CLINICAL TRIAL PROTOCOL

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

NCT Number: NCT06834490

Pharmasoft

April 30, 2020

PROJECT

CLINICAL TRIAL PROTOCOL

Trial Title:	International multicentre randomized, double-blind, placebo-controlled adaptive design clinical trial to evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) in patients with chronic cerebral ischemia (MEMO)
Sponsor:	Limited Liability Company "Research and Production Company PHARMASOFT/ RPC PHARMASOFT LLC Legal address: Russia, 115407, Moscow, Sudostroitelnaya str., 41, floor. 1, room 12. Postal address: Russia, 109544, Moscow, Enthusiastov Boulevard, 2 Tel/fax +7 (495) 626-47-55
Trial code:	PHS-CICADIS-005-MEX-SOL-TAB
Sponsor Responsible Representative:	Medical Director Tatiana Anatolievna Mityushkina Tel: + 7 (495) 626-47- 55, ext. 140 e-mail: mityushkina_t@pharmasoft.ru
Contract Research Organisation:	ClinPharmDevelopment LLC Russia, 150046, Yaroslavl, 68, Uglichskaya str. Tel: +7 (4852) 59-47-79, http://www.cphd.ru/ru
Protocol Version/Date:	5.0 dated 30.04.2020.

2020

RPC PHARMASOFT LLC, RUSSIA

Russia, 115407, Moscow, 41, Sudostroitelnaya St., floor 1, room. 12.

SPONSOR'S SIGNATURE

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

Version 5.0 dated 30.04.2020.

This Protocol has been approved by RPC PHARMASOFT LLC, Russia.

The following signatures confirm this approval.

Medical Director Tatyana Anatolyevna Mityushkina

Signature [*signed*] Date [handwritten]*15.06.2020*

INVESTIGATOR'S SIGNATURE

I have read the Protocol, including all addenda, and agree that it contains all the information necessary for me and all staff to conduct this trial. I will conduct the trial as described in this protocol and comply with all terms and conditions stated therein.

I will provide all the clinical trial personnel under my supervision with copies of the Protocol and access to all information provided by RPC PHARMASOFT LLC, Russia. I will discuss these materials with the trial staff to ensure that they are fully informed about the investigational product and the trial.

Full name of the Principal Investigator	Signature
Date	Site number

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Trial title:	International multicentre randomized, double-blind, placebo-controlled adaptive design clinical trial to evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (RPC PHARMASOFT LLC, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (RPC PHARMASOFT LLC, Russia) in patients with chronic cerebral ischemia (MEMO)
Protocol code, version **Countries**	PHS-CICADIS-005-MEX-SOL-TAB, version 5.0 dated 30.04.2020. Russian Federation, Republic of Kazakhstan, Republic of Uzbekistan, Republic of Belarus.
Type of Trial	Safety and efficacy trial
Purpose and objectives	**Purpose:** • To evaluate the safety and efficacy of sequential therapy with Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml (Pharmasoft, Russia) and Mexidol® FORTE 250 film-coated tablets, 250 mg (Pharmasoft, Russia) in patients with chronic cerebral ischemia **Objectives:** • To assess the dynamics of cognitive impairment using the MoCA scale. • To assess the dynamics of patients' quality of life using the SF-36 questionnaire. • To evaluate the dynamics of asthenic disorders detection using the MFI-20. • Evaluate the dynamics of the level of anxiety on the Beck scale. • To assess the dynamics of autonomic changes according to the Wein questionnaire. • To assess the dynamics of cognitive impairment by the Digit Symbol Substitution Test • To assess the dynamics of motor disorders using the Tinetti test • To assess the dynamics of the overall clinical impression using The Clinical Global Impressions Scale • To assess the safety of therapy with the investigational products based on the presence and severity of adverse events recorded during the trial.

Trial methodology	This trial is planned as an international multicentre, randomised, placebo-controlled, adaptive design clinical trial with inclusion of investigational sites in the Russian Federation, the Republic of Kazakhstan, the Republic of Uzbekistan, and the Republic of Belarus. All patients will receive sequential therapy: parenteral therapy for 14 days followed by oral therapy for 60 days. A subanalysis is planned for patients with diabetes mellitus and metabolic syndrome. Subanalysis by age will be done with the formation of the following subgroups: 40-60 years old, 61-75, 76-90 years old. A subanalysis will be performed in patients with CCI that developed without a previous stroke and with CCI that developed after a previous stroke
Trial duration	Screening - up to 7 days. Parenteral therapy -14 days. Oral therapy - 60 days. The maximum duration of patient participation in the trial will be no more than 83 days.
Number of subjects	There is a lack of information in the open literature that allows for the most accurate estimation of a drug's effect size according to the primary endpoint chosen. For this reason, it is advisable to use a group sequential design to optimise the determination of the required sample size. The trial can be conducted in two stages: the maximum sample size N is divided into two parts. After the first part of the patients have completed the trial, an interim analysis will be performed. If, based on the results of the interim analysis, the sample size is sufficient to reject the null hypothesis or prove that the null hypothesis cannot be rejected, the trial will be terminated early. Otherwise, the trial will be continued and the final decision to accept or reject the null hypothesis will be made based on the data obtained from the full sample of patients.

	Since the objective of this trial is to demonstrate the superiority of the investigational product over the placebo, an asymmetric design was chosen in the planning of the trial. A function from the Hwang, Shih and De Cani family (Hwang I.K., Shih W.J., De Cani J.S. Group sequential designs using a family of type I error probability spending functions, StatMed. 1990 Dec; 9(12):1439-45) was chosen as the spending function for the group sequential design with values of $\gamma = -2$ and $\gamma = -4$ for the β- and α-cost functions, respectively, defining the lower and upper bounds of the acceptable range. The search for the required sample size and boundary conditions was performed using the gs Design module (v.2.4-01,2011, Anderson K.) of the statistical software package R v.3.5.2. Input data corresponded to a fixed sample size in a simple study with no interim analyses. Calculation of the sample size for the trial without interim analysis was done based on the following formula: $$n = (Z_\alpha + Z_\beta)^2 \cdot \frac{2 \times SD^2}{(\mu_o - \mu_p)^2}$$ where Z_α and Z_β - critical values of the normal distribution corresponding to the established error levels α and β (α- and β-errors are 0.05 and 0.2, respectively), μ_o and μ_p - mean values of change on the Montreal Cognitive Assessment Scale in the main group (μ_o) and placebo group (μ_p); SD - standard deviation (Sergienko V.I., Bondareva I.B., Mathematical Statistics in Clinical Trials. - M.: GEOTAR-Media, 2006. - 304 p.; Bland J.M. Sample size in guideline trials. Family Practice 2000; 17: S17-S20.; Chow S.-C., Wang H., Shao J. Sample Size calculation in Clinical Research. Marcel Dekker, Inc. New York, Basel. - 2003. - 371 p.). In estimating the sample size, the standard deviation was assumed to be 4.3 points. The specified value of the standard deviation is the maximum possible value for the analysed performance indicator (Borland E. et al. The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort, Journal of Alzheimer's Disease 59 (2017) 893-901; Yakhno N.N. et al. Treatment of non-dement cognitive disorders in patients with arterial hypertension and cerebral atherosclerosis (according to the Russian multicentre trial "FUETE"), Neurological Journal, No.4, 2012; Pluzhnikova K.A., Fedorova E.A. Application of Montreal scale for assessment of cognitive functions in patients with chronic cerebral ischemia, materials of the 83rd All-Russian Baikal Scientific and Practical Conference of young scientists and students with international participation "Actual issues of modern medicine", dedicated to the 140th anniversary of the birth of Prof. N. D. Bushmakin, Ir.D. Bushmakin, Irkutsk, 25-27 April 2016, ed. by I.V. Malov, A.D. Botvinkin, A.G. Makeev, A.V. Valiulin, INCHT, 2016 - 458 p.).

	Assuming a difference in drug efficacy of at least 1 point, which corresponds to the minimum value of clinically significant differences (Wong G.K.C., et al. Minimum Clinically Important Difference of Montreal Cognitive Assessment in aneurysmal subarachnoid hemorrhage patients, J Clin Neurosci. 2017 Dec; 46: 41-44; Antipenko E.A., Deryugina A.V., Gustov A.V. Systemic stresslimiting effect of Mexidol® in chronic cerebral ischaemia, Journal of Neurology and Psychiatry, 2016.-N 4.-C.28-31., Journal of Neurology and Psychiatry, 3, 2017; Iss. 2) the calculation based on the above values ($Z\alpha$=1.96, $Z\beta$=0.842, SD=4.3, $\mu_o - \mu_p = 1$) resulted in a sample size providing statistical power of the trial of at least 80%, equal to 291 patients in each group (582 patients in total). In order to avoid inflation of first-order error and to maintain the stated power level, the total sample size in a trial with a group sequential design should be higher than in a trial without interim data analysis. According to the calculation made, the sample size for the first phase of the trial will be 150 individuals in one group (300 individuals in total), for the second stage - 300 individuals in one group (600 individuals in total). In case of possible patient attrition during the trial, **318** patients will be randomized for the first phase. Interim analyses will be performed after patients from the first phase of the trial have fully completed the trial.
Inclusion, non-inclusion and exclusion criteria	**Inclusion criteria** 1. Patients of either gender between the ages of 40 and 90 years inclusive. 2. MoCA scale score up to and including 25 points. 3. Patients meeting the criteria for diagnosis: Mild (moderate) cognitive impairment when assessed by DSM-5. 4. Chronic cerebral ischemia (ICD-10 code 167.8). 5. Presence of foci of leukoaraiosis or "silent" brain infarcts documented by MRI/CT performed within the last 12 months. 6. Patients who provided informed consent to participate in the trial. 7. Duration of clinical signs of progressive multifocal or diffuse brain damage from 1 to 5 years according to the history. 8. Patients with unchanged dose and combination of drugs of basic therapy including (if indicated for use): antiaggregant therapy, therapy of cerebral atherosclerosis and arterial hypertension, ischaemic heart disease and other chronic diseases during the previous month. 9. Negative pregnancy test. 10. Patients who agreed to use a reliable method of contraception during the trial until the end of the trial (for women of childbearing potential, including partners of trial participants). 11. Patients who are able to understand the requirements of the trial and who agree to all restrictions imposed by the trial.

	Non-inclusion criteria 1. Any diagnosis of a disease less than 6 months prior to inclusion that may cause symptoms similar to the nosology being investigated. 2. Intolerance to any of the components of the investigational products in the history. 3. Ischaemic stroke less than 12 months prior to inclusion in the trial. 4. Alzheimer's disease, neurodegenerative brain diseases, Parkinson's disease, multiple sclerosis, demyelinating diseases of the nervous system, hereditary degenerative diseases of the CNS, developmental abnormalities of the nervous system, uncontrolled epilepsy, other neurological disorders severely affecting motor or cognitive function, as judged by the investigator based on anamnesis. 5. Haemorrhagic stroke. 6. Mental disorders (F20-F48 (schizophrenia, schizotypal states and delusional disorders), F60-F69 (personality and behavioural disorders in adulthood) according to ICD-10) based on anamnesis. 7. Depression level on the Hamilton Depression Rating Scale (HDRS) at screening ≥14 points. 8. Need for neck or cerebral vascular surgery, including endovascular interventions, during the trial. 9. Evidence of a significant uncontrolled co-morbidity that, in the opinion of the Investigator, would preclude the patient's participation in the trial, including: • Respiratory system disorders; • Cardiovascular disorders; • Severe impairment of renal function (glomerular filtration rate <30ml/min); • Severe liver function impairment (ALT, AST activity> 2 times ULN); • Endocrine disorders; • Gastrointestinal disorders. 10. Systemic autoimmune diseases or vascular collagenosis requiring previous or current treatment with systemic corticosteroid drugs, cytostatics or penicillamine; malignant neoplasms within the last 5 years (except basal cell carcinoma). 11. Diagnosed cancer, including a history of cancer. 12. Use of drugs classified as prohibited in the 30 days prior to inclusion in the trial.

	13. Hypersensitivity or intolerance to any components used in this Investigational Product based on anamnesis. 14. Alcohol or drug dependence based on anamnesis. 15. Pregnancy, lactation period. 16. Participation in other clinical studies within 90 days prior to the screening visit based on medical history. 17. A positive result of at least one of the following tests: blood tests for HIV, syphilis, hepatitis B and C. 18. Lactose intolerance, lactase deficiency, glucose-galactose malabsorption. **Exclusion criteria** 1. Erroneous inclusion (violation of inclusion and non-inclusion criteria). 2. A decision by the Investigator or Sponsor to exclude a patient from the trial due to a clinically significant protocol deviation/protocol violation. 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. Any adverse event (may not be related to the Investigational product) requiring follow-up, procedures and/or medication not authorized by the protocol of this trial. 5. Patient refusal to continue participation in the trial or patient indiscipline. 6. An allergic reaction when using Investigational products that requires their cancellation. 7. The patient's desire to terminate the trial early for any reason. 8. Loss of contact with the patient followed by failure to attend the visit. 9. The need to take therapies prohibited by this protocol: nootropic drugs, ethylmethylhydroxypyridine succinate, trimetazidine or meldonium, drugs affecting the function of the autonomic nervous system and other drugs that may, in the opinion of the investigator, distort the results of the trial. 10. Pregnancy.
Stages and visits of the trial	Screening period (Visit 0) up to 7 days: Collection of baseline patient information and assessment of inclusion/non-inclusion criteria.

