a seizure syndrome.
    - Occurrence of unrelieved hyperthermia.
    - Occurrence of unrelieved hyperglycaemia.
20. Endogenous psychiatric disorders according to anamnesis.
21. Anamnestic information about dementia of the Alzheimer type.
22. Systemic autoimmune diseases or vascular collagenosis requiring previous or current treatment with systemic corticosteroid drugs, cytostatics; malignant neoplasms within the last 5 years.
23. A history of alcohol or drug dependence.
24. Pregnancy or lactation period.
25. The need to use medications that are prohibited in this trial.
26. Administration of unauthorized or off-protocol medications within 2 weeks prior to trial inclusion (except for a single administration of ethylmethylhydroxypyridine succinate at the emergency medical services stage).
27. Positive result of at least one of the following tests: blood tests for HIV, syphilis, hepatitis B and C (including history).
28. Presence of any significant history in the opinion of the investigator, condition that prevents the patient from being included in the trial.
29. Participation in any clinical trial less than 3 months prior to the start of the trial.
30. Positive result of a rapid test for IgM antibodies to SARS-CoV-2 virus.

5.3. Criteria for the exclusion of subjects

1. Withdrawal of informed consent by the patient and/or the patient's legal representative.
2. Need for additional therapy not permitted under this protocol.
3. Serious adverse events or adverse events that do not fulfil the criteria for seriousness and where, in the opinion of the investigator, further participation in the trial would be dangerous to the health or well-being of the patient.
4. Investigator or sponsor's decision to exclude a patient due to a significant protocol deviation/protocol violation.
5. Any patient condition that, in the reasonable judgement of the investigator, requires the

patient to be withdrawn from the trial.

6. Positive result of at least one of the following tests: blood tests for HIV, syphilis, hepatitis B and C, if the test results are obtained after the patient's randomization procedure.
7. Allergic reaction to trial medications requiring their cancellation.
8. Loss of contact with the patient followed by failure to attend the visit.
9. Recurrent stroke.
10. Positive result of the rapid test for IgM antibodies to SARS-CoV-2 virus and/or positive result of laboratory examination for the presence of SARS- CoV-2 RNA using nucleic acid amplification methods, regardless of clinical manifestations.
11. Diseases and/or conditions of the subject detected for the first time during routine medical examinations and procedures that prevent the subject from continuing his/her participation in the trial, and/or indicate that the patient was wrongly included in the trial (failure to meet the selection criteria for the trial at the time of inclusion).

5.4. Termination of subjects' participation in the trial

5.4.1. Procedures for excluding subjects from the trial

Criteria for non-inclusion of patients in the trial (assessed at the screening stage) are presented in section 5.2.

The criteria for exclusion of patients from the trial (assessed throughout the trial in accordance with the description of the trial procedures and the Schedule of Trial Procedures (Appendix 1) are presented in Section 5.3.

If a patient decided to withdraw from the trial or did not complete the trial for any reason, his/her randomization code should not be reused.

Patients who were excluded from the trial during screening prior to the administration of investigational therapy should not be randomized into this trial.

Excluded subjects will be monitored for the development of AE/SAE until their resolution or stabilisation of AE/SAE-induced manifestations.

5.4.2. Data collection by type and timing for subjects who discontinued participation in the trial

The investigator transmits data on patients excluded from the trial to the Sponsor and the Clinical Research Associate within 24 hours in the form of a report that includes information about the patient's status at the end of the trial.

Patient status at the end of the trial:

1. Finished the trial.
2. Did not finish/discontinued because of:

- trial error;
- adverse events;
- serious adverse events;
- pregnancy;
- protocol violations;
- patient's desire to withdraw from the trial;
- due to a patient's failure to appear;
- other reasons (specify).

5.4.3. Substitution of trial participants

This trial does not provide for the replacement of withdrawn trial participants.

5.4.4. Follow-up of excluded subjects

If no dose of the investigational product/comparator product was received by the patient and the patient withdrew from the trial for any reason, he/she is not followed up further and

his/her data are not included in the statistical analysis.

If the investigational product/comparator product was received by the patient and the patient is withdrawn from the trial for any reason unrelated to the development of an AE, including failure to attend the next visit for an unknown reason, the investigator should contact the patient and schedule a date for the patient's end-of-trial visit.

If SAEs occur, the patient should be monitored by a physician according to the AE surveillance guidelines.

Follow-up of excluded patients due to the development of AE/SAE will be carried out until resolution or stabilization of AE/SAE-induced manifestations.

6. Trial design

6.1. Schedule of trial visits and procedures

As part of this trial, the patient will participate in the following clinical trial periods:

- **Screening (Visit 0)** - pre-screening of patients. The duration of the period should not be more than 24 hours from the time of the informed consent procedure to randomization. Screening, randomization and initiation of therapy can be done on the same day.
- **Randomization and initiation of therapy** (Visit 1) - randomization of patients, initiation of trial therapy.
- **Therapy period** (70 days in total), use of investigational product/placebo (10 days - parenteral administration period, 60 days - oral administration), patient assessment, registration of AEs.

Patients will be assessed at the following visits.

Screening:

Visit 0 (Day -1 / Day 1[1]) - screening, preliminary examination of patients, initiation of therapy.

Visit 0 procedures should be carried out within a maximum of 24 hours and may be carried out on the same day as Visit 1 procedures:

- Signing an informed consent form;
- Collection of demographic and anthropometric data, anamnesis;
- Physical examination
- Neurological examination;
- Assessment of vital signs (BP, HR, RR, body temperature);
- Clinical blood test;
- Blood chemistry;
- Blood tests for HIV, syphilis, hepatitis B and C[2]
- SARS-CoV-2 IgM antibody rapid test
- Urinalysis;
- Pregnancy test for women with preserved reproductive potential;
- ECG[3];
- Completion of specialized scales (mRS, NIHSS);
- CT/MRI[3];
- Assessment of prior and concomitant therapy;
- Assessment of inclusion/non-inclusion criteria

[1] Visit 0 - patient screening - is conducted on Day 1 if Visit 0 and Visit 1 are conducted on the same day.

[2] Results obtained within 48 hours prior to Screening may be used.

[3] If data are available for a patient from instrumental examinations performed within 48 hours prior to inclusion in the trial, they can be used to assess the patient's condition and eligibility for inclusion/non-inclusion. The use of such data shall be permitted only if the data are available in full and for all parameters required by the Protocol.

Randomization and initiation of therapy

Visit 1 (Day 1)

- Randomization
- Completion of specialised scales and calculation of indices (HADS, MoCA, Rivermead mobility index);
- Prescribing and initiation of investigational therapy;
- AE registration

Therapy period:

Includes standard therapy prescribed to the patient depending on the clinical picture of the disease and symptomatology.

The investigational therapy is assigned to the patient according to the results of the randomization procedure.

Visit 2 (day 11/12[1] from the start of therapy, Visit procedures are performed at the end of parenteral therapy):

Physical examination, neurological examination, assessment of vital signs (BP, HR, RR, body temperature), assessment of concomitant therapy, registration of AE and assessment of exclusion criteria, clinical and biochemical blood tests, urinalysis, ECG, completion of specialised scales and calculation of indices (mRS, NIHSS, HADS, MoCA, Rivermead mobility index), dispensing of oral medication.

Telephone call 1 (Day 24±2 from initiation of therapy; Day 14±2 from initiation of oral therapy): assessment of concomitant therapy, recording of AE and assessment of exclusion criteria, assessment of compliance.

Visit 3 (Day 40 (+2) from initiation of therapy; Day 30 (+2) from initiation of oral therapy): physical examination, assessment of vital signs (BP, HR, HR, HR, body temperature), assessment of concomitant therapy, recording of AE and assessment of exclusion criteria, dispensing/administration of oral medication, assessment of compliance.

Telephone call 2 (Day 55±2 from initiation of therapy; Day 45±2 from initiation of oral therapy): assessment of concomitant therapy, recording of AE and assessment of exclusion criteria, and assessment of compliance.

Visit 4 (day 71(+2) from the start of therapy; end of therapy): physical examination, neurological examination, assessment of vital signs (BP, HR, RR, body temperature), assessment of concomitant therapy, registration of AE and assessment of exclusion criteria, clinical and biochemical blood tests, general urinalysis, pregnancy test for women with preserved reproductive potential, ECG, completion of specialised scales and calculation of indices (mRS, NIHSS, HADS, MoCA, Rivermead mobility index), return of the IP and assessment of compliance.

Additional in-person/out-person (phone calls) visits may be conducted if necessary, in the reasonable judgement of the investigator, particularly to monitor the progression of SAEs. The scope of activities and procedures performed at additional visits will be determined by the investigator on an individual basis, depending on the indications.

In case of early withdrawal of a patient from the trial, a Visit to End Patient Participation in the Trial is performed, including activities identical to those of Visit 4.

The schedule of the trial procedures is presented in *Appendix 1.*

[1] If the first administration of the investigational product (start of parenteral therapy) falls on the second half of the day (the first day of therapy - one administration of the trial dru), Visit 2 is performed on day 12 in the morning.

6.2. Description of visits

Period of screening, randomization and initiation of therapy

The duration of the screening period is no more than 1 day (24 hours). Visit 0 procedures can be performed on the same day as Visit 1 procedures.

Screening (Visit 0)

The patient being treated in the inpatient department of the neurology department of the investigational site is provided with information about the investigational product and the specifics of the trial in an accessible form. The patient is assured that qualified medical care will be provided if necessary, both during and after the trial, and that information about him/her obtained during the trial will be confidential. The patient must sign the Informed Consent Form in duplicate with his/her own hand (or with the participation of a legal representative if the patient is not physically able to sign). Sufficient time should be allowed to familiarise with the text of the Patient Information Sheet with the Informed Consent Form. One copy of the Informed Consent Form is given to the patient. Together with the Patient Information Sheet with the Informed Consent Form, the patient is given a life and health insurance policy for the patient taking part in a clinical trial of a medicinal product. The procedure for signing informed consent is described in more detail in Section 6.3.1 of this Protocol.

- After signing the informed consent, all patients undergo anthropometric measurements (height, body weight, BMI - the ratio of body weight in kg to height in m^2), followed by examination, including physical examination, neurological examination, measurement of blood pressure (BP), heart rate (HR), respiratory rate (RR), body temperature, electrocardiography (ECG), clinical and biochemical blood tests, urinalysis, blood tests to exclude hepatitis B and C, HIV infection, syphilis (results of serological tests obtained within 48 hours prior to screening can be used), rapid test for IgM antibodies to SARS-CoV-2 virus.

All patients with preserved reproductive potential should have a negative pregnancy test result. It is planned to use CT/MRI data performed within 48 hours prior to inclusion of the patient in the trial to confirm the underlying diagnosis. The patient is assessed using questionnaires (mRS, NIHSS). The investigator collects information about the patient's medical history, previous and current therapy, and assesses the patient's eligibility. If data are available for a patient from instrumental examinations performed within 48 hours prior to inclusion in the trial, they can be used to assess the patient's condition and eligibility for inclusion/non-inclusion. The use of such data shall be permitted only if the data are available in full and for all parameters required by the Protocol. The results of the examination are recorded in the patients' CRF. Based on the results of the examinations, the investigator makes a conclusion, based on which the patient is allowed or not allowed to participate further in the trial (Visit 1).

Thus, the following procedures are provided at this stage:

- Signing an informed consent form;
- Collection of demographic and anthropometric data, anamnesis;
- Physical examination
- Neurological examination;
- Assessment of vital signs (BP, HR, RR, body temperature);
- Clinical blood test;
- Blood chemistry;
- Blood tests for HIV, Syphilis, Hepatitis B and C (results obtained within 48 hours prior to Screening can be used);
- Urinalysis;
- Pregnancy test for women with preserved reproductive potential;

- ECG[1];
- Completion of specialized scales (mRS, NIHSS);
- CT/MRI[2];
- Assessment of prior and concomitant therapy;
- Assessment of inclusion/non-inclusion criteria

Randomization and initiation of therapy

Visit 1

Randomization is performed for patients who meet inclusion criteria and do not have non-inclusion criteria. In the subpopulation of patients involved in the evaluation of the pharmacodynamic effects of the investigational therapy, blood samples are collected for the trial of pharmacodynamic effects. According to the randomization number, the patient is assigned to the investigational therapy. The prescribed therapy is started.