	All relevant information on diseases and demographics at the beginning of the trial are recorded in the patient's source documentation and then transferred to the CRF. The duration of the screening is no more than 7 days. A physical examination is mandatory at all visits. The following activities are performed during the screening visit: • Informed Consent signing • Collection of the patient's subjective complaints • Physical examination • Collection of demographic and anthropometric data • Collection of medical and pharmacotherapeutic history • Measurement of BP, HR, RR, body t° • 12-lead ECG • Complete Blood Count • Biochemical blood test • Determination of the glomerular filtration rate • Clinical urinalysis • Pregnancy test • Blood tests for HIV, syphilis, hepatitis B and C • Head MRI/CT (if not done in the last 12 months) • Evaluation of scales and indices: ✓ MoCA ✓ HDRS ✓ DSM-5 • Assessment of inclusion/non-inclusion criteria Visit 1- randomization Randomisation and day 1 of therapy. The visit is conducted no later than 7 days from visit 0, by which time the results of laboratory and instrumental examination methods should be prepared and evaluated. During the first visit, eligibility for inclusion/non-inclusion criteria is checked based on the laboratory results and other indicators obtained. Patients meeting the inclusion/non-inclusion criteria will be assigned to one of 2 treatment groups by randomisation. During the visit, the following procedures are carried out according to the trial design scheme: • Physical examination • Collection of the patient's subjective complaints

	• Measurement of BP, HR, RR, body t° • Assessment of inclusion/non-inclusion criteria • Randomization • Intravenous IP administration • Evaluation of concomitant therapy • Evaluation of exclusion criteria; • Assessment of adverse events (after the start of the first IP administration) • Issuance of the diary and training in its completion • Evaluation of scales and indices: ✓ MoCA ✓ SF-36 ✓ MFI-20 ✓ Wein questionnaire ✓ Beck Anxiety Rating Scale ✓ Digit Symbol Substitution Test ✓ Tinetti test ✓ Clinical Global Impressions Scale Visit 2 Visit 2 is performed on day 14 after the last intravenous injection of the IP. This visit is the end of parenteral therapy. During the visit, the following procedures are carried out according to the trial design scheme: • Physical examination • Collection of the patient's subjective complaints • Measurement of BP, HR, RR, body t° • Complete Blood Count • Biochemical blood test • 12-lead ECG • Clinical urinalysis • Pregnancy test • Evaluation of scales and indices: ✓ MoCA ✓ SF-36 ✓ MFI-20 ✓ Wein questionnaire ✓ Beck Anxiety Rating Scale

	✓ Digit Symbol Substitution Test ✓ Tinetti test ✓ Clinical Global Impressions Scale • Intravenous IP administration (last injection) • Dispensing of oral medication • Evaluation of concomitant therapy • Evaluation of exclusion criteria; • Assessment of adverse events • Checking that the patient diary has been filled in correctly Visit 3 Visit 3 is performed on 28±2 days after the start of therapy. This visit is done through telephone contact. During the visit, the following procedures are carried out according to the trial design scheme: • Collection of the patient's subjective complaints • Evaluation of concomitant therapy • Evaluation of exclusion criteria; • Assessment of adverse events Visit 4 Visit 4 is carried out on day 44±2 of treatment. The following procedures are carried out according to the trial design scheme: • Physical examination • Collection of the patient's subjective complaints • Measurement of BP, HR, RR, body t° • Pregnancy test • Evaluation of scales and indices: ✓ MoCA ✓ SF-36 ✓ MFI-20 ✓ Wein questionnaire ✓ Beck Anxiety Rating Scale ✓ Digit Symbol Substitution Test ✓ Tinetti test • IP take-back and compliance assessment • Dispensing of oral medication

	• Evaluation of concomitant therapy • Evaluation of exclusion criteria; • Assessment of adverse events • Checking that the patient diary has been filled in correctly Visit 5 Visit 5 is performed on day 75+2 after initiation of therapy. This visit is the final one. During this visit, the following procedures are performed according to the trial design scheme: • Physical examination • Collection of the patient's subjective complaints • Measurement of BP, HR, RR, body t° • 12-lead ECG • Complete Blood Count • Biochemical blood test • Clinical urinalysis • Pregnancy test • Evaluation of scales and indices: ✓ MoCA ✓ SF-36 ✓ MFI-20 ✓ Wein questionnaire ✓ Beck Anxiety Rating Scale ✓ Digit Symbol Substitution Test ✓ Tinetti test ✓ Clinical Global Impressions Scale • IP take-back and compliance assessment • Evaluation of concomitant therapy • Evaluation of exclusion criteria; • Assessment of adverse events • Return of the patient diary, assessment of correctness of completion Allowable and recommended intervals between visits: the time between screening and visit 1 (i.e. the start of treatment) should be no more than 7 days. There should be no deviations from the timing of visits 1, 2. Allowable deviations from the timing of visits 3 - 5 shall not exceed 2 days.

	Early withdrawal In case of early withdrawal from the trial, the patient must complete all procedures according to the schedule of the premature trial termination visit. Early withdrawal visit If for any reason the patient drops out of the trial, the physician should make every effort to carry out procedures for early withdrawal visit, namely: • Physical examination, assessment of vital signs (BP, RR, HR, t°) • Collection of the patient's subjective complaints • 12-lead ECG • Complete Blood Count • Biochemical blood test • Clinical urinalysis • Pregnancy test • Evaluation of scales and indices: ✓ MoCA ✓ SF-36 ✓ MFI-20 ✓ Wein questionnaire ✓ Beck Anxiety Rating Scale ✓ Digit Symbol Substitution Test ✓ Tinetti test ✓ Clinical Global Impressions Scale • Evaluation of concomitant therapy • Evaluation of exclusion criteria; • Assessment of adverse events • Returning the patient diary, checking that the patient diary has been filled in correctly Unscheduled visit This visit is conducted when patient safety is a concern. It may also be conducted when a patient has questions about trial procedures and/or other questions related to the disease or treatment. The procedures for an unscheduled visit depend on the reasons that led to the need for the visit. The investigator determines the scope of the procedures to be performed individually in each case, depending on the situation.

Investigational product	1. Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml, manufactured by RPC PHARMASOFT LLC, Russia. 2. Mexidol® FORTE 250 film-coated tablets, 250 mg, manufactured by RPC PHARMASOFT LLC, Russia.
Dosage regimen and route of administration of the Investigational product	1. Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml, produced by RPC PHARMASOFT LLC, Russia - 10 ml (500 mg) OD by intravenous drip in 100-200 ml of 0.9% NaCl solution / intravenous bolus for 14 days. 2. Mexidol® FORTE 250 film-coated tablets, 250 mg, produced by RPC PHARMASOFT LLC, Russia - 1 tablet TID for the next 60 days.
Comparator product:	1. NaCl 0.9% solution for intravenous and intramuscular injection. 2. Placebo film-coated tablets identical to the Investigational product.
Dosage regimen and method of administration of the comparator product	1. NaCl 0.9% solution for intravenous and intramuscular injection - 10 ml OD by intravenously drip in 100-200 ml of 0.9% NaCl solution/intravenous bolus for 14 days. 2. Placebo identical to the Investigational product - 1 tablet TID for a further 60 days.
Key parameters for efficacy and safety assessment	**Primary efficacy criterion:** • mean change in Montreal Cognitive Assessment Scale (MoCA) score at patient completion of the trial (Visit 5) vs. baseline (Visit 0). **Secondary efficacy criteria:** • dynamics of the severity of cognitive impairment on the MoCA scale between Visit 0 and Visits 2 and 4. • dynamics of patients' quality of life according to the SF-36 questionnaire between Visit 1 and Visits 2, 4, 5. • dynamics of asthenic disorders severity according to the MFI-20 scale between Visit 1 and Visits 2, 4, 5. • dynamics of anxiety level on Beck scale between Visit 1 and Visits 2, 4, 5. • dynamics of autonomic changes according to the Wein questionnaire between Visit 1 and Visits 2, 4, 5. • dynamics of cognitive impairment by the Digit Symbol Substitution Test between Visit 1 and Visits 2, 4, 5. • dynamics of motor changes on the Tinetti test between Visit 1 and Visits 2, 4, 5.

	• dynamics of the Clinical Global Impressions Scale (The Clinical Global Impressions Scale) between Visit 1 and Visits 2, 5. **Safety criteria:** safety of therapy with investigational products based on the presence and severity of adverse events recorded during the trial at all visits.
Statistical hypothesis	The present trial intends to assess the efficacy of therapy by the mean difference between the Montreal Cognitive Assessment Scale (MoCA) scores at patient completion and trial initiation (Webb A.J.S. et al. Validation of the Montreal Cognitive Assessment Versus MiniMental State Examination Against Hypertension and Hypertensive Arteriopathy After Transient Ischemic Attack or Minor Stroke, 2014 Nov;45(11):3337-42. doi: 10.1161/STROKEAHA. 114.006309). The following statistical hypotheses will be tested: - **null hypothesis (H_0):** the efficacy of therapy with the Investigational product <u>is not superior to the</u> efficacy of therapy with placebo: H^0: $\mu_m - \mu_p \leq 0$, where μ_m and μ_p - mean values of change on the Montreal Cognitive Function Assessment Scale in the main group (μ_o) and placebo group (μ_p); **- alternative hypothesis (H_A):** the efficacy of therapy with the Investigational product <u>is superior to that of</u> therapy with placebo: H^A: $\mu_m - \mu_p > 0$.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

BD	Blood pressure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ULN	Upper limit of normal
g	Grams
GABA	Gamma-aminobutyric acid
GI TRACT	Gastrointestinal tract
IP	Investigational medicinal product
PIS with ICF	Patient Information Sheet with Informed Consent Form
BMI	Body mass index
CRF	Case Report Form
LEC	Local ethics committee
mg	Milligram
MRI/CT	Magnetic resonance imaging/computed tomography
RPC	Research and production complex
IEC	Independent Ethics Committee
AE	Adverse event
LLC	Limited Liability Company
SAR	Serious adverse reaction
SAE	Serious adverse event
SOP	Standard operating procedure
ESR	Erythrocyte sedimentation rate
QPPV	Qualified Person Responsible for Pharmacovigilance
ICF	Informed consent form
RR	Respiratory rate
HR	Heart rate
CCI	Chronic cerebral ischaemia
ECG	Electrocardiography
EMHPS	Ethylmethylhydroxypyridine succinate
ANOVA	Analysis of variance

BAI	Beck Anxiety Inventory
CGI	Clinical Global Impressions Scale
CTCAE	Common Terminology Criteria for Adverse Events
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
GCP	Good clinical practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Medicinal Products for Human Use
HDRS	Hamilton Depression Rating Scale
MFI-20	Multidimensional Fatigue Inventory
MoCA	Montreal Cognitive Function Assessment Scale
°C	Celsius

1. GENERAL INFORMATION

Protocol title, protocol identification number and date

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

Identification number of the clinical trial protocol: PHS-CICADIS-005-MEX-SOL- TAB

Protocol version: 5.0 dated 30.4.2020.

Name and address of the Sponsor:

RPC PHARMASOFT LLC
Russia, 115407, Moscow, 41, Sudostroitelnaya St., floor. 1, room 12.
Tel: +7 (495) 626-47-55

Name and address of the CRA:

ClinPharmDevelopment LLC
68, Uglichskaya St., Yaroslavl, 150046, Russia.
Tel: +7 (4852) 59-47-79

Name and title of persons authorized to sign the minutes and amendments to the minutes on behalf of the Sponsor:

Medical Director Tatyana Anatolyevna Mityushkina
Tel: + 7 (495) 626-47-55, ext. 140
e-mail: mityushkina_t@pharmasoft.ru

Name, title, address, and telephone number of the Sponsor's designated medical expert for this trial:

Doctor of Medical Sciences, Professor, Corresponding Member of the Russian Academy of Sciences Alexander Leonidovich Khokhlov
Tel: + 7 (910) 663-11-55
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Name and position of the investigators responsible for the trial and addresses and telephone numbers of the investigational sites are provided in a separate list. Local laboratories of the investigational sites will be used for laboratory research.

2. TRIAL RATIONALE

2.1.Introduction

Chronic cerebral ischaemia (CCI) is a special type of cerebral vascular pathology, which is caused by slowly progressive diffuse impairment of blood supply to the brain with gradually increasing various defects of its functioning [18]. The key role in the pathogenesis of ischaemic disorders is attributed to the processes of activation of lipid peroxidation with the release of large amounts of active oxygen radicals, which leads to the development of oxidative stress [14, 15, 18, 20]. However, traditional therapy aimed at improving blood supply to the brain is mainly based on medicinal products that have a psychostimulant component of action in the spectrum of their pharmacological activity, and does not always prevent the increase of oxidative damage in the patients' body, which determined the need to search for medicinal products that selectively correct these processes [20]. Mexidol containing ethylmethylhydroxypyridine succinate (EMHPS) as an active ingredient may be the medicinal product of choice for the treatment of CCI patients. EMHPS is an inhibitor of free-radical processes, a membrane-protector. It also has antihypoxic, stressprotective, nootropic, antiepileptic and anxiolytic effects [42].