Thus, if the patient fulfils the eligibility criteria, the following procedures are carried out:

- Randomization
- Completion of specialised scales and calculation of indices (HADS, MoCA, Rivermead mobility index);
- Administration and initiation of the investigational therapy
- AE registration

Therapy period

Visit 2 (day 11/12[3] from the start of therapy, Visit procedures are performed at the end of parenteral therapy)

The visit is conducted in the inpatient setting of the investigational site and includes the following procedures:

- physical examination,
- neurological examination,
- assessment of vital signs (BP, HR, respiratory rate, body temperature),
- evaluation of concomitant therapy,
- AEs registration;
- evaluation of exclusion criteria;
- clinical blood test,
- blood chemistry;
- urinalysis;
- ECG
- completion of specialised scales and calculation of indices (mRS, NIHSS, HADS, MoCA, Rivermead mobility index),
- dispensing of oral medication

The investigator decides on the patient's discharge from the hospital, instructs the patient on the rules of the trial, administration of the investigational therapy and planned Visits/procedures.

Telephone visit 1 (Day 24±2 from initiation of therapy; Day 14±2 from initiation of oral therapy).

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[1] If data are available for a patient from instrumental examinations performed within 48 hours prior to inclusion in the trial, they can be used to assess the patient's condition and eligibility for inclusion/non-inclusion. The use of such data shall be permitted only if the data are available in full and for all parameters required by the Protocol.

[2] The plan is to use data from neuroimaging examinations performed within 48 hours prior to patient inclusion in the trial to assess patient status and eligibility for inclusion/non-inclusion. A repeat CT/MRI scan is not required if these findings are present.

[3] If the first administration of the investigational product (start of parenteral therapy) falls on the second half of the day (first day of therapy - one administration), Visit 2 is performed on day 12 in the morning.

The investigator should contact the patient by telephone to assess concomitant therapy, to record AE and assess exclusion criteria, and to assess compliance.

Visit 3 (Day 40 (+2) from initiation of therapy; Day 30 (+2) from initiation of oral therapy):

The visit is conducted in the context of the patient's outpatient visit to the investigational site and includes the following procedures:

- physical examination,
- assessment of vital signs (BP, HR, respiratory rate, body temperature),
- evaluation of concomitant therapy,
- AEs registration;
- evaluation of exclusion criteria;
- dispensing/accounting for oral medication,
- compliance assessment

Telephone visit 2 (Day 55±2 from initiation of therapy; Day 45±2 from initiation of oral therapy):

The investigator should contact the patient by telephone to assess concomitant therapy, to record AE and assess exclusion criteria, and to assess compliance.

Visit 4 (day 71(+2) from start of therapy; end of therapy)

The visit is conducted in the context of the patient's outpatient visit to the investigational site and includes the following procedures:

- physical examination,
- neurological examination,
- assessment of vital signs (BP, HR, respiratory rate, body temperature),
- evaluation of concomitant therapy,
- AEs registration;
- evaluation of exclusion criteria;
- clinical blood test,
- blood chemistry;
- urinalysis;
- pregnancy test for women with preserved reproductive potential,
- ECG
- completion of specialised scales and calculation of indices (mRS, NIHSS, HADS, MoCA, Rivermead mobility index),
- IP take-back and compliance assessment

Additional in-person/out-person (phone calls) visits may be conducted if necessary in the reasonable judgement of the investigator, particularly to monitor the progression of SAEs. The scope of activities and procedures performed at additional visits will be determined by the investigator on an individual basis, depending on the indications.

In case of early withdrawal of a patient from the trial, a Visit to End Patient Participation in the Trial is performed, including activities identical to those of Visit 4.

6.3. Description of the trial procedures

6.3.1. Obtaining written Informed Consent

Before any procedures provided at Screening will be performed, the patient (or his/her legal representative if the patient is not physically able to sign) must sign and date, in duplicate, the Patient Information Sheet with the Informed Consent Form for participation in the trial.

If the subject or his/her legal representative is unable to read, a disinterested witness may be present throughout the explanatory interview. After the written Informed Consent Form and other written materials provided to the subject have been read and explained to the subject or the subject's legal representative and the subject or the subject's legal representative has given

verbal consent for the subject's participation in the trial and, if able, has signed and dated the written Informed Consent Form, the witness must sign and date it. By signing the written Informed Consent Form, the witness certifies that the information contained in the form and all other written materials has been accurately explained and understood by the subject or his or her legal representative and that consent to participate in the trial has been given voluntarily by the subject or his or her legal representative.

The patient must be informed in writing:

1. On the medicinal product for human use and the essence of a clinical trial of this medicinal product;
2. On the safety of a medicinal product for human use and the degree of risk to the patient;
3. On the conditions for patient participation in a clinical trial of a medicinal product for human use;
4. On the purpose, objectives and duration of a clinical trial of a medicinal product for human use;
5. On the patient's actions in case of unexpected effects of a medicinal product for human use on his/her health condition;
6. On the conditions of compulsory insurance of the patient's life and health;
7. On guarantees of confidentiality of patient participation in a clinical trial of a medicinal product for human use.

The Investigator also signs and dates the Patient Information Sheet with the Informed Consent Form, thereby certifying that the interview with the patient was conducted and consent obtained, and that the patient had the opportunity to ask questions and received full answers.

The patient will receive one copy of the Patient Information Sheet with the Informed Consent Form and the second copy will be kept by the Investigator at the investigational site together with other trial documentation.

6.3.2. Medical history

During the screening (Visit 0), a detailed medical history will be collected from the patient: diseases suffered in the last year, comorbidities, surgical interventions, previous (in the last 4 weeks) and concomitant therapy, history of alcohol, medication and/or drug dependence, information about harmful habits (smoking and alcohol intake).

6.3.3. Demographic data and anthropometrics

Demographic data (date of birth, gender, race) will be obtained at the time of screening (Visit 0). Obtaining anthropometric data (body weight (to tenths of a kilogram), height, BMI) is provided at screening (Visit 0).

6.3.4. Physical examination

The physical examination will be performed by the Investigator at Visits 0-4 in accordance with the schedule of trial procedures.

Organs and systems whose condition is assessed during the examination:

- Skin and visible mucous membranes.
- Endocrine system.
- Lymphatic System.
- ENT organs.
- Respiratory system.
- Cardiovascular system.
- Gastrointestinal tract.
- Nervous system.
- Musculoskeletal system.

- Reproductive system.
- Urinary system.

6.3.5. Neurological examination

A neurological examination is performed at screening (Visit 0) and Visits 2 and 4 according to the trial procedure schedule to further assess neurological changes in the patient's condition.

6.3.6. Vital signs

To ensure patient safety, vital signs will be assessed by the Investigator at Visits 0-4 according to the trial procedures schedule.

Vital signs (BP, HR, RR) are measured after a 5-minute rest, if possible in a sitting position. BP (systolic and diastolic) will be determined on the right arm using a validated device. HR is assessed over a 1-minute period.

Axillary temperature will be measured to determine body temperature.

6.3.7. Electrocardiogram

ECG examination in this trial will be performed in 12 leads (I, II, III, aVR, aVL, aVF, V1 - V6) at Visits 0, 2, 4.

The ECG will be recorded for a time sufficient for evaluation (up to 10 seconds) after the patient has been at rest for a minimum of 10 minutes.

The HR will be measured and an opinion will be given as to whether the patient's ECG is normal, clinically significant or clinically insignificant.

At Visit 0, if data are available for a patient from an ECG examination performed within 48 hours prior to the patient's inclusion in the trial, these can be used to assess the patient's status and eligibility for inclusion/non-inclusion. A repeat ECG on Visit 0 is not required in this case.

6.3.8. Laboratory tests

The list of analysed indicators of laboratory tests is presented in Table 6.1.

Table 6.1. List of laboratory tests.

Laboratory tests to assess safety			**Serological tests/other laboratory tests**
Complete blood count	**Biochemical blood test**	**Clinical urinalysis**	
Erythrocyte sedimentation rate (ESR). Haematocrit (Hct). Haemoglobin (Hb). Red blood cell count. Platelet count. White blood cell count. Leucocytic formula: neutrophils: segmented neutrophils, bacilli (in relative and absolute units); eosinophils (in relative and absolute units); basophils (in relative and absolute units); monocytes (in relative and absolute	ALT AST Glucose Creatinine Urea Total protein Triglycerides Total cholesterol	Urine protein. Urine glucose. Urine erythrocytes. Urine leukocytes. Urine pH Bacteria in the urine sediment. Squamous epithelium in the urine sediment.	Syphilis[1] Hepatitis B[1] Hepatitis C[1] HIV_1 Pregnancy test for women with preserved reproductive potential SARS-CoV-2 IgM antibody rapid test

[1] Results obtained within 48 hours prior to Screening may be used

units). eosinophils (in relative and absolute units); basophils (in relative and absolute units); monocytes (in relative and absolute units); lymphocytes (in relative and absolute units).			

Approximately 40 ml of blood will be drawn from the patient in this trial for laboratory tests to assess safety. The blood volume can be increased in case of need for additional laboratory studies to assess the dynamics of changes in the analysed indicators.

In the course of the trial, blood is taken from the patient for clinical and biochemical tests at the screening (Visit 0) and at Visits 2, 4; for serological tests for infections only at the screening (Visit 0) - according to the schedule of conducting test procedures.

During the trial, the patient's clinical urinalysis is performed on Visits 0, 2, 4.

The above standard laboratory tests for blood and urine will be performed in the local laboratory of the investigational site.

A rapid test for IgM antibodies to SARS-CoV-2 (blood collection for a qualitative test based on the immunochromatographic assay method) is performed at screening to avoid inclusion of patients with coronavirus infection (COVID- 19).

6.3.9. Compliance assessment

Compliance is assessed on the basis of records of dispensed/returned medication. The procedure is performed at visits 3 and 4 of the patient to the investigational site. Additionally, the assessment is conducted during telephone visits (calls) by interviewing the patient.

An acceptable compliance rate for this trial, based on a record of dispensed/returned medication, is considered to be 80-120%. If a
patient is unresponsive to therapy, the investigator must assess the appropriateness of the patient's continued participation in the trial and decide whether to continue participation.

6.3.10. CT/MRI

The trial plans to use data from neuroimaging examinations performed within 48 hours prior to patient inclusion in the trial to assess patient status and eligibility for inclusion/non-inclusion criteria at screening (Visit 0). A repeat CT/MRI scan is not required if these findings are present.

6.3.11. Patient assessment using specialised scales

Conducted according to the trial procedure schedule to assess the patient's condition for subsequent analyses of therapy efficacy using the following scales:

- mRS (Modified Rankin Scale) - score on Visits 0, 2, 4;
- NIHSS (The National Institutes of Health Stroke Scale) - score on Visits 0, 2, 4;
- Montreal Cognitive Assessment Scale MoCA - score on Visits 1, 2, 4;
- Hospital Anxiety and Depression Scale (HADS) - scores on Visits 1, 2, 4;
- Rivermead Mobility Index - score on Visits 1, 2, 4.

6.3.12. Recording of adverse events

Adverse Events (AEs) will be recorded by the Investigator during the course of the trial according to the procedures presented in Section 8.2.

6.4. Restrictions of the trial

The Investigator will explain to the patient that the patient must abide by certain restrictions while participating in the trial. Such restrictions are also detailed in the Patient Information Sheet with Informed Consent Form.

Therapeutic regimen

In the present trial, the patient has the responsibility to comply with all recommendations of the investigating physician for primary and concomitant therapy and lifestyle.

Contraception

Prior to participation in the trial, all patients should be informed about the importance of preventing unwanted pregnancy during participation in the trial and the potential risk factors for unwanted pregnancy. The acceptable contraceptive methods considered in this trial are:

- non-hormonal IUD;
- condom with intravaginal spermicide;
- cervical caps with spermicide;
- diaphragm with spermicide.

A prerequisite for participation in this clinical trial is consent to use the contraceptive methods described above for the duration of the trial or complete abstinence from sexual activity for the duration of the trial.

6.5. Concomitant therapy

Patients will receive standard (baseline) therapy according to the Clinical Guidelines "Ischaemic Stroke and Transient Ischaemic Attack in Adults", 2015.

Baseline therapy includes correction of disorders of systemic and cerebral hemodynamics, rheological and coagulation properties of blood, prevention of complications of stroke. However, standard therapy drugs should not be classified as unauthorized in the present trial.

If concomitant pathology is not a criterion for exclusion of the patient from the trial, the treatment of concomitant pathology within the framework of this protocol is carried out according to the accepted standard scheme. Concomitant therapy drugs should not be classified as unapproved protocols.

Concomitant therapy (other than protocol prohibited drugs) for acute or chronic conditions may be continued as indicated. Information on concomitant medications (trade or international nonproprietary name, dose or dose modifications, indication, start date, discontinuation date) should be recorded in the eCRF.