The mechanism of action of EMHPS is due to its antioxidant and membrane-protective effects. The product inhibits lipid peroxidation, increases the activity of superoxide dismutase, increases the lipid-protein ratio, improves the structure and function of the cell membrane. EMHPS modulates the activity of membrane-bound enzymes (calcium-independent phosphodiesterase. adenylate cyclase, acetylcholinesterase), receptor complexes (benzodiazepine, GABA, acetylcholine), which enhances their ability to bind with ligands, contributes to the preservation of structural and functional organisation of biomembranes, transport of neurotransmitters and improvement of synaptic transmission. EMHPS increases dopamine levels in the brain. It 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 ATP and creatine phosphate. activation of energy-synthesising functions of mitochondria. Increases the resistance of the organism to various damaging factors in pathological conditions (shock, hypoxia and ischaemia, cerebral circulatory disorders, intoxication with ethanol and antipsychotic drugs) [45, 46 ,47].

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. 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. It ensures the integrity of morphological structures and physiological functions of ischaemic myocardium. It also improves the clinical course of myocardial infarction, increases the efficacy of therapy, and reduces the incidence of arrhythmias and intracardiac conduction disturbances [43].

In clinical use it normalises metabolic processes in ischemic myocardium, increases antianginal activity of nitrates, improves blood rheological properties, reduces the consequences of reperfusion syndrome in acute coronary insufficiency. It reduces enzymatic toxaemia and endogenous intoxication in acute pancreatitis. It improves metabolism and blood supply to the brain, microcirculation and rheological properties of blood, reduces platelet aggregation.
Another property is to stabilise the membrane of blood cells (erythrocytes and platelets), while reducing the likelihood of haemolysis. It has hypolipidaemic effect, reduces the content of total cholesterol and low-density lipoproteins [44].
The high efficacy and good tolerability of EMHPS have been proven in a number of clinical studies.

2.2.Name and description of Investigational Products

Investigational Products

The investigational products in this clinical trial are Mexidol® in the dosage form "solution for intravenous and intramuscular administration" and Mexidol® FORTE 250 in the dosage form "film-coated tablets".

Trade Name:	Mexidol®
Group name:	Ethylmethylhydroxypyridine succinate
Marketing Authorization Holder/ Claims Receiving Organisation:	RPC PHARMASOFT LLC, Russia
Manufacturer:	Ellara LLC, Russia
Dosage form:	Solution for intravenous and intramuscular administration
Composition per 1 ml:	
Active ingredient:	Ethylmethylhydroxypyridine succinate - 50 mg.

Excipients:	Sodium metabisulphite - 0.4 mg Water - up to 1 ml.
Description:	Transparent colourless or slightly yellowish liquid
Pharmaceutical form:	Solution for intravenous and intramuscular administration 50 mg/ml in ampoules of colourless or light-protective glass with blue breakpoint or white breakpoint and three marking rings (upper - yellow, middle - white, lower - red) of 2 ml, 5 ml or 10 ml. 5 ampoules each in PVC blister. For ampoules of 2 ml - 1, 2 or 4 blisters in a carton pack. For ampoules of 5 ml and 10 ml - 1, 2 or 3 blister in a carton pack. 4, 10 or 20 PVC blisters in a carton pack (for hospitals).
Storage conditions	Store in a place protected from light, out of reach of children, at temperatures not exceeding 25°C. Shelf life: 3 years. Do not use after the expiry date indicated on the packaging.

Trade Name:	Mexidol® Forte 250
Group name:	Ethylmethylhydroxypyridine succinate
Marketing Authorization Holder/ Claims Receiving Organisation:	RPC PHARMASOFT LLC, Russia
Manufacturer:	ZAO ZiO-Zdorovye, Russia
Dosage form:	Film-coated tablets
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.
Pharmaceutical form:	Film-coated tablets, 250 mg. 10 film-coated tablets in a PVC/Alu blister 1, 2, 3, 4, 5, 6 blisters into a carton pack.
Storage conditions	Store in a place protected from light, at a temperature not exceeding 25°C. Keep out of reach of children. Shelf life: 3 years. Do not use after the expiry date indicated on the packaging.

Comparator products

0.9% NaCl in the dosage form "solution for intravenous and intramuscular administration" and placebo "film-coated tablets" will be used as comparator medicinal products.

Trade Name:	Sodium chloride
Manufacturer:	Ellara LLC, Russia
Dosage form:	Solution for intravenous and intramuscular administration
Composition per 1 ml:	
Active ingredient:	Sodium chloride 9 mg
Excipients:	Water for injection up to 1 ml
Description:	Transparent colourless liquid
Packaging:	Identical to Mexidol® solution for intravenous and intramuscular administration, 50 mg/ml

Name:	Placebo
Manufacturer:	ZAO ZiO-Zdorovye, Russia

Dosage form:	Film-coated tablets
Composition per 1 tablet:	
Active ingredient:	Absent
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.
Packaging:	Identical to Mexidol® FORTE 250 film-coated tablets, 250 mg

Pharmacological properties of Mexidol® and Mexidol® FORTE 250 are presented below.

MEXIDOL®

Pharmacodynamics

It has antihypoxic, membrane-protective, nootropic, anticonvulsant, anxiolytic effect, increases the body's resistance to stress. The medicinal product 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 lipid peroxidation, increases superoxide dismutase activity, 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. The time to reach maximum concentration Tmax is 0.45-0.5 h. Cmax at administration of 400500 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 medicinal product 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.

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.

Method of administration and doses

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 2 times a day 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.

Use in pregnancy and during breastfeeding

Mexidol® is contraindicated in pregnancy and during breastfeeding.

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%); common (≥1%, but <10%); uncommon (≥0.1%, but <1%); rare (≥0.01%, but <0.1%); very rare (<0.01%); frequency unknown (frequency cannot be determined from 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 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.

Effect of the drug 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.).

MEXIDOL® FORTE 250

Pharmacodynamics

Mexidol® FORTE 250 is an inhibitor of free-radical processes, membrane protector with antihypoxic, stress-protective, nootropic, antiepileptic and anxiolytic 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. 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. Mexidol® Forte 250 increases the content of dopamine in the brain. 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.

Increases the body's resistance to various damaging factors in pathological conditions (hypoxia and ischaemia, impaired cerebral circulation, intoxication with ethanol and antipsychotic drugs).
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. 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. It ensures the integrity of morphological structures and physiological functions of ischaemic myocardium. 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.
It reduces enzymatic toxaemia and endogenous intoxication in acute pancreatitis.
It improves metabolism and blood supply to the brain, improves microcirculation and rheological properties of blood, reduces platelet aggregation. It stabilizes the membrane structures of blood cells (red blood cells and platelets), reducing the likelihood of haemolysis. It has hypolipidemic action, reduces the content of total cholesterol and low-density lipoproteins.
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.
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. 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.
Mexidol® FORTE 250 improves the functional state 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.

Pharmacokinetics

It is rapidly absorbed when taken orally. The maximum concentration (Cmax) at doses of 400500 mg is 3.5-4.0 μg/ml. It is rapidly distributed in organs and tissues. The mean retention time (MRT) of the drug in the body when administered orally is 4.9-5.2 h. It is metabolized in the liver by glucuron conjugation. Five metabolites have been identified: 3-oxypyridine phosphate - is formed in the liver, with the participation of alkaline phosphatase is broken down into phosphoric acid and 3-oxypyridine; 2nd metabolite - pharmacologically active, formed in large quantities and found in the urine on 1-2 days after administration; 3rd - excreted in large quantities with urine; 4th and 5th - glucuronconjugates. The elimination half-life (T1/2) at ingestion is 2.0-2.6 h. It is rapidly excreted with urine mainly in the form of metabolites and in 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.

Contraindications

- acute liver and/or renal dysfunction;
- hypersensitivity to the drug and its components;
- infancy (due to insufficiently studied effect of the drug);
- pregnancy, breastfeeding (due to insufficient study of the drug action);
- lactose intolerance, lactase deficiency, glucose-galactose malabsorption.

Use in pregnancy and during breastfeeding

Mexidol® FORTE 250 is contraindicated in pregnancy and during breastfeeding.

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.

Side effects

The frequency of side effects was determined according to the World Health Organisation (WHO) classification: very frequent (≥10%); common (≥1%, but <10%); uncommon (≥0.1%, but <1%); rare (≥0.01%, but <0.1%); very rare (<0.01%); frequency unknown (frequency cannot be determined from 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.

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.

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

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

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

2.3.Summary of results of preclinical and clinical studies

2.3.1. Preclinical studies

Information on the results of the conducted preclinical studies is presented in the investigator's brochure.

2.3.2. Clinical studies

Information on the results of the clinical studies conducted is presented in the investigator's brochure.

Programme of planned clinical studies
The aim of the trial is to amend the current instructions for use of Mexidol® and Mexidol® FORTE 250. The essence of the changes to be made will be formulated based on the results of the trial.

2.4.Summary of known and potential risks and benefits to trial subjects

2.4.1. Investigational medicinal products

The investigated medicinal products Mexidol® and Mexidol® FORTE 250 are known medicinal products registered in the Russian Federation in the dosage forms "solution for intravenous and intramuscular administration" 50 mg/ml and "film-coated tablets" 250 mg, respectively.
Mexidol® and Mexidol® FORTE 250 have been used for many years in the treatment of patients with vascular and neurological disorders. Patients participating in the trial will receive direct benefits to their health. This benefit will be made up of all the therapeutic and diagnostic procedures performed as part of the trial. All procedures in the protocol are completely free of charge to the patient.
A possible risk of patients' participation in the trial is the occurrence of adverse events associated with the administration of the investigational medicinal products Mexidol® and Mexidol® FORTE 250 indicated in section 2.2; and unlisted adverse events may be detected.
A high efficacy and safety profile of Mexidol® and Mexidol® FORTE 250 was confirmed in clinical studies [8 - 31].

2.4.2. Comparator products

Despite the good tolerability of the investigational and control products, in order to minimise the risks of participation in the clinical trial, the Protocol provides for continuous medical monitoring of patients, including monitoring of basic vital signs (BP, HR, RR, body temperature), evaluation of laboratory parameters, registration and evaluation of adverse events. Patients will receive reliable information about their health status as a result of the examination and follow-up conducted as part of their examinations.

2.4.3. Risks of trial procedures

The risks associated with the tests and examinations required under the terms of this Clinical Trial Protocol do not exceed the risks of routine medical practice. The existing minimal risk of infection and haematoma development during blood sampling and parenteral drug injection can be eliminated by skilled performance of the procedures and use of quality consumables.

2.5. Description and justification of the method of administration, dosage, dosing regimen, course of treatment

Investigational products will be used:

- in a clinical centre setting (parenteral form).
- by patients on their own at home (tablet form)

These methods of use are specified in the instructions for medical use of the medicinal products Mexidol® and Mexidol® FORTE 250.
Dosage of 500 mg (10 ml) intravenous drip/intravenous bolus slowly OD (daily dose 500 mg) and subsequent use of the drug in tablet form in the dosage of 250 mg (1 tablet) TID (daily dose 750 mg) are therapeutic doses of the drug for adults. A course of treatment at these doses for 14 days for parenteral administration and subsequent use of the tablet form for 60 days will allow the pharmacodynamic effect of the drug to be assessed and also allow possible side effects to be monitored.
Placebo, which has no intrinsic pharmacodynamic properties, will be used as control drugs.

Rationale for the choice of a comparator product

Placebo, which has the same dosage form, similar appearance, route of administration, and packaging and labelling, will be used as comparator products. Neither the investigator nor the patient will know which product is being used in a particular patient.
According to the principles of evidence-based medicine, the reference design for clinical studies is randomized controlled double-blind studies in which randomization is done in a closed-loop fashion and the control group receives a placebo that is indistinguishable from the intervention being studied.

This eliminates the positive impact of reassurance from doctors, clinic management and nursing staff. Thus, a placebo control will provide the most reliable data on the efficacy and safety of the Investigational products.

2.6.Regulatory requirements

This clinical trial will be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) rules, the ethical principles outlined in the World Medical Association Declaration of Helsinki (Fortaleza, 2013) and local legislative requirements:

- Ethical Principles of the 1964 Declaration of Helsinki of the World Medical Association, as revised in 2013.

Federal Law:

- Federal Law No. 61-FZ dated 12.04.2010 "On Circulation of Medicines".
- Federal Law No. 323-FZ of 21.11.2011 "On the Fundamentals of Public Health Protection in the Russian Federation"

Resolution of the Government of the Russian Federation:

- Resolution of the Government of the Russian Federation No. 714 dated 13.09.2010 (ed. 15.10.2014) "On Approval of Standard Rules for Compulsory Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product".
- Resolution of the Government of the Russian Federation of 3 September 2010 N 683 "On Approval of the Rules for Accreditation of Medical Organisations for the Right to Conduct Clinical Trials of Medicinal Products for Medical Use".

Orders:

- Order of the Ministry of Health of the Russian Federation of 1 April 2016 No. 200n "On Approval of the Rules of Good Clinical Practice".
- Appendix 13 to the Order of the Ministry of Industry and Trade of Russia dated 14.06.2013 N 916 (ed. 18.12.2015) On Approval of Good Manufacturing Practice Rules - Medicinal Products for Clinical Trials.
- Order of the Ministry of Health of the Russian Federation No. 137 of 24 March 2015 "On the composition of the Ethics Council".
- Order of the Ministry of Health of the Russian Federation No. 986n of 29.11.2012 On Approval of the Regulations of the Ethics Council.
- Order of the Ministry of Health of the Russian Federation №1359n from 24.12.2012 On the invalidation of the Order of the Ministry of Health and Social Development of the Russian Federation from 31.08.2010 №774n "On the Ethics Council".
- Order of the Ministry of Health of the Russian Federation of 29 August 2012 N 1106-Pr/12 on the invalidation of the order of the Federal Service for Supervision of Health Care and Social Development of 17 August 2007 № 2314-PR/07 "On the Ethics Committee".

- Order of the Ministry of Health and Social Development of Russia N 703n dated 23 August 2010. "On Approval of the Form for Reporting the Completion, Suspension or Termination of a Clinical Trial of a Medicinal Product for Medical Use".
- Order of the Russian Ministry of Health and Social Development No. 748 of 26 August 2010. "On Approval of the Procedure for Granting Permission to Conduct a Clinical Trial of a Medicinal Product for Medical Use" (as amended by Order of the Ministry of Health of Russia No. 111n dated 13.03.2015).
- Order of Roszdravnadzor of 17.08.2007 No. 2314-Pr/07 "On the Ethics Committee".
- Order of Roszdravnadzor of 15 February 2017 No. 1071 "On Approval of the Procedure for Pharmacovigilance".

National Standard:

- National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice";

Guides:

- Decision of the Council of the Eurasian Economic Commission of 03.11.2016 N 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union".
- Rules of Good Laboratory Practice of the Eurasian Economic Union in the field of circulation of medicines", approved by Decision No. 81 of the EEC Council dated 03.11.2016. (EAEU GLP).
- Rules of Good Laboratory Practice, approved by Order of the Ministry of Health of Russia dated 01.04.2016 N199n (in terms of issues not regulated by the EAEU GLP).
- Rules of Good Clinical Practice, approved by Order of the Ministry of Health of Russia dated 01.04.2016 N200n (in terms of issues not regulated by the EAEU GCP).

The clinical trial will be conducted in accordance with the current version of the Clinical Trial Protocol. The protocol and any amendments, as well as the Informed Consent form for trial subjects, must be approved by the regulatory authorities and an independent ethics committee.

2.7.Description of the trial population

The participants of this trial are male and female patients aged 40 to 90 years inclusive with the diagnosis of "Chronic cerebral ischaemia (ICD-10 code 167.8)".
The rationale for the use of the medicinal product "ethylmethylhydroxypyridine succinate" for the treatment of patients with CCI is presented in the section “Rationale of the trial", the Investigator's Brochure, as well as regulated by the typical practice of treatment of patients with this nosology [13 - 32].

2.8.References to literature sources

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3. PURPOSE AND OBJECTIVES OF THE TRIAL

3.1.Trial purpose:

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

3.2.Trial objectives:

The **following tasks** are planned in order to achieve the set purpose:

1. To assess the dynamics of cognitive impairment reduction using the MoCA scale.
2. To assess the dynamics of the patients' quality of life using the SF-36 questionnaire.
3. To evaluate the dynamics of asthenic disorders detection using the MFI- 20.
4. Evaluate the dynamics of the level of anxiety on the Beck scale.
5. To assess the dynamics of autonomic changes according to the Wein questionnaire.
6. To assess the safety of therapy with the investigational products based on the presence and severity of adverse events recorded during the trial.

7. To assess the dynamics of cognitive impairment by the Digit Symbol Replacement Test.
8. To assess the dynamics of motor disorders using the Tinetti test
9. To assess the dynamics of the overall clinical impression using The Clinical Global Impressions Scale

4. TRIAL DESIGN

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

4.1.1. Efficacy parameters

Efficacy will be evaluated using primary and secondary efficacy criteria.

Primary efficacy criterion:

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

Secondary efficacy criteria:

- dynamics of the severity of cognitive impairment on the MoCA scale between Visit 0 and Visits 2 and 4.
- dynamics of patients' quality of life according to the SF-36 questionnaire between Visit 1 and Visits 2, 4, 5.
- dynamics of asthenic disorders severity according to the MFI-20 between Visit 1 and Visits 2, 4, 5.
- dynamics of anxiety level on Beck scale between Visit 1 and Visits 2, 4, 5.
- dynamics of autonomic changes according to the Wein questionnaire between Visit 1 and Visits 2, 4, 5.
- dynamics of cognitive impairment by the Digit Symbol Substitution Test between Visit 1 and Visits 2, 4, 5.
- dynamics of motor changes on the Tinetti test between Visit 1 and Visits 2, 4, 5.
- dynamics of the Clinical Global Impressions Scale (CGI) between Visit 1 and Visits 2, 5.

Safety parameters

The safety and tolerability of the investigational products will be assessed throughout the trial based on the registration of adverse events (from the first use of the Investigational Products to the completion of the trial by the patient); adverse events will be registered on the basis of clinical, laboratory and instrumental parameters.

For more details, see Section 7, Safety Assessment.

4.2.Characterisation of the trial

This trial is planned as an international multicentre, randomised, placebo-controlled, multicentre adaptive design clinical trial, including investigational sites in the Russian Federation, the Republic of Kazakhstan, the Republic of Uzbekistan, and the Republic of Belarus.

All patients will receive sequential therapy: parenteral therapy for 14 days followed by oral therapy for 60 days.

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

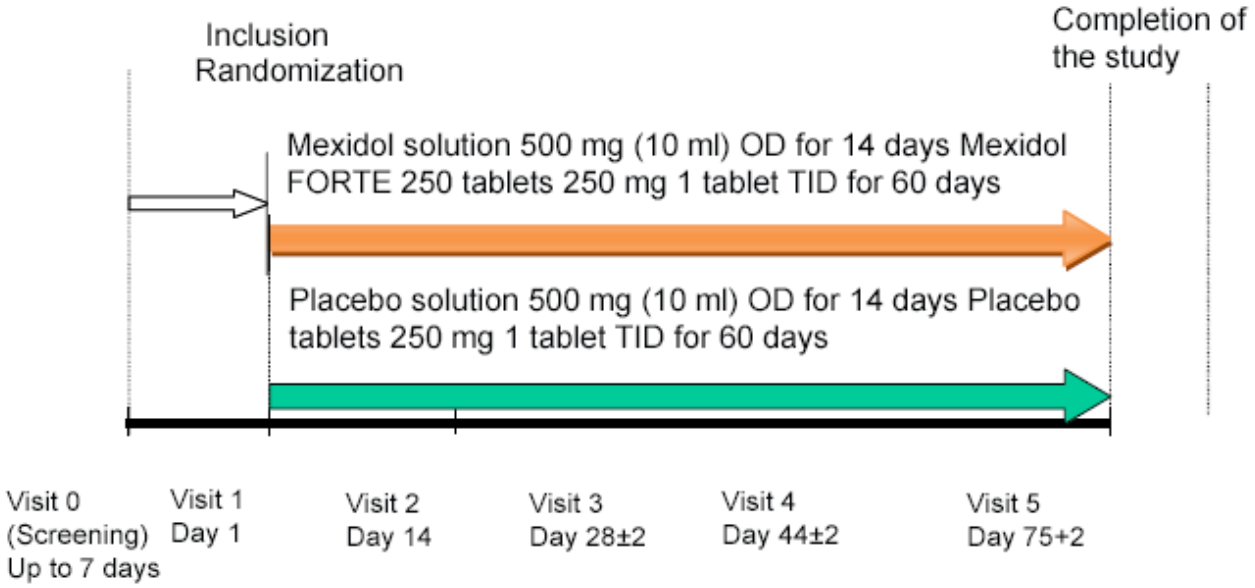
Subanalysis by age will be done with the formation of the following subgroups: 40-60 years old, 61-75, 76-90 years old.

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

4.2.1. Trial design

The clinical trial design (Figure 1) shows the trial steps to be carried out for each trial subject.

Figure 1. Clinical Trial design.



4.2.1.1.Phases and procedures of the trial. Description of visits

The trial will consist of a Screening visit and five treatment/follow-up visits.

4.2.1.2.Trial procedures

4.2.1.2.1. Signing informed consent

Before any trial procedures are performed, the patient must consent to participation in this trial in writing - by signing and dating an Informed Consent to Participate in a Clinical Trial in duplicate. The patient will be provided with a "Patient Information Sheet with Informed Consent Form", which will reflect complete, objective, reliable, patient-adapted information about the trial, including information about:

- experimental nature of the trial;
- absolute voluntariness in deciding whether the patient should participate in the trial and the possibility to terminate participation in the trial at any time without giving reasons;
- purpose of the clinical trial, its nature and all aspects of the trial;
- data on treatment options in the trial and the likelihood of random assignment to one of the treatment groups;
- trial procedures;
- expected risks and benefits of participation in the trial, inconveniences associated with the trial;

- responsibilities of patients when participating in a clinical trial;
- aspects of the trial that are experimental in nature;
- availability of alternative treatments other than those provided in the protocol, available procedures and treatments;
- number of patients planned to be included in the trial;
- expected duration of the patient's participation in the trial;
- additional information during the trial;
- procedure for providing the patient with medical care or covering the costs thereof in the event of damage to the patient's health during the trial, the conditions for providing the patient with medical care;
- persons who can be contacted for further information about the trial and the rights of trial subjects, as well as in the event of harm to the subject's health as a result of his or her participation in the trial;
- possible circumstances and/or reasons why the subject's participation in the trial may be terminated;
- information about the patient's health insurance, terms of insurance or other guarantees, providing the address of the insurance company;
- conditions of confidentiality.

The investigator will also sign and date the Informed Consent to participate in the clinical trial, thereby certifying that consent has been obtained, the patient has had sufficient time to review the consent, and the patient has had the opportunity to ask questions and have them fully answered. The patient will receive one original copy of the Informed Consent and the other original copy will be kept by the investigator along with other trial documentation at the investigational site.

Together with the informed consent, the patient is given a life and health insurance policy for the patient participating in a clinical trial of a medicinal product.

4.2.1.2.2. Demographic and anthropometric data

Demographic data including date of birth, age, gender, race will be recorded at Screening.

The Screening will also determine anthropometric parameters, including height (measured in standing position, without shoes; the result is rounded to the nearest centimetre), weight (measured without street clothes and shoes; the result is rounded to tenths of a kilogram), BMI (calculated using the formula: weight (in kilograms) divided by squared height (in metres) BMI= weight (kg): (height $(m)^2$).

4.2.1.2.3. Medical and pharmacotherapeutic history

The Screening will collect a history of the patient's present illness detailing the patient's complaints, lifetime illnesses, and present infectious, cardiovascular, respiratory, gastrointestinal, neurological, endocrine, skin, psychiatric, urogenital, musculoskeletal, liver and kidney diseases; in addition, information on the presence of other disorders and surgical interventions will be collected.

The history of cardiovascular and neurological diseases is assessed in the most detail.

The pharmacotherapeutic history should also be reviewed: currently used medications, their efficacy, possible side effects and intolerance.

Allergological history, allergen and manifestations of allergic reactions, facts of hospitalisations for allergic reactions and their dates should also be assessed.

Concomitant therapy will be evaluated at all visits.

4.2.1.2.4. Key vital signs

Heart rate (HR), respiratory rate (RR), and systolic and diastolic blood pressure (BP) will be measured after a 5-minute rest in a sitting position. HR and RR are assessed for 1 minute. Body temperature in the axilla will be measured.

Key vital signs will be measured at Screening and at Visits 1, 2, 4, 5 (or the Early Termination Visit).

4.2.1.2.5. Physical examination

The physical examination will include an assessment of all physiological systems of the body.

Organs and systems whose condition is assessed during the examination:

- General condition (satisfactory, moderate, severe, extremely severe, agonal).
- Skin and visible mucous membranes.
- Endocrine system.
- Lymphatic System.
- ENT organs.

- Respiratory system.
- Cardiovascular system.
- Gastrointestinal tract.
- Nervous system.
- Musculoskeletal system.
- Reproductive system.
- Urinary system.

Any new or worsened condition or impairment recorded during the course of the trial should be investigated as per the requirements of general practice and recorded as an adverse event.

The examination will be performed using standard technique at Screening and at Visits 1, 2, 4, 5 (or the Early termination visit).

4.2.1.2.6. Laboratory tests

Laboratory tests will be performed in local laboratories of the Investigational sites.

Any clinically significant abnormalities from laboratory parameters detected at post-administration visits should be considered an adverse event and recorded accordingly. Exceptions may be those changes that are classic signs of underlying disease.

Laboratory tests are performed during the Screening visit, Visit 2 and Visit 5 (or Early termination visit).

The total volume of blood taken from patients will be approximately 35 ml.

Complete blood count	**Biochemical blood test**	**Clinical urinalysis**	**Serological tests**
Haemoglobin Erythrocytes Platelets Leukocytes Haematocrit Leukocyte count formula ESR	ALT AST Glucose Creatinine Urea	pH protein; glucose ketone bodies erythrocytes and leucocytes epithelium	Syphilis Hepatitis B Hepatitis C HIV

- Pregnancy test with test strips, for women with preserved reproductive potential (Screening, Visits 2, 4, 5);

- Determination of the glomerular filtration rate using the Cockcroft-Gault formula (Screening only).

Results of serological tests performed earlier, but not later than 30 days before the patient's inclusion in the trial may be taken into account.

4.2.1.2.7. ECG

A 12-lead ECG will be performed using standard technique at the Screening Visit, Visit 2 and Visit 5 (or Early termination visit). An ECG will be recorded after the patient has been at rest for a minimum of 10 minutes. The ECG should be interpreted by a suitably qualified person.