6.6. Drugs prohibited in the trial

Unapproved or off-protocol drugs include drugs and/or dietary supplements from the following groups:

A) preparations containing succinic acid and its salts (including reamberin, remaxol, cytoflavin);

B) preparations containing vitamin B6 and/or its derivatives.

B) preparations belonging to the groups of antioxidants and antihypoxants (including preparations - 3-hydroxypyridine derivatives: methyl ethylpyridinol, ethylmethylhydroxypyridine succinate (except as used in the investigational therapy).

C) drugs with nootropic type of action:

- citicoline preparations.
- choline alphoscerate preparations.
- nootropic drugs of the pyrrolidine series, including piracetam.
- dimethylaminoethanol derivatives: deanol aceglumate, meclofenoxate.
- pyridoxine derivatives: pyritinol, pyridoxine+threonine.
- GABA derivatives and analogues: γ-aminobutyric acid, nicotinoyl-GABA, γ- amino-R-phenylbutyric acid hydrochloride, gopantenic acid, calcium γ-hydroxybutyrate.
- ginkgo biloba preparations and its derivatives.

- neuropeptides and their analogues with nootropic action.
- 2-mercanthobenzimidazole derivatives: ethylthiobenzimidazole.
- polypeptides and organic composites: cattle cerebral cortex polypeptides, cerebrolysin.
- correctors of cerebral circulation disorders - vinpocetine, xanthinol nicotinate, vincamine, naphthidrofuryl, cinnarizine; combined preparation hexobendine+etamivan+etofylline.
- general tonic agents and adaptogens of plant origin.
- preparations containing acetylaminoanthartaric acid.

7. psychostimulants - salbutiamine. EFFICACY EVALUATION

7.1. Efficacy parameters under trial

According to the purpose and objectives of the present trial, the efficacy of the investigational product vs. comparator product will be assessed by the following parameters:

Primary efficacy criterion:

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

Secondary efficacy criteria:

— The magnitude of change in the patient's **mRS** (Modified Rankin Scale) score at the end of parenteral therapy vs. baseline (in points).
— Proportion of disabled patients (**mRS** score 3 or more) at the end of therapy;
— Proportion of disabled patients (**mRS** score 3 or more) at the end of parenteral therapy;
— Proportion of patients with mRS score 0-1 at the end of therapy;
— Proportion of patients with mRS score 0-1 at the end of parenteral therapy;
— The magnitude of change in the patient's **NIHSS** (National Institutes of Health Stroke Scale) score at the end of therapy vs. baseline (in points).
— 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 points).
— The magnitude of change in the patient's **MoCA** cognitive status score at the end of therapy vs. baseline (in points).
— The magnitude of change in the patient's **MoCA** cognitive status score at the end of parenteral therapy vs. baseline (in points).
— The magnitude of change in the patient's **Rivermead** Mobility Index score at the end of therapy vs. baseline (in points).
— 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 points).
— The magnitude of change in the patient's **HADS** score at the end of therapy vs. baseline (in points).
— The magnitude of change in the patient's **HADS** score at the end of parenteral therapy vs. baseline (in points).

7.2. Methods for estimating, recording and analysing efficacy parameters

The efficacy of the trial therapy will be assessed using a number of scales and questionnaires at Visits 0, 1, 2, 4 of the trial
according to the trial procedures schedule and visit descriptions.

8. Safety and tolerability assessment

8.1. List of safety and tolerability parameters

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

— Physical examination data, vital signs (BP, HR, respiratory rate, body temperature),
— 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 SAs with at least a possible association with the use of the investigational product.

The Investigator is responsible for notifying the Sponsor of any event that appears unusual, including deviation of a patient's test results from normal values, even if the event may be considered an unanticipated benefit to the patient.

8.2. Methods and timelines for estimating, recording and analysing safety and tolerability parameters

— Physical examination data - assessed at Visits 0, 2, 3, 4.
— Vital signs (BP, HR, RR, body temperature) - assessed at Visits 0, 2, 3, 4.
— Clinical blood test data, blood chemistry, urinalysis - assessed at Visits 0, 2 and 4.
— ECG data - assessed at Visits 0, 2 and 4.
— Frequency and severity of adverse drug reactions (tolerability of therapy) - assessed at all Trial Visits since the first administration of the investigational product/comparator product.

8.3. AE recording and reporting

Adverse events (AEs)

The protocol provides for the recording of all AEs that occur to the patient after the first administration of the trial therapy and until the end of the patient's participation in the trial.

During screening, information about medical adverse events will be attributed to the patient's medical history (pre-existing/concomitant conditions).

The planned trial will record all deviations in the health status of patients (based on the results of physical examination, laboratory and instrumental methods of investigation) from the data obtained at the Screening and from the accepted reference values.

After obtaining the necessary information, the investigating physician will categorise the patient's condition as 'normal', 'clinically insignificant abnormalities' or 'clinically significant abnormalities'. In case the abnormalities detected during the trial have not been previously reported, or there is an aggravation of the patient's condition vs. the data obtained at Screening, the detected abnormalities will be classified as AEs.

If the abnormalities detected during the trial have been recorded at Screening and there is no significant negative trend in the reasonable opinion of the investigator, the detected abnormalities will be classified as clinically insignificant abnormalities (CIA).

All detected abnormalities, irrespective of whether they are attributed to AE or CIA, will be analysed when reporting the results of the clinical trial.

An adverse event is defined as any adverse change in the health status of a patient or subject of a clinical trial/trial to whom a medicinal product has been administered, irrespective of the causal relationship with its use.

An adverse event may be any unfavourable and unintended change (including a deviation of a laboratory indicator from the norm), symptom or disease, the time of occurrence of which does not exclude a causal relationship with the use of the medicinal product, regardless of the presence or absence of a relationship with the use of the medicinal product. The parameters of an AE will be assessed in relation to the variables: severity (non-serious, serious AE), foreseeability (foreseen, unforeseen), severity (mild, moderate, severe, life-threatening, fatal), causality (no/yes; if yes: definite, probable, possible, doubtful, conditional, unclassifiable) and outcome (progression to SAE, stabilisation of condition, recovery without consequences, recovery with consequences, improvement in condition, unknown) as follows:

Serious adverse events (SAEs)

For the purposes of this protocol and in accordance with the legal requirements (National

Standard of the Russian Federation "Good Clinical Practice" GOST R52379-2005 dated 25.09.2005), a serious adverse medical event will be considered to be any adverse medical event that, regardless of the dose of the medicinal product, has resulted in death, is life-threatening, requires hospitalisation or its prolongation hospitalization or its prolongation, has resulted in permanent or significant disability or incapacity for work, is a congenital anomaly or birth defect or other medically significant event.

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:

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

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 investigational 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 IP 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 investigational product, 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 IP 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 investigational product; 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 treated as 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.

Outcome:

The outcome of an AE is assessed as follows:

Transition to the 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 (no change in condition):	AE has not resolved
Recovery with consequences	The resolution of the AE has occurred, but the patient still has some residual effects
Recovery/termination of an AE without consequences:	The AE has completely resolved without observed residual events
Improved condition:	Decrease 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)

Terms used in relation to a medicinal product:

An adverse *reaction* is an unintentional adverse reaction of the body associated with the use of a medicinal product/investigational product, suggesting at least a possible relationship with the use of the suspected medicinal product/investigational product.

Unexpected adverse reaction - 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.

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

8.3.1. Recording of adverse events

It is the responsibility of the Investigator to ensure that an AE in a clinical trial is registered. At each visit (other than screening), the Investigator should record all observed subjective or objective AEs.

When a patient has an AE, the investigator should describe the AE in as much detail as

possible and record the AE in the CRF.

The Investigator should complete the relevant pages of the AE in the CRF, indicating the classification of the AE (seriousness, severity, IP relationship). The date and time (if applicable) of the occurrence and resolution of the AE, unexpected AE or previously described/known AE, possible association with investigational product administration, patient and drug interventions, drug therapy for the AE, and outcome/resolution of the AE should also be recorded in the CRF.

Any available information related to the recorded AE, such as results of diagnostic tests (laboratory tests, ECG, etc.) should also be reflected in the CRF.

Categories of actions taken

One of the following categories is used to record actions taken in relation to an AE:

- No action required (continuation of the trial according to the protocol).
- Reducing the dose, which could mean:
  - reducing the dose of the investigational product;
  - reducing the frequency of administration/intake.
- Cancellation of investigational product followed by resumption.
- Complete withdrawal of the investigational product (complete discontinuation of the investigational product).
- Prescribing other treatments, such as:
  - for the treatment of an AE,
  - changing the dosage of concomitant therapy, prescribing non-drug therapy.

8.3.2. SAE reporting

Requirements for reporting of SAEs by the Investigator

All SAEs should be traced back to their resolution or stabilization.

If a SAE develops, it should be recorded in the patient's source documentation and CRF and an NPT SAE Registration Form should be completed. The SAE form is completed and submitted to the Sponsor's APP/CRO representative within 24 hours of the Investigators' receipt of the SAE information.

Representative of a contract research organisation (CRO):

Name of the contract research organisation:	*Limited Liability Company Klin PharmDevelopment*
Responsible for receiving SAE reports:	*Person responsible for pharmacovigilance in the CRO*
e-mail:	safety@cphd.ru

Authorized Person for Pharmacovigilance RPC PHARMASOFT LLC:

Name of the Sponsoring Company:	*RPC PHARMASOFT LTD*
Name of the person responsible for receiving reports on the development of SAE:	*Irina Vladimirovna Medvedeva*
Phone:	+7 (495) 626-47-55 ext. 162
e-mail:	pv@pharmasoft.ru

The Investigator must comply with the following deadlines for sending SAE communications to the Sponsor's APP/ CRO representative:

- Within 24 hours of being informed of the SAE onset.
- When new information on the SAE becomes available.
- After 30 days, if the SAE is still in progress.
- After the end of the SAE.

Each message should contain as much information as possible, including:

- Trial number (identifier or protocol number).

- Patient number.
- Investigator's full name and contact details.
- Description of the adverse event (date of onset, outcome as of the date of the report).
- Result of the investigator's assessment of the seriousness and severity.
- The result of the investigator's assessment of relationship with the investigational product.

The investigator should apply maximum effort to uncover new information on the course of the SAE.

Additional information (follow-up data) on all SNPs not available at the time of the initial report must be provided by the investigational site to the Sponsor's APP/CRO representative, within 24 hours of the Investigator becoming aware of this additional information.

The SAE form is completed, dated and signed by the Investigator who is authorized to complete the source documentation and the CRF.

Investigational site personnel should report SAEs to the local Ethics Committee in accordance with the rules and procedures established by the institutional board.

Responsibilities of the Sponsor

The sponsor is responsible for assessing the safety of the investigational product in the clinical trial.

The Sponsor is responsible for promptly informing the Investigator, the local ethics committee, and regulatory authorities of any findings that may adversely affect patient safety and the conduct of the trial.

The sponsor must submit information on all serious unexpected adverse reactions (hereinafter referred to as SUARs) for the investigational medicinal product identified during the clinical trial to the regulatory authorities:

- no later than 7 calendar days from the date of receipt of information on the identification of SUARs, if they have resulted in death or were life-threatening;
- no later than 15 calendar days from the date of receipt of information on the identification of SUARs for other serious unexpected adverse reactions.

Within 15 calendar days, the sponsor must submit to the regulatory authority and the Ethics Committee other safety information that may change the assessment of the risk/benefit ratio of the investigational medicinal product or serve as a basis for changes in the recommendations for its prescribing, as well as a basis for reconsideration of the possibility of further conduct of the trial.

The Sponsor may delegate to the contract research organisation its authority to communicate information about the SAE to regulatory authorities, ethics committees, and to the Investigator.

Duration of follow-up of patients after the development of AE

The investigator is responsible for documenting information about AEs during the clinical trial period.

In the event of a patient's death, the investigator shall provide the Sponsor's APP/CRO representative and the Ethics Committee with all necessary additional information.

If a patient develops an AE, the investigator should enter the necessary information into the CRF by completing the appropriate pages and assess whether the patient can continue to participate in the trial (continue the IP or exclude the patient from the trial). If a SAE develops, the investigator completes the SAE registration form provided by the Sponsor/contract research organisation representative, assesses whether it is associated with the investigational product and faxes the completed form to the Sponsor/contract research organisation representative. The original SAE form and fax receipt acknowledgement sheet should be retained in the source documentation, and the information should be entered into the patient's CRF. SAEs are reported to the LEC; SAEs deemed to be SUARs are reported to regulatory authorities, in accordance

with pharmacovigilance practices. The CRO/Sponsor representative has the right to urgently request additional information from the Investigator about such SAEs for reporting to the regulatory authorities.