4.2.1.2.8. Magnetic resonance computed tomography of the brain (MRI), computed tomography (CT)

MRI of the brain should be performed on a magnetic resonance tomograph with magnetic induction of at least 1.0 Tesla using the following modes: standard modes T2-, T1-weighted images - for general assessment of the brain substance;
T2-FLAIR (dark-fluid, d-f) and proton density mode - for differentiating lacunar infarcts and dilated perivascular spaces; FLΛIR mode suppresses the MR signal from free (cerebrospinal) fluid, which has a hypointense signal, thus improving visualisation of the ischaemic focus as well as focal changes in the white matter of the large cerebral hemispheres, especially those located periventricularly and subcortically; in proton density mode, dilated perivascular spaces are isointense to liquor; diffusion-weighted images - to exclude "acute" ischaemic focal changes in the brain substance;
T2*-weighted images - obtained using a gradient echo pulse sequence - are the most sensitive mode to deoxyhaemoglobin, with a strongly hypointense MR signal on the images; the need for such a study is to exclude small intracerebral haemorrhages and their consequences, especially those localised in the deep parts of the brain.
It is only performed at Screening. It may not be performed if there are MRI results available within the last 12 months.
Alternatively, a multispiral CT scan may also be performed instead of MRI.

4.2.1.2.9. Assessment of cognitive function

Cognitive function will be assessed using the Montreal Cognitive Function Assessment Scale (MoCA) [32]. It is conducted at Screening, Visits 1, 2, 4, 5 (or Early termination visit) - Appendix 2.

4.2.1.2.10. Quality of life assessment

General health will be assessed using the SF-36 health questionnaire. It is conducted at Visits 1, 4, 5 (or Early termination visit) - Appendix 3.

The SF-36 is a non-specific questionnaire for assessing patient quality of life that is widely used in quality of life studies in Europe and in the United States. The questionnaire consists of 36 items grouped into 8 scales: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, emotional well-being, and mental health. The scores of each scale range between 0 and 100, where 100 represents total health, all scales form two measures: mental and physical well-being [37, 38].

4.2.1.2.11. Assessing the level of depression

It will only be performed at Screening n the Hamilton Depression Rating Scale (HDRS) - Appendix 4. The scale was developed to quantify the severity of symptoms of depression [35]. The total score is determined from the first 17 items. The last four items of the Hamilton scale (18 to 21) are used to assess additional symptoms of depression and identify subtypes of depressive disorder and are not included in the calculation of the Hamilton scale total score, which determines the severity of depressive disorder.

Each item is scored from 0 to 2 or 0 to 4. The sum of all the scores makes up the total score, which is used to quantify the severity of depression.

The cumulative score of the first 17 items:

- 0-7 - norm
- 8-13 - mild depressive disorder
- 14-18 - moderate depressive disorder
- 19-22 - major depressive disorder
- more than 23 - depressive disorder of extreme severity

4.2.1.2.12. Assessment of asthenic disorders using the MFI-20

MFI-20 (Smets E.M. etal. 1995). It is used to obtain a subjective quantitative assessment of the overall severity of asthenia and its various manifestations [33, 34, 53]. The scale contains 20 statements within a structure of 5 subscales: general asthenia (statements 1, 5, 12, 16), physical asthenia (statements 2, 8, 14, 20), decreased activity (statements 3, 6, 10, 17), decreased motivation (statements 4, 9, 15, 18), and mental asthenia (statements 7, 11, 13, 19). Each of the listed subscales has 5 cells expressing some degree of compliance with each specific statement (from 1 to 5 points). The maximum score (5 points) indicates the highest severity of asthenia. The subscale score is the sum of the scores of its individual items, with variations ranging from 4 to 20 points. A total score of more than 12 points on at least one subscale, as well as a total score of more than 60, diagnoses clinically pronounced asthenia. Asthenic disorders are considered absent when the total score is less than 24 (Appendix 5). Statistical processing will calculate the score for each statement. For statements 1, 3, 4, 6-8, 11, 12, 15, 20 for cells 1-5 when calculating from left to right correspond to points from 1 to 5 (cell 1=1 point, 2=2 points, 3=3 points, 4=4 points, 5=5 points), for statements 2, 5, 9, 10, 13, 14, 16-18, 19 the reverse calculation is made: cell 1=5 points, 2=4 points, 3=3 points, 4=2 points, 5=1 point) [53]. It is conducted at Visits 1, 4, 5 (or Early termination visit)

4.2.1.2.13. Assessment of autonomic changes using the Wein questionnaire

To assess the autonomic changes, a scoring questionnaire developed by A.M. Vein et al. at I.M. Sechenov Moscow Medical Academy will be used, which includes 11 main signs of autonomic disorders [36]. The presence of each of the autonomic symptoms is assessed by a specific score from 7 to 3. The final sum of points reflecting the degree of severity of vegetative dystonia is calculated (Appendix 6). It is conducted at Visits 1, 4, 5 (or Early termination visit)

4.2.1.2.14. Assessment of anxiety level on the Beck scale

The Beck Anxiety Scale is a clinical test method designed to screen anxiety and assess its severity [33]. The questionnaire consists of 21 items. Each item includes one of the typical symptoms of anxiety, bodily or mental. Each item should be rated by the respondent from 0 (symptom did not bother) to 3 (symptom bothered very much).

The scale is a simple, easy-to-use instrument for the preliminary assessment of anxiety disorder severity in a wide range of individuals: young people from 14 years of age, mature and elderly, clinic contingent and in screening studies. Filling out the scale takes no more than 10 minutes, and can usually be entrusted to the test taker. Individuals who score high on the scale should be referred for specialist counselling.

The scale is usually used in occupational examinations, when it is necessary to distinguish the contingent that needs more detailed examination and counselling of a specialist, in clinical practice, when there is a suspicion that somatic disorder is comorbid with anxiety (including interdependent).

Scoring is done by simply summing the scores for all items on the scale. A value between 0 and 9 points inclusive indicates no anxiety (normal condition). A value of 10 to 18 points inclusive indicates a mild to moderate degree of anxiety. A value between 19 and 29 points inclusive indicates a moderate to severe degree of anxiety. A value of 30 or more points (with a maximum of 63 points) indicates a severe degree of anxiety.

The questionnaire is presented in Appendix 7. It is conducted at Visits 1, 4, 5 (or Early termination visit)

4.2.1.2.15. Digital Symbol Substitution Test

DSST (Digital Symbol Substitution Test) assesses information processing speed, concentration and maintenance of attention and working memory. The legend contains 9 digit-symbol pairs. This is followed by a sequence of digits, under each of which the test taker must write the corresponding symbol within 90 s. The total number of correct pairs is determined [50], Appendix 8. It is conducted at Visits 1, 4, 5 (or Early termination visit)

4.2.1.2.16. Tinetti Motor Activity Scale

The scale includes an assessment of both balance and walking. Equilibrium parameters are scored on a scale from 0 to 2, where 0 corresponds to the concept of "impossible to fulfil", 1 to “fulfilled incorrectly", and 2 - "norm". Walking tests are scored 0 or 1, depending on incorrect or normal performance. Initially, the patient's condition should be assessed using two scales: "General stability" and "Gait." The total cumulative score should then be calculated and the degree of impairment of the patient's general motor activity should be determined [49], Appendix 9. It is conducted at Visits 1, 4, 5 (or Early termination visit)

4.2.1.2.17. DSM-5 score

Symptoms are assessed using the revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association DSM-5 (APA, 2013) [48]. It is only performed at Screening.

4.2.1.2.18. Clinical Global Impressions Scale (CGI)

The CGI scale is an assessment tool developed in schizophrenia research to enable the clinician to quantify the severity of the illness and the degree of improvement over the course of therapy.

The CGI scale is described in detail in W.Guy (1976) [51], Appendix 10. It is presented as suitable for assessing any trial population. For disease severity, the time interval assessed is defined as "now or within the last week"; for overall improvement, it is defined as "since first assessment". It is performed at Visits 1, 2, and 5.

4.2.1.2.19. Patient diary

At Visit 1, a diary will be given to each patient immediately after randomization. Careful patient trainin on how to complete the diary will be provided. In the diary, the patient will record each dose of medication (both parenteral and oral forms) administered/taken.
At Visits 2 and 4 the correct completion of the patient diary will be assessed, at Visit 5 (or the Early termination visit) the diary should be returned to the investigator.

4.2.1.2.20. Compliance assessment

Compliance with the prescribed therapy will be assessed at the end of the trial by analysing the diary data (the summary result of the data will be reported in the eCRF) and counting the amount of drug residue. A compliance rate of more than 80% is considered an adequate level of compliance [39 - 41]. Deviations of ±1 hour from the preset administration/dosing time are allowed, deviations beyond this interval are considered deviations from the protocol.

4.2.1.2.21. Contraceptive regimen during the trial

Women are eligible for participation in the trial if they:

- Are incapable of childbearing (i.e. physiologically unable to become pregnant, including postmenopausal women or after surgical sterilisation). Surgically sterile women were defined as patients with documented hysterectomy and/or bilateral ovariectomy or fallopian tube ligation. Postmenopausal women are defined as women with amenorrhoea for more than 1 year with an appropriate clinical profile, e.g. age >45 years, in the absence of hormone replacement therapy.

or

- Are capable of childbearing, but the pregnancy test is negative at the time of the Screening visit and the patient agrees to use sexual abstinence at all times and correctly (starting from screening and for 4 weeks after the trial). Reliable contraceptive methods include: double barrier method or single barrier method combined with a spermicidal agent, intrauterine contraceptive or oral contraceptives, complete abstinence from sexual activity for the duration of the trial.

Female patients taking part in the trial, in case of pregnancy, and male patients, in case of pregnancy of their partner, are obliged to inform the investigator.

4.2.1.3.Trial phases

Screening period (Visit 0) up to 7 days:
Collection of baseline patient information and assessment of inclusion/non-inclusion criteria.
All relevant information on diseases and demographics at the beginning of the trial are recorded in the patient's source documentation and then transferred to the CRF. The duration of the screening is no more than 7 days.
The following activities are performed during the screening visit:

- Informed Consent signing
- Collection of the patient's subjective complaints
- Physical examination
- Collection of demographic and anthropometric data
- Collection of medical and pharmacotherapeutic history
- Measurement of BP, HR, RR, body t°
- 12-lead ECG
- Complete Blood Count
- Biochemical blood test

- Determination of the glomerular filtration rate
- Clinical urinalysis
- Pregnancy test
- Blood tests for HIV, syphilis, hepatitis B and C
- Head MRI/CT (if not done in the last 12 months)
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ HDRS
  - ✓ DSM-5
- Assessment of inclusion/non-inclusion criteria

Visit 1- randomization

Randomisation and day 1 of therapy. The visit is conducted no later than 7 days from visit 0, by which time the results of laboratory and instrumental examination methods should be prepared and evaluated.

During the first visit, eligibility for inclusion/non-inclusion criteria is checked based on the laboratory results and other indicators obtained. Patients meeting the inclusion/non-inclusion criteria will be assigned to one of 2 treatment groups by randomisation.

During the visit, the following procedures are carried out according to the trial design scheme:

- Physical examination
- Collection of the patient's subjective complaints
- Measurement of BP, HR, RR, body t°
- Assessment of inclusion/non-inclusion criteria
- Randomization
- Administration of the IP by IV drip in 100-200 ml of 0.9% solution/IV bolus slowly
- Evaluation of concomitant therapy
- Evaluation of exclusion criteria;
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ SF-36
  - ✓ MFI-20
  - ✓ Wein questionnaire
  - ✓ Beck Anxiety Rating Scale
  - ✓ Digit Symbol Substitution Test
  - ✓ Tinetti test
  - ✓ Clinical Global Impressions Scale

- Assessment of adverse events (after the first administration of the IP)
- Issuance of the diary and training in its completion

Visit 2

Visit 2 is performed on day 14, after the last intravenous injection of the IP. This visit is the end of parenteral therapy. During the visit, the following procedures are carried out according to the trial design scheme:

- Physical examination
- Collection of the patient's subjective complaints
- Measurement of BP, HR, RR, body t°
- 12-lead ECG
- Complete Blood Count
- Biochemical blood test
- Clinical urinalysis
- Pregnancy test
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ SF-36
  - ✓ MFI-20
  - ✓ Wein questionnaire
  - ✓ Beck Anxiety Rating Scale
  - ✓ Digit Symbol Substitution Test
  - ✓ Tinetti test
  - ✓ Clinical Global Impressions Scale
- IP administration by IV drip in 100-200 ml of 0.9% NaCl solution/ IV bolus (last administration)
- Dispensing of oral medication
- Evaluation of concomitant therapy
- Evaluation of exclusion criteria;
- Assessment of adverse events
- Checking that the patient diary has been filled in correctly

Visit 3

Visit 3 is performed on 28±2 days after the start of therapy. This visit is done through telephone contact. During the visit, the following procedures are carried out according to the trial design scheme:

- Collection of the patient's subjective complaints
- Evaluation of concomitant therapy
- Evaluation of exclusion criteria;

- Assessment of adverse events

Visit 4

Visit 4 is carried out on day 44±2 of treatment. The following procedures are carried out according to the trial design scheme:

- Physical examination
- Collection of the patient's subjective complaints
- Measurement of BP, HR, RR, body t°
- Pregnancy test
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ SF-36
  - ✓ MFI-20
  - ✓ Wein questionnaire
  - ✓ Beck Anxiety Rating Scale
  - ✓ Digit Symbol Substitution Test
  - ✓ Tinetti test
- IP take-back and compliance assessment
- Dispensing of oral medication
- Evaluation of concomitant therapy
- Evaluation of exclusion criteria;
- Assessment of adverse events
- Checking that the patient diary has been filled in correctly

Visit 5

Visit 5 is performed on day 75+2 after initiation of therapy. This visit is the final one. During this visit, the following procedures are performed according to the trial design scheme:

- Physical examination
- Collection of the patient's subjective complaints
- Measurement of BP, HR, RR, body t°
- Complete Blood Count
- Biochemical blood test
- Clinical urinalysis
- Pregnancy test
- 12-lead ECG
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ SF-36

- ✓ MFI-20
- ✓ Wein questionnaire
- ✓ Beck Anxiety Rating Scale
- ✓ Digit Symbol Substitution Test
- ✓ Tinetti test
- ✓ Clinical Global Impressions Scale

- IP take-back and compliance assessment
- Evaluation of concomitant therapy
- Evaluation of exclusion criteria;
- Assessment of adverse events
- Returning and checking that the patient diary has been completed correctly

Allowable and recommended intervals between visits: the time between screening and visit 1 (i.e. the start of treatment) should be no more than 7 days. There should be no deviations from the timing of visits 1, 2. Allowable deviations from the timing of visits 3 - 5 shall not exceed 2 days.