In the context of reporting of SAEs, the trial period is defined as the period from the first administration of the investigational product to the end of the follow-up period.

During the trial period, the investigator is obligated to provide patients with necessary medical services.

If, prior to completion of the trial, patients develop an AE that results in exclusion from the trial, it is the responsibility of the investigator to ensure follow-up of that patient. Follow-up of the patient to ensure patient safety should take precedence over establishing the cause(s) for the development of the AE. The frequency of examinations during the follow-up period is determined by the investigator. All AEs/SAEs should be monitored until they are resolved or stabilized.

8.3.3. Pregnancy reports

Patients should be cautioned to report pregnancy immediately. If pregnancy is confirmed while taking the investigational product, the IP should be discontinued and the patient should be excluded from the trial. Within 24 hours of confirmation of pregnancy, the investigator must notify the CRO/Sponsor representative. This is done by completing the "Pregnancy Notification Form" and submitting it to the CRO/Sponsor representative.

Pregnancy is not considered to be an AE or SAE. However, pregnancy-related AEs must be treated as AEs or SAEs and reported to the Sponsor as appropriate.

Information should be collected on patients who become pregnant while participating in the trial. In addition, when children are born from these pregnancies, they should be evaluated for health status. The investigator should obtain the following information (if possible) from each pregnant woman who has taken the investigational product:

- results of an ultrasound scan performed early in pregnancy.
- information about the outcome of the pregnancy.

The following events will be considered SAEs:

- spontaneous abortion;
- ectopic pregnancy;
- congenital anomaly (defect);
- death of a child during the first month of life, regardless of the cause;
- death of a child over 1 month of age that the principal investigator believes is related to the effect of the investigational product.

Pregnancy forms should be sent to the CRO/Sponsor representative. Only pregnancies reported after initiation of the investigational products were observed.

The pregnancy should be followed up as part of a planned clinical trial until the outcome of the pregnancy is determined (up to 30 days after delivery), including spontaneous or induced abortion, and to obtain information on the delivery and the presence or absence of congenital malformations or anomalies or maternal and infant complications.

The procedure for submitting pregnancy forms is similar to the procedure for reporting SAEs.

9. STATISTICS

9.1. Calculation of 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 trial of the efficacy and safety 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.

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 points)"

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

Ho: $\varepsilon = \mu_\tau$ - $И_p \leq \delta$, H_1: $\varepsilon > \delta$, $\delta > 0$, where

- ε is the 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 (μ_τ - μ_p) must be greater than δ, where $\delta > 0$, i.e. CI must fall within the interval $(\delta, +\infty)$.

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. The results of the previously conducted EPICA clinical trial are summarized in Table 9.1.

Table 9.1. *Change in mRS score at the end of therapy relative to baseline [Visit 1 (Day 1) to Visit 5 (Day 67-71)] in patients enrolled in the ITT population.*

[μ - arithmetic mean; SD - standard deviation, DM - difference in mean averages]

Patient group	**Group**	**μ ± SD**	**Efficacy evaluation:**	
			95% CI for the difference in mean (μmex. - μp.)	**Comparison between groups**
ITT population (n = 144)	Group I (Mexidol®, n = 72)	2.278 ± 0.755	DM = 0.292	p = 0.029 (Mann-Whitney U-test)
	Group II (Placebo, n = 72)	1.986 ± 0.847	(0.027; 0.556)	

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) points, in the placebo group - 1.986 (0.847) points 2.278 (0.755) points, in the group of placebo therapy - 1.986 (0.847) points, the difference (Mexidol® - placebo) is 0.292 points, 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, δ = **0.027** points.

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 power $1-\beta = 0.8$ (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 products $\varepsilon = 0.292$ and with a mixed standard deviation (SD) of the in-group efficacyσ = **0.802** points.

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

$$n_T = n_R \frac{(1 + 1/k) * (z_\alpha + z_\beta)^2 * \sigma^2}{(\varepsilon — \delta)^2} = \frac{2 * (1.6449 + 0.8416)^2 * 0.802^2}{(0.292 - 0.027)^2} \approx$$

$$\approx 114 \text{ people/gr},$$

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 in accordance with the protocol must be at least $N = 2 * 114 = 228$ 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**.

Given the potential dropout of patients during the Screening phase, approval is planned for a clinical trial with a total of **336 screened patients**.

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 IP, followed by pooling of all data for the final analysis. The choice of this approach[1] 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)[2]. 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.

9.2. Statistical analysis software

Statistical processing of data obtained during the trial will be performed using the R statistical programming language (version 3.4.4 or higher), SAS statistical software (version 9.4 or higher), or other specific applicable software that ensures appropriate quality of the data obtained.

9.3. Review of deviations from the protocol and analysis plan

Statistical analyses will take into account violations / deviations from protocol, if any. If significant deviations from the protocol are detected that may affect the assessment of therapy efficacy, the patient should be excluded from the main statistical analysis of efficacy data (from the PP population).

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[1] Potvin D et al. Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceutical Statistics, 2007 (Method C).

[2] Pocock SJ. Group sequential methods in the design and analysis of clinical studies. Biometrika 1977;64:191199.

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.

9.4. Dealing with dropped out, excluded patients and missing data

No missing data will be completed, missing data will not be taken into account when performing statistical analyses.

9.5. Outliers

Identification of questionable data and data that cannot be analysed can be done by visual analysis of scatter plots, boxplots, etc. Statistical analyses will be performed on outlier data and then on the outlier-cleaned sample.

9.6. Population to be analysed

The following population groups will be used for the analyses:

1. The ITT (Intent-to-treat) population will include all randomized patients regardless of investigational product/placebo administration.
2. 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.
3. The PP (Per protocol) population will include patients who completed the trial in accordance with the Protocol.

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.

9.7. Statistical methods

The choice of statistical analysis method will be determined by the type of raw data and the type of distribution. The feasibility of using a range of statistical techniques will be assessed after data collection is completed, as the nature of the data distribution, sample homogeneity, etc. is not known in advance.

During the course of the analysis, it is possible to expand the list of methods used if this is necessary for the qualitative treatment of the data.

9.7.1. Assessment of demographics and data at the start of the trial

A summary of the group distribution of patients randomized into the trial will be presented. Comparative analyses will be performed to demonstrate comparability of treatment groups on demographic and other baseline patient characteristics.

Categorical (qualitative) data will be described using frequencies, percentages or fractions. Comparison of the frequencies of indicators between patient groups (I and II) will be performed using Pearson's χ^2 test if the frequency in each cell is ≥ 5, otherwise using Fisher's exact criterion.

Interval (quantitative) data will be described using: arithmetic mean, standard deviation, median, minimum, maximum, lower (25%) and upper (75%) quartiles, coefficient of variation. Comparison of indicator values between groups I and II will be performed using the non-parametric Mann-Whitney U-test for two independent samples distributed according to a non-normal distribution law, or using the parametric Student's t-test for two independent samples if the data in each group follow a normal distribution law.

The Shapiro-Wilk criterion will be checked for conformity to the normal distribution law.

9.7.2. Statistical methods for assessing efficacy

The primary population for the evaluation of efficacy criteria, proof of the hypothesis of superiority of the trial grug 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.

This approach in selecting the population for analysis is based on the design of the planned clinical trial: patients in both the investigational product and placebo groups will receive standard (baseline) therapy (according to the Clinical Guidelines "Ischaemic Stroke and Transient Ischaemic Attack in Adults", 2015) with proven efficacy. Therefore, the use of the ITT population for a more conservative assessment of ongoing therapy is inappropriate, as this approach markedly offsets the clinical effects of the investigational product. Therefore, to compensate for the therapeutic effects of baseline therapy and to properly evaluate the effects of IP, the PP population is considered as the primary population for analysing efficacy parameters in the planned trial.

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) relative to baseline (in points)".

In the case of a superiority trial, the null hypothesis (H_0) and the alternative hypothesis (H1) are formulated as follows:

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

- ε is the true difference between the value of the primary efficacy index (μ_T) 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 the investigational product compared to placebo therapy, the lower bound of the 95% (or 97.06% in the case of a phase II trial) 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 $(\delta, +\infty)$.

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.

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 criterion.

The test for conformity to the normal law of distribution will be carried out using the Shapiro-Wilk test.

Comparisons of frequencies of indicators between treatment groups will be made using Pearson's $\chi 2$ test or Fisher's exact test.

9.7.3. Statistical methods for assessing the safety of using the investigational product and the comparator product

Safety parameters will be analysed in the ITT population.

Safety data will be analysed using the methods outlined for the application of the efficacy data assessment. Analyses of AEs will be performed based on an assessment of the incidence of adverse events / serious adverse events. Adverse events reported during the course of the trial will be presented by frequency (number of patients with AEs and number of such AEs in the group). AEs will also be presented by severity and relationship to investigational product

administration. Comparison of the number of patients with AE between therapy groups will be performed using Fisher's exact test or Pearson's χ^2 test.

9.8. Significance level and power of the criterion

The level of significance (genus I error α) was chosen to be 0.05 (5%) and the power of the criterion was chosen to be at least 0.8 (80%).

Since an interim data analysis is planned, a genus I error correction approach α (α = 0.0294)[1] will be used to prove the hypothesis of "superiority" of investigational product therapy over placebo therapy on the primary efficacy criterion.

9.9. Statistical criteria for trial discontinuation

In the first phase, at the end of the trial, all randomized patients (304 patients) will undergo an interim analysis of the data for the primary endpoint[2]:

- 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.

9.10. Procedures for improving the accuracy of statistical analyses

During monitoring visits to the investigational site, Clinical Research Associates will analyse the Case Report Forms for missing data. In case of missing data in the CRF and the availability of relevant information in the source documentation, Questions to Investigators and prescriptions for correction of discrepancies will be formulated.

The Statistician and Principal Investigator while checking the database of the trial results will analyse for questionable, missing and unanalyzable data which will also result in formulating questions to the Investigators.

If necessary, Investigators will correct identified errors in the CRF and inform the Principal Investigator and Clinical Research Associates. If the identified errors in the data cannot be resolved after the subjects' participation in the trial is completed, the sensitivity of the resulting parameters to questionable data is analyzed during the statistical analysis of the data. Where available, information on missing, questionable and unanalysable data will be reported in the clinical trial report.

10. Direct access to source data/source documentation

Source data - information contained in the original medical records and their certified copies describing the results of clinical observations, examinations and other activities, allowing to reproduce the course of a clinical trial and assess its quality. Source data are contained in source

[1] Pocock SJ. Group sequential methods in the design and analysis of clinical studies. Biometrika 1977; 64:191-199.

[2] Potvin D et al. Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceutical Statistics, 2007 (Method C).

documentation (originals or certified copies) and, if an electronic data collection system is used, electronically.

The investigator must permit trial-related monitoring (by an authorized representative of the Sponsor and/or CRO), audits (by an authorized representative of the Sponsor or a company authorized by the Sponsor to conduct audits of the research facility) and inspections by regulatory authorities with direct access to source data and source documentation.

11. Quality assurance and quality control

11.1. General information on quality assurance and quality control

The Sponsor must provide an adequate quality assurance and quality control system for the conduct of this clinical trial in accordance with the Trial Protocol, Good Clinical Practice guidelines and applicable regulatory requirements.

The research procedures specified in the Protocol must be strictly adhered to by the Investigator and members of the trial team.

11.2. Risk management

The methods used to ensure and control the quality of the trial must be commensurate with the risks accompanying the clinical trial at all stages and the importance of the data generated by the trial. The quality management system should utilize a risk-based approach.

It is the Sponsor's responsibility to establish a risk management plan for the clinical trial. The risk management plan is part of the clinical trial design plan.

11.3. Monitoring of the clinical trial

Monitoring of the clinical trial shall be conducted by the Sponsor or its authorized organization for the purpose of:

- ensuring the protection of patients' rights and health;
- checking the accuracy and reliability of the data entered in the CRF against the data in the source documentation;
- verifying that the Investigator, trial team members are following the procedures of the approved Trial Protocol, the current version of the protocol amendments (if applicable), Good Clinical Practice and applicable regulatory requirements.

The clinical trial is monitored according to the approved plan. The Clinical Research Associate must comply with the Sponsor’s/CRO's written standard operating procedures, as well as procedures specifically identified by the Sponsor/CRO for monitoring a particular trial.