4.2.1.4.Early termination

In case of early withdrawal from the trial, the patient must complete all procedures according to the schedule of the premature Trial Termination Visit.

4.2.1.5.Early withdrawal visit

If for any reason the patient drops out of the Trial, the physician should make every effort to carry out procedures for early withdrawal visit, namely:

- Physical examination, assessment of vital signs (BP, RR, HR, t°)
- Collection of the patient's subjective complaints
- 12-lead ECG
- Complete Blood Count
- Biochemical blood test
- Clinical urinalysis
- Pregnancy test
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ SF-36
  - ✓ MFI-20

- ✓ Wein questionnaire
- ✓ Beck Anxiety Rating Scale
- ✓ Digit Symbol Substitution Test
- ✓ Tinetti test
- ✓ Clinical Global Impressions Scale

- IP take-back and compliance assessment
- Evaluation of concomitant therapy
- Evaluation of exclusion criteria;
- Assessment of adverse events
- Returning and checking that the patient diary has been completed correctly

4.2.1.6.Unscheduled visit

This visit is conducted when patient safety is a concern. It may also be conducted when a patient has questions about trial procedures and/or other questions related to the disease or treatment. The procedures for an unscheduled visit depend on the reasons that led to the need for the visit. The investigator determines the scope of the procedures to be performed individually in each case, depending on the situation.

4.3.Measures to minimise subjectivity

During Visit 0 (screening), all patients who preliminarily fulfil the inclusion criteria are given detailed information about the trial. After signing the Patient Information Sheet with the Informed Consent Form, each patient is assigned a unique four-digit screening number.

Screening Number Structure:

1 - serial number of the investigational site according to the permission to conduct a clinical trial issued by the Ministry of Health of the Russian Federation.

2 - number reflecting the order of priority of inclusion of patients in the trial in each particular investigational site.

For example:

At investigational site 2, the fifth patient was included in the trial. This trial participant should be assigned a screening number **0205**, where 02 is the site number and 05 is the serial number of the patient included in the trial at this investigational site.

During Visit 1, all patients meeting all inclusion criteria and not meeting any non-inclusion criteria will be randomized and assigned a three-digit randomization number.

Distribution of patients into 2 groups in a 1:1 ratio (Investigational product: Placebo) will be conducted according to the randomization design of the clinical trial protocol. The randomization scheme will be generated as a separate document and will not be an Appendix to the trial protocol.

Randomization by electronic system (IWRS).

Assigning a randomization number to each patient will be done using a special interactive system with internet access. Users will receive training and a user manual to gain proficiency with the system.

The trial will use a competitive patient recruitment. The number of patients included on the basis of each specific investigational site is not regulated. Patient enrollment will stop simultaneously at all sites after randomization of the 318th patient, and the trial physicians will be notified immediately.

If a patient discontinues participation in the clinical trial early, **his/her randomization number will not be re-used** and the withdrawn patient cannot subsequently be included in the trial. For patients who withdraw from the clinical trial prematurely, the investigator must complete the appropriate section of the CRF.

Patient enrollment will be on a competitive basis.

The patient code is indicated in documents for use outside the investigational site (CRFs, SAEs reports, etc.). The assigned patient code is entered into the CRF and related forms. The patient code does not change during the course of the trial. The randomization plan is stored for control access. Trial personnel are responsible for ensuring compliance with randomization.

4.4. Therapy, dosages and administration regimens of the investigational products. Packaging and labelling

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

Group 1 will receive the following therapy: Mexidol in the pharmaceutical form "solution for intravenous and intramuscular administration" in the dosage of 500 mg (10 ml) by IV drip in 100-200 ml 0.9% NaCl solution/ IV bolus OD (daily dose 500 mg) for 14 days; then Mexidol FORTE 250 in the dosage form "film-coated tablets" in a dosage of 250 mg (1 tablet) TID (daily dose 750 mg) for 60 days.

Group 2 will receive the following therapy: Placebo in the dosage form "solution for intravenous and intramuscular injection" 10 ml by IV drip in 100200 ml of 0.9% NaCl solution/IV bolus slowly OD for 14 days; then Placebo in the dosage form "film-coated tablets" 1 tablet TID for 60 days.

Intravenous injections will be administered in a clinical centre setting following all aseptic and antiseptic rules. Tablets will be self-administered by the patient.

A description of the dosage forms is provided in the section **"Name and Description of Investigational products".**

The medicinal products used in this trial will be delivered to the investigational sites in the required quantity and under temperature controlled conditions.

Labelling of investigational medicinal products must comply with the Order of the Ministry of Industry and Trade of Russia dated 14.06.2013 N 916 (ed. 18.12.2015) "On Approval of the Rules of Good Manufacturing Practice". It should be stated on the packages:

- name, address and telephone number of the Sponsor, the legal entity engaged by the Sponsor to organize the conduct of the clinical trial (contract research organisation) or the investigator (primary contact person for information regarding the medicinal product, clinical trial and for emergency decoding);
- dosage form, route of administration, number of dosage units, and in case of an open trial - name and (or) code of the medicinal product and its dosage and (or) activity;
- batch number and/or code to identify the contents and the packaging operation;
- trial number (code) to identify the trial, medical organisation, investigator and Sponsor, unless specified elsewhere;
- patient identification code and visit number (if available);
- directions for use (reference may be made to a leaflet or other explanatory document intended for the patient or the person administering the medicinal product);
- inscription: "For clinical trials";
- storage conditions;

- period of use, specifying the month and year in such a way as to avoid any uncertainty (the date by which the medicinal product is to be used for clinical studies, the expiry date or the date of re-control may be specified);
- "Keep out of reach of children".

The address and telephone number of the primary contact person for communicating information regarding the investigational product, clinical trial may be omitted from the label if the subject has been provided with instructions for use or a card on which these data are indicated and instructed to keep them with him or her at all times.

Symbols or pictograms may be used to explain the above information. Additional information, cautions and/or instructions on how to handle the medicine may be provided.

The data must be given in Russian, must be on both trial staff and secondary packaging. Labels may also include information in other languages.

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).

4.5.Expected duration of subjects' participation in the trial

Screening - up to 7 days.

Parenteral therapy - 14 days.

Oral therapy - 60 days.

Taking into account a possible deviation of 2 days from the date of the last scheduled Visit (Visit 5, Day 75+2), the duration of patient participation in the trial will be up to 83 days.

4.6.Rules for trial termination Completion of the trial

The Sponsor or the Investigator may temporarily or permanently stop the conduct of the trial for safety or other reasons (in accordance with Article 40 of Federal Law No. 61-FZ dated 12.04.2010 "On Circulation of Medicines", as amended by Federal Law No. 192-FZ dated 27.07.2010, No. 271-FZ dated 11.10.2010, No. 313-FZ dated 29.11.2010). Should such a need arise, the Sponsor will take steps to notify the investigational site in advance. If the trial is suspended or terminated, the Sponsor and Investigator must inform the Local Ethics Committee and regulatory authorities in a timely manner.

The Principal Investigator may suspend or terminate the trial for other reasons without prior consent of the Sponsor, but must notify the Sponsor as soon as possible (within 24 hours) and provide the Sponsor with a written explanation of the reasons for the suspension or termination of the trial.

In any case, the Investigator is obliged to inform the trial subjects immediately of the suspension or termination of the trial and to provide them with appropriate treatment and supervision.

The trial may be terminated by decision of the authorized federal executive body based on a report from the head of the medical organisation or the Sponsor.

The patient must be excluded from the trial directly by the investigator for the reasons listed below:

1. Patient's inability or refusal to follow the requirements of the protocol.
2. Withdrawal of informed consent by the patient or his/her legal representative.
3. Need for additional therapy not permitted under this protocol.
4. 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.
5. Need for surgical intervention.
6. Patient noncompliance with trial procedures.
7. Any patient condition that, in the reasonable judgement of the investigator, requires the patient to be withdrawn from the trial.

4.7. Accounting for trial medications

The investigational product and comparator product for the trial will be transferred by the Sponsor/organization conducting the trial to the investigational sites conducting the trial, under temperature control, with a bill of lading confirming delivery of the medicinal products.

Delivery of the investigational/comparator product is documented by the investigator or other responsible persons on protocol-specific forms indicating the quantity, batches and expiry date of the medicinal product transferred. These forms will be submitted to each investigational site by the organization conducting the clinical trial prior to the actual start of the trial.

Medicinal products delivered to the investigational site will only be used for the purposes of this clinical trial in strict accordance with the clinical trial protocol.

All unused product and empty packages of the used product will be returned to Sponsor.

The investigator or other authorized persons will keep records of the investigational product. It is the responsibility of the investigator to ensure that the investigational/comparator product:

- is used only by patients in this trial;
- is stored in a locked and secure, temperature-controlled location that is accessible only to staff who are participating in the trial;
- is strictly accounted for, the medicinal product record is documented on forms provided by the organization conducting the trial, indicating the patient to whom the medicinal product was dispensed/administered, the dates of dispensing/administration, the number of packs dispensed and returned by the patient. Empty packs and unused product will be retained and returned to the Sponsor.

Delivery and return of the medicinal product must be signed by the responsible person, the acts must specify the quantity, expiry date and batches of the transferred medicinal product. Counts of investigational/comparator product must be documented throughout the trial.

4.8.Storage of randomization codes and procedure for their disclosure

The double-blinding condition is observed throughout the trial.

The following measures will be used in order to implement a blind trial design and to prevent both patients and the investigator from being aware of the product being administered:

– identical labelling of medicines given to patients;

– use of the code tampering procedure using the unblinding procedure in IWRS.

Fully automated web-based communications - IWRS - are used to perform centralized randomization. The system shall provide the investigator with the ability to randomize the subject according to the randomization requirements. The investigator should not be able to see the treatment group assigned to a subject as a result of randomization.

The IP codes remain unknown to the Investigator until the database is closed. 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. The system shall allow a user with appropriate rights to enter all required parameters to perform the subject unblinding procedure. The treatment code for any patient may only be opened by the investigator or a person authorized by the investigator if it is absolutely necessary to establish the true nature of the intervention received. If it is necessary to obtain information about ongoing therapy if an adverse event develops, it can be obtained by using the unblinding procedure in the IWRS. Blinding can only be removed if the patient's choice of subsequent treatment depends on the product the patient has been taking.
The investigator should make every effort to contact with the trial coordinator before uncovering the patient's therapeutic group code. In case of de-masking (code breaking), a representative of the CRO/Sponsor should be notified immediately by telephone.

4.9.List of data recorded directly in the CRF

Source data are medical documents containing original medical records, copies of previous medical examination, results of clinical-instrumental and laboratory examination of patients, which allow to reconstruct the course of clinical examination and evaluate it. If it is necessary to keep copies of documents, they must be appropriately certified.
All source information received, including information about AEs/SAEs or pregnancy, will first be entered into source documentation and then transferred to the CRF. The CRF will not contain data not reflected in the source documents (if applicable).
Completed CRFs will be checked against the source data by the CRA. All deviations and errors will be corrected by the investigator and reflected in the CRA’s report.

5. SELECTION AND EXCLUSION OF SUBJECTS

5.1.Inclusion criteria

1. Patients of either gender between the ages of 40 and 90 years inclusive.
2. MoCA scale score up to and including 25 points.
3. Patients meeting the criteria for diagnosis: Mild (moderate) cognitive impairment when assessed by DSM-5.

4. Chronic cerebral ischaemia (ICD-10 code 167.8).
5. Presence of foci of leukaemia or "silent" brain infarcts documented by MRI/CT performed within the last 12 months
6. Patients who provided informed consent to participate in the trial.
7. Duration of clinical signs of progressive multifocal or diffuse brain damage from 1 to 5 years according to the history.
8. Patients with unchanged dose and combination of drugs of basic therapy including (if indicated for use): antiaggregant therapy, therapy of cerebral atherosclerosis and arterial hypertension, ischaemic heart disease and other chronic diseases during the previous month.
9. Negative pregnancy test.
10. Patients who agreed to use a reliable method of contraception during the trial until the end of the trial (for women of childbearing potential, including partners of trial participants).
11. Patients who are able to understand the requirements of the trial and who agree to all restrictions imposed by the trial.

5.2.Inclusion criteria

1. Any diagnosis of a disease less than 6 months prior to inclusion that may cause symptoms similar to the nosology being investigated.
2. Intolerance to any of the components of the investigational products in the history.
3. Ischaemic stroke less than 12 months prior to inclusion in the trial.
4. Alzheimer's disease, neurodegenerative brain diseases, Parkinson's disease, multiple sclerosis, demyelinating diseases of the nervous system, hereditary degenerative diseases of the CNS, developmental abnormalities of the nervous system, uncontrolled epilepsy, other neurological disorders severely affecting motor or cognitive function, as judged by the investigator based on anamnesis.
5. Haemorrhagic stroke.
6. Mental disorders (F20-F48 (schizophrenia, schizotypal states and delusional disorders), F60-F69 (personality and behavioural disorders in adulthood) according to ICD-10) based on anamnesis.
7. Depression level on the Hamilton Depression Rating Scale (HDRS) at screening ≥14 points.
8. Need for neck or cerebral vascular surgery, including endovascular interventions, during the trial.
9. Evidence of a significant uncontrolled co-morbidity that, in the opinion of the Investigator, would preclude the patient's participation in the trial, including:

- Respiratory system disorders;

- Cardiovascular disorders;
- Severe impairment of renal function (glomerular filtration rate <30ml/min);
- Severe liver function impairment (ALT, AST activity> 2 times ULN);
- Endocrine disorders;
- Gastrointestinal disorders.

10. Systemic autoimmune diseases or vascular collagenosis requiring previous or current treatment with systemic corticosteroid drugs, cytostatics or penicillamine; malignant neoplasms within the last 5 years (except basal cell carcinoma).
11. Diagnosed cancer, including a history of cancer.
12. Use of drugs classified as prohibited in the 30 days prior to inclusion in the trial.
13. Hypersensitivity or intolerance to any components used in this Investigational product based on anamnesis.
14. Alcohol or drug dependence based on anamnesis.
15. Pregnancy, lactation period
16. Participation in other clinical studies within 90 days prior to the screening visit based on medical history.
17. A positive result of at least one of the following tests: blood tests for HIV, syphilis, hepatitis B and C.
18. Lactose intolerance, lactase deficiency, glucose-galactose malabsorption.

5.3.Exclusion criteria

5.3.1. Criteria for exclusion from the trial

1. Erroneous inclusion (violation of inclusion and non-inclusion criteria).
2. A decision by the Investigator or Sponsor to exclude a patient from the trial due to a clinically significant protocol deviation/protocol violation.
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. Any adverse event (may not be related to the investigational product) requiring follow-up, procedures and/or medication not authorized by the protocol of this trial.
5. Patient refusal to continue participation in the trial or patient indiscipline.
6. An allergic reaction when using investigational products that requires their cancellation.
7. The patient's desire to terminate the trial early for any reason.
8. Loss of contact with the patient followed by failure to attend the visit.

9. The need to take therapies prohibited by this protocol: nootropic drugs, ethylmethylhydroxypyridine succinate, trimetazidine or meldonium, drugs affecting the function of the autonomic nervous system and other drugs that may, in the opinion of the investigator, distort the results of the trial.
10. Pregnancy.

5.3.2. List of excluded patient data and timelines for data collection

All cases and reasons for premature termination of participation in the trial are recorded in writing by the investigator in the source documentation and the CRF.
When a patient is excluded from the trial by the investigator, every effort must be made to carry out all procedures of the early termination visit. When a patient withdraws informed consent, the investigator should make every effort to find out the reason.
When a patient is excluded due to an AE/SAE, recording and reporting should follow the procedures described in Section 7.2. If the withdrawal from the trial was due to a SAE, the procedure for immediately notifying the Sponsor on the SAE must be followed.
For excluded patients, all the data required by the trial protocol are collected to the extent of visits and procedures completed by the patient within the same timeframe as for patients who completed the trial according to the protocol.

5.3.3. Replacement of withdrawn patients

Up to 350 subjects are planned to be screened and included (randomized) into two groups of 159 patients each (318 patients in total) in the Trial (phase I). There is no provision for replacement of patients who drop out after randomization.

5.3.4. Follow-up of excluded patients

Follow-up of patients excluded after receiving at least one dose of trial medication should be conducted within 14 days after dropout in the same manner as for the main group of patients. However, only those parameters responsible for the safety of the therapy will be analysed (i.e. efficacy criteria will not be assessed). The safety criteria under investigation are described in the Safety Assessment section.

5.4.TREATMENT OF TRIAL SUBJECTS

Therapy used and duration of trial phases

Section 2.5 provides a description of the treatment regimen with the investigational products. Medicinal products should only be used in accordance with the information provided in the protocol.

In intravenous drip method of administration, the investigational product Mexidol ®/ Placebo should be diluted in 100-200 ml of 0.9% sodium chloride solution.

5.5.Concomitant therapy

Patients with unchanged dose and combination of drugs of basic therapy including (if indicated) antiaggregant therapy, therapy of cerebral atherosclerosis and arterial hypertension, ischaemic heart disease and other chronic diseases (during the previous month) should be included in the trial.

Prescribing drugs for comorbid conditions is possible, standardization of therapy is determined by routine medical practice approaches. In this clinical trial, baseline therapy and therapy for comorbid conditions may be continued along with the administration of the investigational product, with the exception of drugs whose administration would result in the patient being excluded from the trial.

Prohibited drugs and/or dietary supplements include:

1. psychotropic drugs (antidepressants, tranquillisers, etc.).
2. preparations containing succinic acid and its salts (including reamberin, remaxol, cytoflavin).
3. preparations containing vitamin B6 and/or its derivatives.
4. drugs belonging to the groups of antioxidants and antihypoxants (including drugs - derivatives of 3-hydroxypyridine: emoxipin, mexicor, mexiprim, mexifin, medomexy, mexidant, mexipridol, metostabil, neurox, cerecard, ethoxidol, etc.).
5. 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, biotredine.
   - ✓ GABA derivatives and analogues: γ-aminobutyric acid, nicotinoyl-GABA, γ-amino-R-phenylbutyric acid hydrochloride, gopantenic acid, pantogam, calcium γ-hydroxybutyrate.
   - ✓ ginkgo biloba preparations and its derivatives.
   - ✓ neuropeptides and their analogues with nootropic action.
   - ✓ 2-mercanthobenzimidazole derivatives: ethylthiobenzimidazole hydrobromide.
   - ✓ polypeptides and organic composites: cattle cerebral cortex polypeptides, cerebrolysin.
   - ✓ correctors of cerebral circulation disorders - vinpocetine, xanthinol nicotinate, vincamine, naphthidrofuryl, cinnarizine; combined drug Instenon.
   - ✓ general tonic agents and adaptogens of plant origin.
   - ✓ preparations containing acetylaminoanthartaric acid.

5.6.Methods of monitoring compliance with procedures

All used and unused primary/secondary packaging will be subject to inventory.

Parenteral administration of IPs will be carried out by authorized medical staff. The tablet form of the medication will be self-administered by the patient. Complacency will be assessed at Visits 4 and 5 by counting the number of tablets taken / drug residue.

Compliance with trial restrictions and procedures will be monitored based on patient anamnestic data.

5.7.Deviations from protocol

In general, any deviation from the protocol may be accepted only in an urgent case or after obtaining written agreement from the Sponsor and subject to approval by the Ethics Committee. Any deviation from the protocol should be clearly explained in the source documentation and in the CRF.

All deviations from the protocol are categorised into "Significant" and “Nonsignificant".

Significant deviations from the protocol will render the resulting data unusable for analysis. A patient with significant deviation from the protocol should be excluded from the final analysis.

A nonsignificant deviation from the protocol may reduce the quality of the data for analysis, but the data can still be used.

Significant deviations from protocol include, but are not limited to, the following list:

- taking medications not prescribed in the protocol.
- significant deviations from visit schedules, including skipping any visit.
- significant deviation from the visit procedures that may meaningfully affect the interpretation of the results of the efficacy and safety assessment).
- detection of missed administration of prescribed medication (compliance less than 80% for parenteral therapy and less than 80% for oral therapy).
- inclusion in the trial of a patient who does not fulfil the inclusion and non-inclusion criteria of the protocol.
- performing trial procedures before obtaining written informed consent from the patient.
- other relevant abnormalities in the opinion of the investigator or Sponsor.

If a situation of direct threat to the patient's life occurs during the trial and additional administration of any medication other than approved medications is required, the CRA and the Trial Sponsor must be informed of the protocol deviation within 24 hours.

In this case, a patient who additionally received drugs not authorized by the protocol should be excluded from the final analysis.

Observation by the investigator will continue until the condition that caused the protocol violation has ceased.

Nonsignificant deviations from protocol

All other deviations that are not significant, do not affect patient safety, and do not substantially interfere with the procedures of the protocol.

Classification of protocol deviations into nonfignificant deviations and significant deviations will be made by the Sponsor's authorized representatives upon submission of data on the facts of deviations from the Protocol (according to monitoring reports and other sources). A full list of protocol deviations will be approved prior to statistical analysis and allocation of patients to populations for analysis. Deviations from the Protocol are always dealt with on a case-by-case basis, with analysis of the causes, which should be recorded in the source documentation. The decision to exclude a patient with abnormalities and Protocol violations from the trial must be made on a case-by-case basis in consultation with the Trial Sponsor.

The decision to include these patients' data in the statistical analyses is made before the trial database is closed.

If significant deviations from the protocol are found, the patient should be excluded from the final data analysis.

Changing the format of clinical trial visits during a pandemic

In connection with the declaration by the World Health Organization of a pandemic of a new type of coronavirus COVID-19, the introduction of a high alert regime in the Russian Federation and taking into account the current situation in the subjects of the Russian Federation, taking into account Letter of the Ministry of Health of the Russian Federation dated 27.03.2020 № 20-1/I/2-3651 and the recommendations of the Guidelines for clinical studies during the COVID-19 (Coronavirus) pandemic, which allow for changes to be made to the trial procedures by the clinical trial organizers together with the investigators and local ethics committees; in the interests of the clinical trial participants to ensure patient safety, compliance with the treatment regimen in the trial patients, and to maintain the integrity of the clinical trial itself, changes to the format of some trial procedures are permitted. During a pandemic, alternative ways of conducting Visits (telephone contact, virtual visits; home visits, home delivery of medicines, biosamples and home ECGs) and rescheduling of Visits may be used.

The following visits may be performed at the patient's home: visit 4, visit 5, early termination visit.

The following procedures may be performed at patient's home as part of these visits:

- Collection of the patient's subjective complaints
- Physical examination
- Measurement of BP, HR, RR, body t^0 *(using mobile devices)*
- ECG in 12 leads (using a mobile device)
- Complete Blood Count
- Biochemical blood test *(with home sampling)*
- Clinical urinalysis *(with home biosampling)*
- Pregnancy test (for women with preserved reproductive potential) *(with home biosampling)*
- Evaluation of scales and indices:
  - ✓ MoCA
  - ✓ SF-36
  - ✓ MFI-20
  - ✓ Wein questionnaire
  - ✓ Beck Anxiety Rating Scale
  - ✓ Digit Symbol Substitution Test
  - ✓ Tinetti test
  - ✓ Clinical Global Impressions Scale
- Assessment of adverse events (starting from the first administration of the IP)
- Evaluation of exclusion criteria;
- Assessment of inclusion/non-inclusion criteria
- IP take-back and compliance assessment
- Dispensing of oral medication
- Checking that the patient diary has been filled in correctly
- Returning and checking that the patient diary has been completed correctly

All procedures, despite the modified format, must be carried out under appropriate conditions (IP transfer and biosample transfer under specific temperature conditions, source documentation with confidentiality conditions, etc.).

Any changes in the format of procedures (from face-to-face to distance/remote) must be recorded in the source documentation of the investigational site.

6. EFFICACY EVALUATION

6.1.List of efficacy parameters

Evaluation of the efficacy of therapy will be based on primary and secondary efficacy criteria.

Primary efficacy criterion:

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

Secondary efficacy criteria:

- dynamics of the severity of cognitive impairment on the MoCA scale between Visit 0 and Visits 2 and 4.
- dynamics of patients' quality of life according to the SF-36 questionnaire between Visit 1 and Visits 2, 4, 5.
- dynamics of asthenic disorders severity according to the MFI-20 between Visit 1 and Visits 2, 4, 5.
- dynamics of anxiety level on Beck scale between Visit 1 and Visits 2, 4, 5.
- dynamics of autonomic changes according to the Wein questionnaire between Visit 1 and Visits 2, 4, 5.
- dynamics of cognitive impairment by the Digit Symbol Substitution Test between Visit 1 and Visits 2, 4, 5.
- dynamics of motor changes on the Tinetti test between Visit 1 and Visits 2, 4, 5.
- dynamics of the Clinical Global Impressions Scale (CGI) between Visit 1 and Visits 2, 5.

6.2.Methods and timeframes for estimating, recording and analysing efficacy parameters

For statistical analysis of quantitative signs, it is preliminary necessary to assess the compliance with the law of normal distribution by the Shapiro-Wilk criterion. For indicators whose distribution conforms to the law of normal distribution, the arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, variation spread will be calculated as parameters of descriptive statistics. For indicators whose distribution will differ from normal, the median, 25th and 75th percentiles, minimum and maximum values, and interquartile range will be calculated as parameters of descriptive statistics. In order to test the hypothesis of homogeneity of variance, Levene's test will be applied. When testing statistical hypotheses, parametric criteria will be used for indicators that have a normal distribution, and non-parametric criteria will be used for indicators with distribution other than normal. Comparison of groups on quantitative traits can be done using Student's T-test and Mann-Whitney test. Comparisons between pre- and post-treatment rates within groups can be made using the T-test for related samples, or the Wilcoxon test. Qualitative traits can be analysed using Pearson's $\chi 2$ criterion, the $\chi 2$ criterion with Yates correction and Fisher's exact test (if the frequency of a trait in at least one of the subgroups is 5 or less). Differences with p values of <0.05 will be considered statistically significant.