The Clinical Research Associate shall ensure that the trial is properly conducted and documented. The Clinical Research Associate's responsibilities include performing the following functions:

- to be the primary liaison between the Sponsor and the Investigator;
- to verify that the Investigator has the necessary qualifications and sufficient resources, including laboratories, equipment and personnel throughout the trial;
- to exercises control over the investigational medicinal product (storage conditions and terms, sufficient quantity of the medicinal product in the investigational site, correct prescribing of the investigational medicinal product, accounting of the medicinal product);
- to verify the Investigator's compliance with the approved Protocol and any approved Protocol Amendments (if applicable);
- to control the timely, i.e. before the patient's participation in the trial, signing of the Patient Information Sheet with the Informed Consent Form for participation in the clinical trial;
- to ensure that the Investigator has the current version of the documents for conducting

the clinical trial (Protocol, Protocol Amendments (if applicable), Investigator's Brochure, Patient Information Sheet with the Informed Consent Form for participation in the clinical trial);

- to ensure that the Investigator and members of the trial team are sufficiently informed about the trial;
- to monitor the performance by the Investigator and members of the trial team of their trial-related duties in accordance with the Protocol and other applicable agreements/contracts between the Sponsor and the Investigator/medical institution, as well as the autonomy of the performance of their assigned duties (detection of the transfer of the performance of the Investigator's functions to unauthorized persons);
- to monitor the Investigator's compliance with the selection criteria for the trial;
- to inform the Sponsor of the rate at which subjects are being enrolled into the trial;
- to control the accuracy and completeness of data in the CRF, source documentation and other records relevant to the trial by comparing them;
- to inform the Investigator of any errors, omissions and illegible entries in the CRF;
- to verify compliance with the reporting deadlines for adverse events defined in this Protocol;
- to verify the Investigator's maintenance of basic documents;
- to inform the Investigator about deviations from the Protocol, SOPs, regulatory requirements, and takes necessary actions to prevent the recurrence of such deviations.

In accordance with the recommendations of the Ministry of Health of the Russian Federation (Letter of the Ministry of Health of the Russian Federation dated 27.03.2020 "On the issues of conducting clinical studies of medicinal products in the COVID-19 coronavirus pandemic") and the Guidance on the Management of Clinical studies during the COVID-19 (Coronavirus) pandemic (Guidance on the Management of Clinical studies during the COVID-19 (Coronavirus) pandemic) of the European Medicines Agency, centralised and/or remote monitoring may be provided as part of the planned clinical trial.

11.4. Audit by the Sponsor

The Sponsor's audit is separate and independent from the routine monitoring and quality control functions of the clinical trial. The purpose of the audit is to assess the compliance of the trial being conducted with the protocol, SOPs, and regulatory requirements.

The Sponsor shall appoint individuals independent of the conduct of this clinical trial to conduct the audit.

It is the sponsor's responsibility to ensure that the auditors are qualified to perform the audit properly. The auditor's qualifications must be documented.

The Sponsor or Designated Entity shall develop an audit plan and audit procedures for this trial under which audits are performed.

11.5. Sponsor's actions in the event of non-compliance with applicable requirements

Failure to comply with the Protocol, SOPs and/or relevant regulatory requirements by the Investigator/investigational site, CRO or Sponsor's employees shall result in prompt action by Sponsor to ensure compliance.

If serious and/or repeated non-compliance with applicable requirements by the Investigator/Medical Institution/CRO is discovered during monitoring or auditing, the Sponsor may terminate the violating party's participation in the trial. If an investigator/investigational site's participation is terminated as a result of serious or repeated instances of non-compliance with applicable requirements, the Sponsor must notify the regulatory authorities.

11.6. Documents related to the conduct of the clinical trial

The Sponsor company will provide the following key documents and materials to the

investigational site:

- trial protocol (and amendments to it, if any).
- Investigator's Brochure.
- Patient Information Sheet with the Informed Consent Form for participation in the clinical trial;
- Investigator Site File.
- Investigational product.
- comparator product
- Agreement;
- Approval of regulatory authorities, Ethics Council;
- Documents required for submission to the local ethics committee.

The Investigator shall provide the Sponsor with the following key documents prior to the trial star:

- Letter of direction to the local ethics committee (if available);
- Signed confidentiality agreement.
- Signed statement from the Investigator agreeing to the protocol;
- Approval by the local ethics committee of the protocol;
- List of members of the local ethics committee;
- CVs of all Investigators and co-investigators (signed and dated);
- Laboratory standards with the signature and date of the responsible laboratory officer;
- Medical/laboratory equipment certificates (if requested by Sponsor).

The investigator must retain documentation related to the conduct of the clinical trial (source documentation and Investigator Site File). Clinical Trial documents may be destroyed only with the written permission of the Sponsor.

11.7. Amendments to the protocol

Amendment to the Protocol - a written description of changes or communication of changes made, or an official clarification of the Protocol.

Amendments to the protocol are significant if the changes to the protocol affect the safety or physical/mental well-being of the patient, the scientific value of the trial, the trial procedures, the quality or safety of the investigational medicinal product, or if there are plans to replace the responsible Investigator at a investigational site or to add a new investigational site to the trial.

Any changes or additions to this Protocol require the execution of written Amendments to the Protocol, which must be approved prior to entry into force.

Any changes or additions to this Protocol require the execution of written Amendments to the Protocol, which must be approved prior to entry into force.

Any amendments affecting patient safety, the conduct of the trial or the scientific value of the trial must be further approved by the Ethics Council, local ethics committee and regulatory authorities.

Protocol amendments affecting only administrative aspects of the research do not require the approval of the Ethics Board, Local Ethics Committee and regulatory authorities, but written notification of such amendments is required.

The final clinical trial report should outline the frequency and type of Protocol Amendments and explain the impact of the changes on the trial results.

11.8. Compliance with the Protocol

The Investigator shall conduct the trial in accordance with the approved Protocol.

A deviation from the Protocol is any change, inconsistency, or departure from the trial design or procedures of the Trial Protocol.

Any deviation from the Protocol during the conduct of a clinical trial must be recorded and reflected in the trial documentation.

All deviations from the Protocol are categorized into major deviations and minor deviations.

Minor deviation from the protocol - does not significantly affect the rights, safety and welfare of the patient or the completeness, accuracy and reliability of the trial data.

A significant protocol deviation (or protocol violation) is a deviation that may affect the rights, safety and welfare of the patient or the completeness, accuracy and reliability of the trial data.

Examples of significant deviations from protocol:

- patient met the exclusion criteria for the trial but was not excluded;
- patient has received a prohibited concomitant therapy drug;
- patient was included in the trial although he/she did not fulfil the selection criteria;
- performing trial procedures without obtaining written informed consent from the patient;
- violations of the procedure of IP administration by the patient (prescribing to one patient an IP with different randomization codes, inconsistency of labelling and randomization code in the source documentation, CRF, on all types of product packaging and in the patient registration and dispensing logs of the investigational product);
- patient indiscipline, failure to comply with restrictions during participation in the trial;
- systematic (repeated at least 2 times) negligent loss at a investigational site of data or samples collected for trial; and the negligent loss of data or samples collected for trial at a investigational site;
- skip of visits.

Major deviations must be reported to the ethics committee. If major deviations from the protocol are found, the patient should be excluded from the final analysis of efficacy data.

In the event that the visit procedures exceed the timeframes outlined in this protocol, the possibility of the patient's continued participation in the trial will be considered by the Sponsor, at the request of the investigator, on a case-by-case basis.

11.9. Final trial report

The clinical trial report will be written with input from the trial medical expert/medical consultant. The discussion of the results and conclusions will clearly state the conclusion about the safety and tolerability profile and efficacy parameters of the investigational products.

The clinical trial report will include the number and type of Protocol Amendments (if applicable), the number of violations and deviations from the Protocol found during the trial.

The final version of the report will be signed by the specific implementers, the trial medical expert/medical consultant, the head of this trial, and approved by the head of the institution and stamped with the institution's seal.

12. Regulatory and ethical aspects of the trial

12.1. Authorization to conduct a clinical trial

In accordance with the current legislation, documents for obtaining approval to conduct a clinical trial are submitted for expert review to the relevant regulatory authorities. Based on the results of the expert review, a written conclusion on the expert review of the documents and a notification on the possibility or impossibility of granting aurhorization for the clinical trial in question is issued.

The protocol and Patient Information Sheet with the Informed Consent Form for Participation in the clinical trial must be approved by an independent ethics committee (e.g. Ethics Council under the Ministry of Health of the Russian Federation) and the local ethics committee (LEC) of the institution prior to the start of the trial.

Patients may not participate in the trial until regulatory approval for this trial and ethical approval of the trial by the institution's Ethics and LEC Board.

12.2. Adherence to ethical standards

Investigators and the trial team, CRO staff, Sponsor staff, and others involved in the conduct of the clinical trial must follow the ethical principles set out in the WMA Declaration of Helsinki (latest version) and Good Clinical Practice regulations.

12.3. Patient information and consent procedure for participation in the trial

Before any trial procedures are performed, patients are given verbal information and written materials about the objectives and methods of the trial. They are informed of the expected benefits and possible risks associated with participation in the trial. In addition, patients must be made aware of the voluntary nature of participation in the trial and that they have the right to withdraw from the trial at any time and that this withdrawal will not affect the quality of care provided. Patients are not obliged to disclose their reasons for terminating their participation in the trial, but the Investigator must endeavour to ascertain these reasons without violating the patient's rights.

The patient should have sufficient time to reflect on their participation in the trial. The patient should be given the opportunity to ask additional questions.

Voluntary consent to participate in a clinical trial of a medicinal product for human use is documented in the Patient Information Sheet with the Informed Consent Form for participation in the clinical trial with dating, personal signature of the patient and the Investigator, thus certifying that the voluntary consent was obtained; the patient had the opportunity to ask questions and received full answers to them. The Patient Information Sheet with the Informed Consent Form for participation in the clinical trial is prepared in 2 copies; one copy, together with the Compulsory Insurance Policy, is kept by the patient, the second copy is kept at the investigational site together with other documentation on the trial

12.4. Confidentiality

Personal medical information about trial participants obtained during the trial is considered confidential and may not be disclosed to third parties. Such information may be shared with the patient's attending physician or other health care provider only after obtaining the patient's consent.

Each trial participant will be assigned a screening number to maintain the confidentiality of their data when communicating information about adverse events or other data related to trial procedures.

The screening number of the research subject will be a five-digit number of the form XXYYYY, where XX is the number of the investigational site (e.g. 01, 02, 03), YYY is the serial number of the patient (starting from 001), according to the order of inclusion (3 digits).

The patient's randomization code will be presented as a three-digit RRR format number.

The Investigator should ensure that the anonymity of the patients is respected. In the CRF, patients are identified only by assigned screening numbers.

Full identifying information about each patient will be held only by the Investigator, who must provide it when requested by an auditor, insurance company, or regulators. The storage of screening numbers and randomization codes of patients should be done appropriately, taking into account the confidentiality of such information.

All persons involved in the conduct of the trial must treat the patient information received, as well as information about this trial, as confidential.

13. Data handling and record keeping

13.1. General Provisions

The patient is identified in the Case Report Form (CRF) by a screening number. If, for safety or regulatory reasons, it becomes necessary to identify a patient, the Investigator has a duty to keep such information confidential.

13.2. Source documentation

The availability of source documentation at the investigational site is necessary to confirm that patients exist and that the information collected is correct. Source documentation includes original documents that are relevant to the trial, treatment, history and description of the patient's condition. For example, these documents include medical history and lab reports.

Source documentation is maintained in accordance with approved clinical practice guidelines, including registration of source documentation with the relevant division of the investigational site. Entries in the patient's source patient record are made during each patient assessment. The required data is transferred to the CRF within the timeframe agreed upon with the Sponsor.

When results of laboratory tests and instrumental investigations are received, the Investigator is obliged to evaluate, date and sign them. Forms of laboratory analyses and instrumental examinations are considered source documentation.

Source medical records should reflect the following information:

- demographic data;
- information regarding inclusion and non-inclusion criteria;
- fact of participation in the trial, indicating the trial number and patient number;
- date and time of all examinations;
- history and physical examination findings;
- adverse events;
- prior therapy and concomitant treatment;
- examination results;
- lab results;
- information on the prescribing of the investigational therapy;
- reason for early termination of participation in the trial (if applicable).

All entries in source documentation must be made in clear, legible handwriting.

If it is necessary to make corrections in the source documentation, the incorrect entry shall be crossed out with a single horizontal line, the correct entry, the date of correction, initials and signature of the person who made the correction shall be written next to it. The use of any means that destroys a previous entry or makes it difficult to read is not permitted.

An electronic data collection system can also be used to collect source data (e.g. results from completion of specialized scales). If an electronic data collection system is used, the source documentation is presented electronically (electronic database). Such source documentation has similar requirements for record keeping, tracking of corrections, etc.

13.3. Rules for filling in the CRF

Electronic versions of CRFs (eCRFs) are used in this trial. It is the responsibility of the Investigator to maintain correct and accurate data regarding the progress of the trial.

All entries in source paper documentation must be made in clear, legible handwriting.

If it is necessary to make corrections in the source documentation on paper, the incorrect entry shall be crossed out with a single horizontal line, the correct entry, the date of correction, initials and signature of the person who made the correction shall be written next to it. The use of any means that destroys a previous entry or makes it difficult to read is not permitted.

No CRF cells should be left blank.

The processing of CRF data may generate additional queries to which the Investigator is obliged to respond by confirming or modifying the requested data.

Completion of the eCRF must be done within the timeframe agreed upon with the Sponsor.

13.4. Data collection

The data obtained during the trial are recorded in the eCRF.

Completion of the CRF must be done within the timeframe agreed upon with the Sponsor.

If a patient drops out of the trial early, the eCRF is completed up to the time of dropout, stating the reason for early completion of trial participation.

It is the responsibility of the Investigator to ensure that the data entered into the eCRF are complete and correct. The data recorded in the eCRF should be appropriately supported by source documentation.

It is the The Clinical Research Associate's responsibility to verify the information entered into the eCRF for compliance with the source documentation. The Investigator is required to provide source documentation to the Clinical Research Associate for data reconciliation.

If any discrepancies in the data are identified, the Clinical Research Associate should inform the Investigator. The Clinical Research Associate is not authorized to make corrections to the eCRF.

Corrections to the eCRF shall be made by the Investigator or a member of the trial team authorized to record data in the CRF in accordance with the relevant instructions.

13.5. Data transmission and processing

Once data entry is complete, a check will be performed to verify the validity, consistency and completeness of the data.

All missing data and discrepancies will be submitted to the investigational site as queries and clarified by the responsible Investigator. If no further adjustments to the base are needed, it will be declared closed and used for statistical analyses.

Data management activities will be conducted in accordance with the Sponsor's / CRO's current standard operating procedures (SOPs).

13.6. Storage and archiving of documents

By signing this Protocol, the Investigator agrees to comply with the procedures for retention and archiving of trial documentation. Source documentation and the Investigator Site File, including the participant identification sheet and trial-related correspondence, shall be retained. Key clinical trial documents should be kept at the investigational site. Clinical Trial documents may be destroyed only with the written permission of the Sponsor.

The Sponsor is responsible for archiving the Trial Master File.

If the Sponsor discontinues clinical development of the investigational product, the Investigator and regulatory authorities must be notified. The Sponsor must inform the Investigator in writing of the need to retain trial-related records.

14. FINANCING AND INSURANCE

14.1. Funding for the conduct of the clinical trial

In accordance with Federal Law No. 61-FZ dated 12.04.2010. "On Circulation of Medicines", financing of the clinical trial is carried out at the expense of the Sponsor in accordance with the terms of the agreement between the Sponsor, medical institutions (investigational sites) and clinical diagnostic laboratory centres.

14.2. Material compensation

This Protocol does not provide for material compensation to patients for participation in the trial.

14.3. Insurance

Patients participating in this trial are guaranteed insurance of the risk of harm to life, health in accordance with the requirements of the legislation of the Russian Federation. The Investigator must inform the patient of the availability of such insurance.

The amount of insurance payments will be determined by the insurance company in accordance with Government Decree No. 714 of 13 September 2010 (as amended) "On

Approval of Model Rules for Compulsory Life and Health Insurance for Patients Participating in Clinical studies of a Medicinal Product" and related regulations.

This trial is insured by JSC AlfaStrakhovanie, Russia, 115162, Moscow, Shabolovka St., 31 p. B.

During the examination, the patient receives an original copy of the compulsory insurance policy, which stipulates the amount and procedure of insurance payment in case of an insured event.

When completing the Patient Information Leaflet and the Mandatory Life and Health Insurance Policy, the Investigator must complete the Individual Patient Identification Code (33 digits).

The Policyholder (Clinical trial Organiser/Sponsor) shall inform the Insurer about the patients involved in the clinical trial by transferring the register of individual identification codes of the trial participants by the Policyholder to the Insurer.

15. Use of information and publication of data

Information about the investigational product, the conduct of this trial, and unpublished data about the results of the trial are considered confidential.

Intellectual property in the results of the trial and the right to commercially exploit the information obtained from the trial is owned solely by the Sponsor.

Information obtained in the course of the research may be disclosed only to persons from regulatory authorities, who carry out the expertise on the possibility or impossibility of conducting this research and issuing permits for conducting the trial, to the participants of the trial under conditions of confidentiality. No information may be disclosed to third parties without separate written authorization from Sponsor.

The public presentation or publication of the results of this research is considered a joint effort between the Investigator, the Sponsor, and others involved in the conduct of the trial.

Investigator must be informed and agree that Sponsor may use information about the results of the clinical trial for publication and thereby make such information publicly available.

Publication of trial results by the Investigator is possible only after prior approval of the Sponsor. The investigator must submit the manuscript of the planned publication to the Sponsor for approval.

The Investigator is informed that data obtained during the trial may be used by the Sponsor or persons authorized by the Sponsor to provide to other Investigators or government agencies.

16. APPENDICES

APPENDIX 1. *A schedule of trial procedures.*

Procedures	**Screening**	**Randomization and initiation of therapy**	**Therapy period**				
	Visit 0	**Visit 1**	**Visit 2**	**Telephone visit 1**	**Visit 3**	**Telephone visit 2**	**Visit 4**
Timing (days of the trial)	-1/1 day[1]	1 day	11/12[2] day	24±2 day	40(+2) day	55±2 day	71(+2) day
Informed Consent signing	X						
Anamnesis collection	X						
Collection of demographic and anthropometric data	X						
Prior/concomitant therapy	X		X	X	X	X	X
Physical examination	X		X		X		X
Neurological examination	X		X				X
Assessment of vital signs (BP, HR, respiratory rate, body temperature)	X		X		X		X
Clinical blood test	X		X				X
Biochemical blood test	X		X				X
Clinical urinalysis	X		X				X
Blood tests for HIV, syphilis, hepatitis B and C	X[3]						
SARS- CoV-2 IgM antibody rapid test	X						
Pregnancy test for women with preserved reproductive potential	X						X
ECG	X[4]		X				X
CT/MRI	X[4]						
mRS (Modified Rankin Scale)	X		X				X

[1] Visit 0 and Visit 1 procedures can be carried out on the same day.

[2] If the first administration of the investigational product (start of parenteral therapy) falls on the second half of the day (first day of therapy - one administration), Visit 2 is performed on day 12 in the morning.

[3] Results obtained within 48 hours prior to Screening may be used

[4] The plan is to use data from examinations performed within 48 hours prior to patient inclusion in the trial to assess patient status and eligibility for inclusion/non-inclusion. A repeat CT/MRI scan is not required if these findings are present.

Procedures	Screening	Randomization and initiation of therapy	Therapy period				
	Visit 0	Visit 1	Visit 2	Telephone visit 1	Visit 3	Telephone visit 2	Visit 4
NIHSS (The National Institutes of Health Stroke Scale)	X		X				X
Assessment of inclusion/non-inclusion criteria	X						
Randomization		X					
Montreal Cognitive Assessment Scale MoCA		X	X				X
Hospital Anxiety and Depression Scale (HADS)		X	X				X
Rivermead Mobility Index		X	X				X
Start of trial therapy		X[1]					
Dispensing			X		X		
Medication administration and/or compliance assessment				X	X	X	X
Return of the medication							X
Recording of adverse events		X	X	X	X	X	X
Evaluation of exclusion criteria;			X	X	X	X	X

[1] The first administration of the prescribed investigational product is performed at Visit 1. The duration of the parenteral course of administration is 10 days (20 administrations of the investigational product).

APPENDIX 2.

mRS (Modified Rankin Scale)
Example form
Tick only one box

- ☐ Complete absence of symptoms (0 points)
- ☐ No significant disability despite the presence of symptoms: the patient can perform all his/her daily duties and activities (1 point)
- ☐ Mild incapacity: the patient is unable to perform his/her usual work, but is capable of self-care without assistance (2 points)
- ☐ Moderate disability: sometimes requires assistance but can walk independently (3 points)
- ☐ Moderately severe disability: the patient cannot walk unaided and is unable to perform self-care without assistance (4 points)
- ☐ Severe disability: patient is bedridden, incontinent of urine and faeces, needs constant care (5 points)
- ☐ Death (6 points)

APPENDIX 3.

NIHSS (The National Institutes of Health Stroke Scale)
Example form

INSTRUCTIONS

- Assess the scale items in the sequence indicated.
- Record the result for each item of the scale immediately after the corresponding survey.
- Do not go back to the preceding paragraphs or change the assessment.
- Follow the instructions provided for each examination procedure.
- The assessment should reflect what the patient does, not what the Investigator thinks the patient is capable of doing.
- The Investigator should record results as the survey progresses and work quickly.

Unless indicated, the patient should not be forced to perform the test (e.g., repeating a question to the patient to get his/her attention)

IF ANY SECTION OF THE SCALE WAS NOT TESTED, THE INVESTIGATOR MUST PROVIDE A DETAILED WRITTEN EXPLANATION OF THE REASON. ALL UNTESTED SECTIONS OF THE SCALE WILL BE REVIEWED BY THE CLINICAL RESEARCH ASSOCIATE AND DISCUSSED WITH THE INVESTIGATOR IN PERSON OR BY TELEPHONE

INSTRUCTIONS	Scale description	Scores
1a. **Level of consciousness**: The investigator should assess the patient's level of consciousness even if a complete examination is not possible due to obstacles such as an endotracheal tube, language barrier, orotracheal trauma or bandage. A score of 3 is given if the patient does not demonstrate a motor response (other than a reflexive change of posture) in response to pain stimulation	0 = Clearly conscious; responds quickly. 1 = Unconscious, but with minimal stimulation it is possible to execute a command, receive a verbal response or reaction. 2 = Unconscious, repeated stimulation is required to elicit a response, or the sense of pain is blunted and strong or painful stimulation is required to elicit a motor response (not stereotyped). 3 = Response only in the form of a reflex motor or autonomic nervous system response, or the patient is unresponsive, has decreased muscle tone and no reflexes	
lb. LOC questions to assess level of consciousness (LOC = Level of Consciousness): The patient must answer questions about what month it is and state his/her age. The answer must be correct - no half marks will be awarded for an approximate answer. Patients with aphasia and stupor who do not understand the questions receive a test score of 2. Patients unable to speak due to endotracheal intubation, orotracheal injury, severe dysarthria of any etiology,	0 = Both questions are answered correctly 1 = One question is answered correctly. 2 = No question is answered correctly.	

language barrier, or other problems that are not secondary to aphasia receive a score of 1. It is important that only the immediate response is assessed and that the examiner does not assist the patient verbally or non-verbally with signs.		
1c. LOC Commands: The patient is asked to open and close his/her eyes and then clench and unclench the healthy hand. If the healthy hand cannot be used, this task can be replaced with a similar simple command. A task is considered complete if a purposeful attempt to execute the command was made but not completed due to weakness. If the patient does not respond to a command, demonstrate the task (pantomime) and assess the outcome (i.e., not completing the command, completing one or two commands). Patients with trauma, amputation or other physical limitations should be offered alternative simple single-storey teams.	0 = Both tasks are completed correctly 1 = One task completed correctly 2 = None of the tasks are completed correctly.	
2. The oculomotor apparatus: Only eyeball movements in the horizontal plane. Only voluntary or reflex eye movements (oculocephalic reflex) are assessed , the caloric test is not provided. If the patient has co-operative eyeball movements that are attenuated by voluntary or reflex movements, a score of 1 is given. If a patient is diagnosed with isolated peripheral paresis of oculomotor nerve (III, IV or VI pairs of the HMMN), a score of 1 is given. Oculomotor nerve function is tested in all patients with aphasia. Patients with ocular trauma, bandages, pre-existing blindness, or other visual acuity or visual field deficits should be	0 = Norm 1 = Partial gaze paralysis. This assessment is given if there is a violation of function of the oculomotor nerves on one or both sides, but there is no forced deviation of the eyeballs or complete paralysis of gaze. 2 = Forced deviation of the eyeballs or complete paralysis of gaze that is not relieved by oculocephalic reflexes.	

evaluated for reflex movements. Making eye contact and subsequent moving around the patient can sometimes help to identify partial gaze paralysis.		
3. Vision: The visual fields (upper and lower quadrant) are tested in the patient's face-to-face position with the clinician, using finger counting or visual threat, as appropriate. The patient's attention should be attracted, but if he or she follows the finger movements with the eyes, this can be assessed as normal. If a patient is diagnosed with unilateral blindness or enucleation of the eyeball, visual fields should be assessed in the remaining eye. A score of 1 is only given if clear asymmetry is found, including quadrant hemianopsia. If the patient is blind for any reason, he/she is given a score of 3. When testing this item of the scale, a simultaneous dual stimulation is performed : if the inhibited patient receives a score of 1, the results of this test can be used to test item 11 of this scale.	0 = No visual impairment 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia (total blindness including cortical blindness)	
4. Facial nerve palsy: Ask the patient or pantomime that they need to show their teeth or raise their eyebrows and close their eyes. Assess facial grimace symmetry as a response to painful stimulus in unconscious patients. If an injury/face bandage orotracheal tube, leukoplasty or other physical obstruction covers the face, the obstruction should be removed if possible.	0 = Normal symmetrical movements 1 = Minor paralysis (smoothed nasolabial fold, asymmetrical smile) 2 = Partial paralysis (complete or almost complete paralysis of the lower part of the face) 3 = Complete uni- or bilateral facial nerve palsy (no facial expression in the upper and lower face)	
5 & 6. Motor domain: Place the limb in the appropriate position: arms extended (palms down) at 90 degrees (if the patient is sitting) or 45 degrees (if the	0 = No movement, arm held at a 90 (or 45) degree angle for 10 seconds. 1 = Moving, arm held at a 90 (or 45) degree angle, but lowered before 10 seconds; lowered	

patient is lying on the back) and legs at 30 degrees (tested in the supine position only). The patient is asked to hold the limb in this position. Movement is recorded if the patient's arm goes down in less than 10 seconds and the leg goes down in less than 5 seconds. Patients with aphasia are recruited to administer this test by stern voice and pantomime movements, but not by pain stimulation. Each limb is tested in turn, starting with the non-paralysed arm. Only in cases of amputation or arthrodesis of a joint in the shoulder or hip can a grade of "9" be given, and the Investigator must state the reason for the grade	without hitting the bed or other support. 2 = Patient makes gravitational effort, arm cannot be raised to 90 (or 45) degrees and held in that position, it drops down onto the bed but with some gravitational effort. 3 = Lack of effort to overcome gravity, limb falls. 4 = Lack of movement 9* =Amputation, arthrodesis (comment required): **5a. Left hand** **5b. Right hand**	
	0 = No movement, foot held at a 30 degree angle for 5 seconds. 1 = Moving, the leg is lowered before 5 seconds; when lowering, it does not hit the bed or other support. 2 = Patient makes gravitational effort, leg is lowered onto the bed before the 5 second period has elapsed but with some gravitational effort. 3 = Lack of effort to overcome gravity, foot falls on bed immediately. 4 = No movement 9* = Amputation, arthrodesis (comment required): **6a. Left foot** **6b. Right foot**	
7. Limb ataxia: This item of the scale is designed to detect evidence of unilateral cerebellar lesions. The test is conducted with eyes open. If there is a visual defect, ensure that testing is performed in a preserved visual	0 - Absent 1 = Present in one limb 2 = Present in two limbs If there's ataxia, it is ataxia in the Right hand 1 = Yes 2 = No	

field. Palcenosal and heel-knee tests are performed on both sides, and ataxia is only assessed if it is disproportionate to the weakness. Ataxia is absent in paralysed patients, patients who do not understand spoken language or who are unconscious. Only in the case of amputation or arthodesis may this item be scored as a "9" and the Investigator must state the reason for this score. In blindness, the palpebral test should be performed from baseline with the arm extended.	9* = Amputation or arthrodesis Comment: _____ Left hand 1 = Yes 2 = No 9* - Amputation or: arthrodesis Comment: _____ Right foot 1 = Yes 2 = No 9* = Amputation or arthrodesis Comment: _____ Left foot 1 = Yes 2 = No 9* = Amputation or arthrodesis Comment: _____	
*** - Do not include a "9" in your total score on this scale**	**# For information only, do not include in the total number of points on this scale**	
8. Sensitivity: sensitivity is tested by assessing the patient's response to pin pricks, in patients with aphasia a grimace or jerking of a limb in response to a painful stimulus is assessed. Only sensory impairment due to stroke is assessed, the investigator should thoroughly test all parts of the patient's body [arms (excluding palms), legs, trunk, face] necessary to clearly define the sensory impairment by hemitype. A score of 2, "severe impairment or complete loss of sensation" should only be given if severe or complete loss of sensation is unequivocally identified. Patients in stupor or with aphasia will receive a score of 1 or 0. A patient with a stem stroke and bilateral hypoesthesia receives a score of 2. A patient with tetraplegia who does not respond to stimulation receives a score of 2. A patient in a coma (item 1a=3) by definition receives a score of 2 on this scale item.	0 = Normal, no reduction in sensitivity. 1 = Mild to moderate decrease in sensitivity; patient feels the prick less acutely or muffled on the affected side: or there is a decrease in superficial sensitivity to the prick, but the patient feels when he/she is touched. 2 = A marked decrease or complete loss of sensation; the patient cannot feel when their face, arm or leg is touched.	

9. Speech: Much of the information about the patient's understanding of addressed speech will be obtained from the surveys presented in the previous sections. The patient is asked to describe the proposed picture, name the objects shown on the attached sheet and read the sentences written on it. Speech comprehension is assessed based on patient responses as well as response to physician instructions during previous neurological examination. If reduced visual acuity prevents the patient from performing the tasks in this section of the scale, the patient is asked to name the objects placed in his/her hands, to repeat a statement, or to tell something him/herself. Intubated patients are asked to write down their answers/statements on paper. Patients in coma (item 1a=3) automatically receive a score of 3 on this scale item. For a patient in a stupor or a patient with limited contact , the Investigator gives a score at her/his discretion, but a score of 3 is only given to patients with mutism who do not follow any simple commands.	0 = No aphasia, normal 1 = Mild to moderate aphasia; there is some reduction in fluency and comprehension of speech, with no significant limitation in the ability to express thoughts or the form of speech production. However, a decrease in speech production and/or difficulty in understanding speech makes it difficult or even impossible to talk about the proposed material. The Investigator, in a guided conversation, can identify a picture or card with the name of an object from the patient's response. 2 = Expressed aphasia; communicating only in short phrases, the listener must constantly interrogate the patient, and guess. The amount of information communicated is limited; the main communicative load is borne by the listener. The Investigator cannot identify the visual material from the patient's response. 3 = Mutism, total aphasia; lack of diction or auditory comprehension of speech	
10. Dysarthria: A conclusion that the patient does not have dysarthria can be obtained by asking the patient to read or repeat words from a list provided. In a patient with severe aphasia, clarity of articulation can be assessed from spontaneous speech. If there is a physical obstacle to speech (e.g., intubation), this item may be scored as a "9" and the Investigator must provide a reason for this score. Do not tell the patient the purpose of this testing.	0 = Norm 1 = Mild to moderate dysarthria; the patient may slur some words, at worst may be understood with some difficulty. 2 = Pronounced dysarthria; the patient's speech is unintelligible to the point of complete unintelligibility in the absence of dysphasia (disproportionate to it) or mutism. 9 * = Patient is intubated or has another physical impediment to speech. Comment: _____	

Do not include a "9" in your total score on this scale		
11. Neglect Syndrome (Neglect): Information to identify the presence of neglect syndrome in a patient can often be obtained from a previous examination. If the patient has a significant visual impairment that makes simultaneous dual stimulation impossible, but tactile sensitivity is not impaired, a score of "0" is given to . If the patient has aphasia but pays attention to both sides of their body and space, a score of "0" is given. The presence of visual spatial neglect or anosognosia is also sufficient to prove the presence of this syndrome. Since the severity of the syndrome is only assessed when it is present this item of the scale is never left unassessed.	0 = No deviation. 1 = Visual, tactile, auditory, spatial or personality neglect, or lethargy in response to simultaneous bilateral stimulation of one of the sensory modalities. 2 = Profound hemi-ignorance in more than one modality. Does not recognise his own hand or is only oriented to one side of space.	
A. Distal motor function: The Investigator holds the patient's hand at forearm level and asks the patient to straighten their fingers as far as possible. If the patient cannot straighten their fingers, the Investigator does it for them and observes the flexion for 5 seconds. Only the patient's first attempt is evaluated. Repetition of instructions or testing is prohibited.	0 = Normal (no finger flexion for more than 5 seconds) 1 = After 5 seconds there is some straightening of the fingers, but not complete straightening. Any other finger movement not provided for in the instructions is disregarded. 2 = No voluntary straightening of the fingers after 5 seconds. Finger movements at other times are not taken into account. a. Left hand b. Right hand	
DO NOT INCLUDE DISTAL MOTOR FUNCTION ASSESSMENT IN THE TOTAL NIHSS SCORE		

APPENDIX 4.

Montreal Cognitive Assessment Scale (MoCA)
Example form

Guidelines for application and evaluation

The Montreal Cognitive Assessment Scale (MoCA) was developed as a rapid assessment tool for moderate cognitive dysfunction. It assesses various cognitive domains: attention and concentration, executive functions, memory, language, visual-constructional skills, abstract thinking, numeracy and orientation. The time to perform a MoCA is approximately 10 minutes. The maximum possible score is 30 points; 26 points or more is considered normal.

1. Creating an Alternating Pathway:

Application: The investigator instructs the subject, "Please draw a line going from number to letter in ascending order. Start here [point to (1)] and draw a line from 1, then to A, then to 2, and so on. Finish here [dot (D)]."

Evaluation: One point is awarded if the testee successfully draws a line as follows: 1-A-2-B-3-C-3-D-4-E-5-F, without crossing lines. Any error that is not immediately corrected by the testee him(her)self earns 0 points.

2. Visual Constructive Skills (Cube):

Application: The Investigator gives the following instructions while pointing to the cube: "Copy this drawing as accurately as you can in the space below the drawing."

Evaluation: One point is awarded when the drawing is accurately executed:

- The drawing should be three-dimensional;
- All the lines are drawn;
- There are no extra lines;
- The lines are relatively parallel and their lengths are the same (rectangular prism is acceptable).

No point is given if any of the above criteria are not met.

3. Visual Constructive Skills (Hours):

Application: Point to the right third of the available space on the form and give the following instructions: "Draw a clock. Spread out all the numbers and give the time as 10 minutes past 12."

Evaluation: One point is assigned for each of the following three items:

- Contour (1 point): The dial must be circular, only a slight curvature (i.e. a slight imperfection in the closing of the circle) is allowed;
- Numerals (1 point): all numerals on the watch must be represented, with no additional numbers; numerals must stand in the correct order and be placed in the appropriate quadrants on the dial; Roman numerals are acceptable; numerals: may be placed outside the outline of the dial;
- Hands (1 point): there should be two hands jointly showing the correct time; the hour hand should be obviously shorter than the minute hand; the hands should be positioned in the centre of the dial, with them joined close to the centre.

No point is awarded for this item if any of the above criteria are not met.

4.Naming:

Application: Starting from the left, point to each figure and say, "Name that animal."

Score: one point is awarded for each of the following answers: (1) camel or one-humped camel, (2) lion, (3) rhinoceros.

5. Memory:

Application: The investigator reads a list of 5 words at a rate of one word per second, the following instructions should be given: "This is a memory test. I am going to read you a list of words that you will have to memorise. Listen carefully. When I'm done, tell me all the words

you've memorized. It doesn't matter what order you name them in". Make a mark in the space provided for each word when the subject names it on the first attempt. When the subject indicates that he/she is Finished (named all the words), or cannot recall more words, read the list a second time with the following instructions: "I will read the same words a second time. Try to remember and repeat as many words as you can, including the words you repeated the first time." Put a mark in the space provided for each word that the subject repeats on the second attempt. At the end of the second attempt, inform the subject that he/she will be asked to repeat the given words: "I will ask you to repeat these words again at the end of the test".

Score: no points are given for either the first or second attempt.

6. Warning:

Straight Digital Row:

Application: Give the following instructions. "I will name some numbers and when I am finished, repeat them exactly as I named them." Read the five numbers consecutively at a rate of one number per second.

Reverse Digital Row:

Application: Give the following instructions: "I will name some numbers, but when I am finished, you will need to repeat them in reverse order." Read a sequence of three numbers at a frequency of one number per second.

Evaluation: Award one point for each sequence exactly repeated (N.B.: exact answer for counting backwards from 2-4-7).

Vigilance:

Application: The investigator reads a list of letters at a rate of one letter per second, following the instructions: "I am going to read you a series of letters. Every time I say the letter A, clap your hand once. If I say a different letter, you don't have to clap your hand".

Evaluation: One point is awarded if there are no errors or only one error (an error is when the patient claps his/her hand when naming another letter or does not clap when naming the letter A).

Serial subtraction by 7:

Application: The investigator gives the following instructions: "Now I will ask you to subtract 7 from 100, and then continue subtracting 7 from your answer until I Say Stop." Repeat the instructions if necessary.

Evaluation: This item is rated at 3 points. Award 0 points if there is no correct score, 1 point for one correct answer, 2 points for two or three correct answers and 3 points if the testee gives: four or five correct answers. Count each correct subtraction by 7, starting with 100. Each subtraction is scored independently; thus, if: a participant gives an incorrect answer but then continues to accurately subtract 7 from it, give a point for each accurate subtraction. For example, a participant may answer "92-85-78-71-64" where "92" is incorrect, but all subsequent values are subtracted correctly. This is one error and 3 points are awarded in this paragraph.

7. Repetition of the phrase:

Application: The investigator gives the following instructions: "I am going to read you a sentence.

Repeat it exactly as I say (pause): All I know is that Ivan is the one who can help today." Following your answer, say, "Now I will read you another sentence. Repeat it exactly as I say (pause): The cat always hid under the sofa when the dogs were in the room."

Evaluation: Award 1 point for each correctly repeated sentence. The repetition must be exact. Listen carefully for errors due to word omissions (e.g., omission of "only", "always") and substitutions/additions (e.g., "Ivan is the only one who helped today"; Substitution of "hides" instead of "hid", use of plurals, etc.).

8. Fluency:

Application: The investigator gives the following instructions: "Name me as many words as you can that begin with a certain letter of the alphabet that I am going to tell you now. You

can name any kind of word except proper names (such as Peter or Moscow), numbers, or words that start with the same sound but have different suffixes, such as love, lover, lovely. I'll stop you in one minute. Are you ready? (Pause) Now name me as many words as you can think of that begin with the letter L. (Time 60 sec). Stop."

Evaluation: Award one point if the testee names 11 words or more in 60 seconds. Write your answers at the bottom or side of the page.

9. Abstraction:

Application: The investigator asks the subject to explain what each pair of words has in common, starting with the example: "Tell me what an orange and a banana have in common". If the patient responds in a certain manner, say only one more time, "Name what else they are alike." If the subject does not give the correct answer (fruit), say, "Yes, and also they are both fruit." Do not give any other instructions or explanations. After a trial run, say, "Now tell me what a train and a bicycle have in common." After answering, give a second task by asking: "Now tell me what a ruler and a clock have in common". Do not give any other instructions or prompts.

Evaluation: Only the last two pairs of words are considered. 1 point is given for each correct answer. The following answers are considered correct: Train-bicycle = means of transport, means for travelling, both can be ridden; Ruler-watch = measuring instruments, used for measuring. The following answers are not considered correct: Train-bicycle = they have wheels; Ruler-clock they have numbers on them.

10. Delayed presentation:

Application: The investigator gives the following instructions: "I read a number of words to you earlier and asked you to memorise them. Name me as many words as you can remember." Make a mark for each word correctly named without a clue in the space provided.

Evaluation: Award 1 point for each word named without any clues.

Optional:

After a delayed attempt to recall the words without a cue, give the subject a cue, in the form of a semantic categorical key for each unnamed word. Make a mark in the designated space if the testee recalled the Word using a categorical or multiple choice prompt. Clue in this way all the words that the subject did not name. If the subject does not name the word after the categorical prompt, give him/her a multiple-choice prompt using the following instructions: "Which of the words do you think was named NOSE, FACE, or HAND?" Use the following categorical and/or multiple choice prompts for each word: FACE categorical clue: body part multiple choice: nose, face, hand VELVET categorical clue: type of fabric multiple choice: denim, cotton, velvet CHURCH categorical clue: type of building multiple choice: church, school, hospital VIOLET categorical clue: type of flower multiple choice: rose, tulip, violet RED categorical clue: colour multiple choice: red, blue, green

Evaluation: No points are given for playing words with a clue. Clues are used for informational clinical purposes only and may provide the test interpreter with additional information about the type of memory impairment. When memory is impaired due to retrieval impairment, performance is improved with clueing. In memory impairments due to encoding impairment, test performance does not improve after prompting.

11. Orientation:

Application: The investigator gives the following instructions: "Tell me today's date".

If the subject does not give a complete answer, give the appropriate prompt, "Name (year, month, exact date, and day of the week)." Then say, "Now, name me this place, and the city in which it is situated."

Assessment: one point is awarded for each correctly named item.

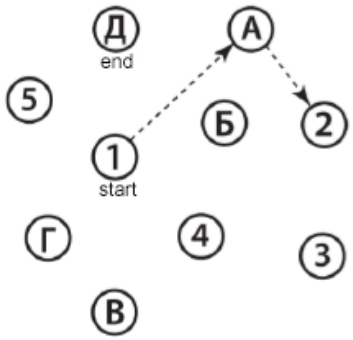
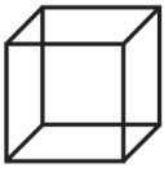
The testee must give the exact date and the exact place (name of the hospital, clinic, polyclinic). No score is assigned if the patient makes an error in the day of the week or date.

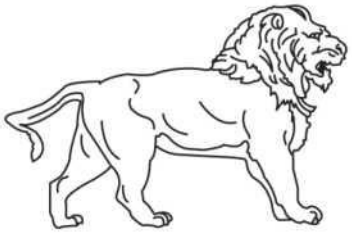
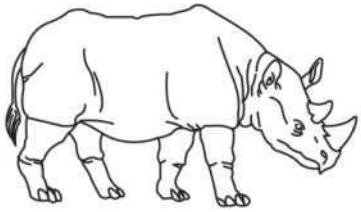
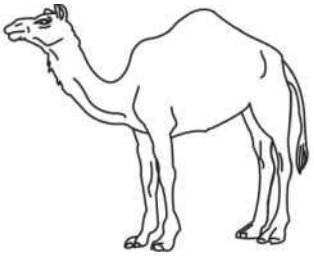
Total Score:

All scores in the right-hand column are summed. Add one point if the patient has 12 years of education or: less, up to a possible maximum of 30 points. A final total score of 26 or more is considered normal.

Montreal Cognitive Function Assessment Scale

NAME: **Date of birth:**
Education: **DATE:**
Gender

Visual-constructional/performance skills	Copy the cube	Draw a WATCH (Ten minutes past twelve) (3 points)	POINTS
 [ ]	 [ ]	[ ] Contour [ ] Figures [ ] Arrows	__ /5

NAME			
 [ ]	 [ ]	 [ ]	__ /3

MEMORY	Read the list of words, the subject must repeat them. Make two attempts. Ask them to repeat the words after 5 minutes.		FACE	VELVET	CHURCH	VIOLET	RED	no points
		Attempt 1						
		Attempt 2						

ATTENTION	Read the list of digits (1 digit/sec). I The testee must repeat them in direct order. [ ] 2 1 8 5 4	
	The testee must repeat them in reverse order. [ ] 7 4 **2**	__ /2
Read a series of letters. The testee must clap his/her hand on each letter A. No points for > 2 errors.	**[ ] F B A B A IN M N A A G L L B A F A C D E A A A G A M O F A B**	__ /1
Serial subtraction by 7 from 100.	**[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65**	
	4-5 correct answers: 3 points, 2-3 correct answers...: 2 points, 1 correct answer..: 1 point, 0 correct answers...: 0 points.	__ /3
SPEECH	Repeat: All I know is that Ivan is the one who can help today. [ ] The cat always hid under the sofa when the dogs were in the room. [ ]	__ /2
Speech fluency/in one minute, name the maximum number of words beginning with the letter L	[ ] **(N ≥ 11words)**	__ /1
ABSTRACTION	What do words like banana-apple = fruit have in common, for example [ ] train - bicycle [ ] watch - ruler	__ /2

DELAYED PRESENTATION	You have to say the words without prompting	FACE [ ]	**VELVET** [ ]	**CHURCH** [ ]	**VIOLET** [ ]	**RED** [ ]	Points only for words WITHOUT clues	__/5
OPTIONALLY	Category hint							
	Multiple choice							

ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day of the week [ ] Location [ ] City	__ /6

 Version 7.1 **www.mocatest.org** norm 26 / 30 NUMBER OF POINTS __ /30

Conducted by: _____ translation: Posokhina 0. C Smirnova A. YU.

Add 1 point if education ≤ 12

APPENDIX 5.

Rivermead Mobility Index
Example form

Value of the ***Rivermead Mobility Index*** corresponds to the score assigned to a question to which the doctor can give a positive answer regarding the patient. The index value can range from 0 (inability to perform any voluntary movements independently) to 15 (ability to run 10 metres).

No.	Skill	Question
1	Turns in bed	Can you turn from your back to your side without assistance?
2	Transition from the supine position to the sitting position.	Can you sit on the edge of the bed by yourself from the supine position?
3	Maintaining balance in a sitting position.	Can you sit on the edge of your bed without support for 10 seconds?
4	Transition from sitting to standing.	Can you stand up (from any chair) in less than 15 seconds and hold a standing position beside the chair for 15 seconds (using your arms or, if required, aids)?
5	Standing without support	The patient is observed to stand unsupported for 10 seconds.
6	Relocation	Can you move from bed to chair and back again without any assistance?
7	Walking around the room, including with aids if necessary.	Can you walk 10 metres using aids if necessary, but without the assistance of a stranger?
8	Climbing the stairs	Can you climb one flight of stairs without assistance?
9	Walking outside the flat (on a flat surface)	Can you walk outside your flat, on the pavement without assistance?
10	Walking around the room without the use of aids.	Can you walk 10 metres within the flat without a crutch, orthosis and without the assistance of another person?
11	Lifting objects off the floor	If you drop something on the floor, can you walk 5 metres, pick up the object you dropped and walk back?
12	Walking outside the flat (on uneven ground)	Can you walk outside your flat on uneven ground (grass, gravel, snow, etc.) without assistance?
13	Taking a bath	Can you get in and out of the bathtub (shower cubicle) without supervision and wash yourself?
14	Climbing and descending 4 steps	Can you climb up 4 steps and back down without leaning on the handrail, but using aids if necessary?
15	Running	Can you run 10 metres without limping in 4 seconds (fast walking is allowed)?

APPENDIX 6.

Hospital Anxiety and Depression Scale (HADS)
Example form

Part I (assessing the level of ANXIETY)

I'm feeling tense, I'm uncomfortable
3 - all the time
2 - often
1 - occasionally, sometimes
1 - never

I feel scared, like something terrible is about to happen
3 - definitely it is, and the fear is very great
2 - yes, that's true, but the fear is not very great
1 - sometimes, but it doesn't bother me
1 - never

Anxious thoughts are running through my head
3 - permanently
2 - most of the time
1 - once in a while and not too often

It is easy for me to sit back and relax
0 - definitely, it is
1 - I guess that's true
2 - only occasionally, that's true
3 - I cannot do it at all

I feel an inner tension or trembling
4 - never
1 - sometimes
2 - often
3 - very often

I'm restless, I constantly need to move around
4 - definitely, it is
2 - I guess that is true
1 - only to some extent, that is true
0 - not at all

I get a sudden sense of panic
3 - very often
2 - quite often
1 - not so often
0 - not at all

Part II (assessment of the level of DEPRESSION)

Something that gave me great pleasure still gives me the same feeling now
0 - definitely, it is
1 - I guess that is true
2 - only in a very small way, that's true
3 - it's not like that at all

I am capable of laughing and seeing the funny in an event
4 - definitely, it is

1 - I guess that is true
2 - only in a very small way, that's true
3 - completely incapable

I feel invigorated
4 - never
2 - very rarely
1 - sometimes
2 - practically all the time

I feel like I've been taking things very slowly
3 - practically all the time
2 - often
1 - sometimes
1 - not at all

I don't look after my appearance
3 - definitely, it is
2 - I don't spend as much time on it as I should
1 - maybe I've been spending less time on it
0 - I look after myself the same way I used to

I find that what I do (activities, hobbies) can bring me a sense of fulfilment
0 - just like always
1 - yes, but not as much as I used to
2 - much less than usual
3 - I don't think so at all

I can enjoy a good book, radio - or TV programme 0 - often
1 - sometimes
2 - rarely
3 - very rarely

Number of points:

0-7 points - Normal
8-10 points - subclinical symptoms
More than 11 points - clinically significant symptoms