All efficacy parameters will be evaluated after completion of the clinical part of the trial and finalisation of the electronic database.

7. SAFETY ASSESSMENT

7.1. List of safety parameters

The following **safety assessment parameters** are provided by this protocol:

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

7.2. Methods and timelines for assessing, recording and analysing safety parameters

7.2.1. Definition of an adverse event

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

A **new condition** or **worsening of an existing** condition will be treated as an AE Stable chronic conditions, such as arthritis, noted in the patient prior to inclusion in the trial, the course of which did not worsen during the trial, will not be considered as AEs.

Abnormalities in the results of diagnostic procedures, including laboratory abnormalities, will be considered as AEs if:

- as a result of their presence, the investigator excluded the subject from the trial;
- they are accompanied by the development of SAEs;
- they are accompanied by clinical signs or symptoms;
- they are deemed by the investigator to be of clinical significance.
- any combination of one or more of the above factors.

As noted above, the term "adverse event" does not imply any causal relationship to the Investigational product.

If any adverse events develop, the investigator must record them in the source documentation, complete the relevant pages of the patient's CRF, assess the clinical significance of the adverse events and the appropriateness of the patient's continued participation in the trial. Information on adverse events will be recorded from the first administration of the Investigational product until the patient completes the trial. For serious AEs (SAEs), the SAE form must be completed (see 7.2.3. for the algorithm of actions).

The patient is warned to report any new symptoms they develop to the investigator between visits.

7.2.2. Determination of adverse event parameters

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:

Severity:

A serious adverse event is any AE that:

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

Significant medical events are defined as events that are not immediately life threatening but may be life threatening to the trial subject and require intervention to prevent one or more of the serious outcomes listed above. Examples of such events include intensive treatment in the emergency department or at home for allergic bronchospasm, persistent pathological changes in blood cellular composition or seizures that do not require hospitalization. An AE that meets this definition is usually considered to be serious.

An inpatient **hospitalization** or extension of a current hospitalization means that these measures were necessary for the treatment of an AE or were required as a consequence of the AE onset. This **does not** apply to planned hospitalizations for the treatment of existing illnesses or for diagnostic procedures.

The term **"life-threatening"** in the definition of **a serious** event refers to an event in which the patient was at immediate risk of death during its development, and does not refer to an event that hypothetically could have caused death had it been more severe.

Death is usually the outcome of the underlying clinical event causing it. Therefore, it is the cause of death that should be considered the SAE. The only exception is "sudden death" when no cause has been determined. In this case, "sudden death" should be considered an AE, the reason for its "seriousness" being "lethality".

Disability is defined as a significant impairment in a person's ability to perform activities of daily living.

Congenital abnormality (defect), i.e. any congenital abnormality observed in an infant, or later in a child, should be considered a SAE if:

- The mother was taking a medicinal product at the time of conception or pregnancy, or at the time of delivery.
- The baby's father was taking a medicinal product prior to fertilization.

AEs that do not fulfil the criteria for SAE should be recorded by the investigator in the source documentation and CRF. No urgent reports are required to be made to the Sponsor or its representatives with respect to these events. An assessment of these events is provided in the clinical study report (CSR).

Any new SAEs occurring during the trial period should be recorded and reported immediately.

Listedness: Unlisted adverse reaction - an adverse reaction whose nature, severity or outcome is not consistent with the information contained in the investigator's brochure.

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:

Degree of 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

Relationship with the Investigational product:
The investigator will need to assess the association of the development 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 unlikely (doubtful, conditional, unclassifiable), possible, probable, or certain relationship.
Yes - there is a definite 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 association of AR with the use of the trial products will be assessed using World Health Organisation (WHO) criteria:

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

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

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

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

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

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

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)

Stabilisation of the condition:	AE has not resolved
Recovery with consequences	The resolution of the AE has occurred, but the patient still has some residual effects
Recovery/ cessation of an AE:	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)

7.2.3. AE registration

The investigator and members of the trial team at the investigational site are responsible for identifying, providing appropriate medical care, documenting and reporting cases falling within the definition of adverse events and serious adverse events.
Throughout the trial from the first use of trial medication to the end of the trial, the patient will have a record of the AEs. After the first dose of Investigational product, the Investigator will record any identified AEs and SAEs. The Investigator must notify the Sponsor of all SAEs. SAEs reports should be provided in the form of express reports.
If a patient develops an AE, the investigator should record it in the source documentation, enter the necessary information in the CRF by filling in the relevant pages, and assess the possibility of continued participation in the trial for this patient (continue taking the drug or exclude the patient from the trial).
For each AE, the investigator should assess and record its severity (whether the AE is serious), duration, foreseeability, seriousness, relationship to the investigational product, actions taken, and outcome of the event.
If any abnormality is detected during the examination of the patient, the Investigator will assess its clinical significance. Clinically significant abnormalities detected by objective examination and laboratory and instrumental examination at screening should not be reported as AEs, but should be recorded as associated pathology. A worsening of the original disease/condition, if it occurred during the trial, should be recorded as an AE. A conclusion on the safety of the investigational product will be made after statistical evaluation of all AEs, including serious AEs with at least a possible association with the use of the investigational product.

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 the AE;
  - change in the dosage of the drug of concomitant therapy, prescription of non-drug therapy.

7.2.4. SAE reporting

The investigator must report all cases of developing an AE to the Sponsor's APP/CRO representative, within 24 hours of becoming aware of it, or after such adverse event has been deemed serious.

The SAE Report Form should be completed immediately and forwarded to the appropriate staff member, even if not all information is available at the time of the initial report.

Representative of a contract research organisation (CRO):

Full name Maria Igorevna Shunikova
Tel./fax: + 7 (4852) 59-47-79
Email address: mi_shunikova@cphd.ru

Qualified Person Responsible for Pharmacovigilance (QPPV) of RPC PHARMASOFT LLC:

Irina Vladimirovna Medvedeva
Tel: +7 (495) 626-47-55 ext. 162
E-mail address: 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).
- The 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 SAEs not available at the time of the initial report must be provided by the Investigational site to the Contract Research Organisation Representative of the Trial Sponsor, within 24 hours of the investigator becoming aware of this additional information.

In order to make an accurate and complete report of the event, the investigator should provide the following information for the CRO/Sponsor representative:

- name of the investigator and the site number.
- patient number.
- patient initials.
- patient demographics.
- information about a clinical event:
  a. description:
  b. date of onset;
  c. severity;
  d. treatment;
  e. relationship to the Investigational product (causal relationship);
  f. actions taken regarding the Investigational product;

1) whether the AE resulted in death:
   a. cause of death (regardless of the relationship of the death to the Investigational product);
   b. autopsy data (if available);
2) medical history in the CRF (copy);
3) data on concomitant therapy in CRF (copy);
4) all other relevant data (laboratory results, discharge summaries, radiological findings).

This information should be forwarded to the Trial Sponsor’s APP/CRO representative.

Investigational site personnel should report SAEs to the local Ethics Committee in accordance with the rules and procedures established by the institutional board. Patients who develop SAEs during the drug administration period should be clinically monitored until all parameters (including laboratory data) normalize or stabilize or until another explanation for these changes is found.

7.2.5. 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, regulatory authorities of all data received that may adversely affect patient safety and the conduct of the trial.
The sponsor must report all SUARs to regulatory authorities and ethics committees within 7 calendar days of the date of discovery (or being informed of discovery) if they resulted in death or were life-threatening, and within 15 calendar days for other SAEs.
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.

7.3.Methodology and duration of follow-up of patients after the development of an 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 must provide the Sponsor/representative of the contract research organisation and the Ethics Committee with any additional information required.
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 drug or exclude the patient from the trial). Upon development of a SAE, the investigator completes the SAE registration form provided by the Sponsor/contract research organisation representative, assesses whether it is related to the investigational product and faxes the completed form to the Sponsor's APP/CRO representative. The original SAE form and fax receipt acknowledgement sheet should be kept in the source documentation, with a copy in the patient's CRF.
The CRO/Sponsor representative has the right to urgently request additional information from the researcher about the SAE 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.

Notice of pregnancy

Patients should be cautioned to report pregnancy immediately. If pregnancy is confirmed while taking the drug, the drug 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.
Pregnancies occurring after the initiation of trial medication are not considered to be AEs or SAEs. 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 Sponsor's APP/CRO representative. Only pregnancies reported after initiation of the Investigational products were observed.
The pregnancy should be monitored until the outcome of the pregnancy is determined (up to 30 days after delivery), including spontaneous or induced abortion, and 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.

8. STATISTICAL PROCESSING

8.1.Statistical methods used in the trial

Statistical processing of the data (Case Report Forms of all sites) at the end of the trial will be carried out by staff not involved in the management of the patients participating in the trial, in order to create conditions for independent evaluation of the results obtained. The data will be processed in an electronic database using statistical programmes with the necessary functions.
Descriptive statistics are provided for demographics, baseline values of indices, and values of efficacy and safety indicators at trial visits for the drugs being compared. Descriptive statistics will include mean, standard deviation, minimum and maximum values, - for quantitative variables; number, proportion, distribution - for qualitative variables.
The following population groups will be identified to analyse the efficacy and safety of the Investigational products:

- Safety population - patients who received investigational medicinal products and for whom there is an assessment of status and/or AE for at least 1 time point after administration.
- ntent-to-treat, ITT: patients who received investigational medicinal products and for whom data are available for at least one visit after Visit 1.
- Per protocol, PP: patients who completed the trial according to the clinical trial protocol.

The Shapiro-Wilk criterion will be applied to select parametric or non-parametric methods of analysis. Demographic characteristics and descriptive statistics for baseline values will be presented for all patients in the safety population.
The primary performance variable will be analysed based on the statistical hypothesis of superiority. The primary efficacy variable will be analysed in the ITT population as well as in the PP population.
Secondary efficacy and safety endpoints and their changes will be presented using descriptive statistics by visit and therapy group. On trial visits, qualitative (dichotomous) measures will be compared between groups based on the x2 criterion (Fisher's exact test).

The dynamics of quantitative safety data relative to baseline values will be evaluated and compared for Investigational product and placebo using ANOVA analysis of variance with repeated measures. This method allows to simultaneously check the presence of statistically significant dynamics (at least one mean value in one time point differs from the rest), as well as to compare the dynamics and ranges of values of the indicator when receiving the compared medicinal products. In case of inappropriateness of parametric methods, similar analysis of changes in the distributions of indicators during therapy will be performed using non-parametric analogues - Friedman's criterion and Wilcoxon sign rank criterion, and intergroup comparisons of changes will be performed using Wilcoxon-Mann-Whitney criterion.
A description of the statistical methods will be detailed in the statistical plan of the trial.
A subanalysis is planned for patients with diabetes mellitus and metabolic syndrome.
Subanalysis by age will be done with the formation of the following subgroups: 40-60 years old, 61-75, 76-90 years old.
A subanalysis will be performed in patients with CCI that developed without a previous stroke and with CCI that developed after a previous stroke
An interim analysis will be conducted once efficacy and safety data from 318 patients are available. As part of the interim analysis, the primary efficacy criterion under trial will be evaluated.
For the intermediate analysis, the critical Z values will be 0.40 and 2.75, respectively. During the interim data analysis, Z is calculated from the current values of the effect size. If $|Z| \leq 0.40$, the trial will be stopped due to "futility" (futility: the effect of the drug is not strong enough according to the chosen endpoint, the null hypothesis could not be rejected). If $|Z| > 2.75$, the trial will be stopped due to "superiority" and the null hypothesis will be rejected (the drug will be considered superior to placebo in terms of efficacy). Otherwise, the trial will be continued, the null hypothesis will be tested for the value of 1.96 for the full sample size: if $|Z| > 1.96$, it will be concluded that the null hypothesis is rejected, if $|Z| \leq 1.96$, it will be concluded that the trial failed to reject the null hypothesis.

Statistical hypothesis
The present trial intends to assess the efficacy of therapy by the mean difference between the Montreal Cognitive Assessment Scale (MoCA) scores at patient completion and trial initiation
The following statistical hypotheses will be tested:
- **null hypothesis (H_0):** the efficacy of therapy with the investigational product is not superior to the efficacy of therapy with placebo:

H^0: $\mu_o - \mu_p \leq 0$,
where μ_m and μ_p - mean values of change on the Montreal Cognitive Function Assessment Scale in the main group (μ_o) and placebo group (μ_p);
- alternative hypothesis (HA): the efficacy of therapy with the Investigational product is superior to that of therapy with placebo:
H^A: $\mu_m - \mu_p > 0$.

8.2.Justification of sample size

There is a lack of information in the open literature that allows for accurate estimation of a drug's effect size according to the primary endpoint chosen. For this reason, it is advisable to use a group sequential design to optimise the determination of the required sample size. The trial can be conducted in two stages: the maximum sample size N is divided into two parts. After the first part of the patients have completed the trial, an interim analysis will be performed. If, based on the results of the interim analysis, the sample size is sufficient to reject the null hypothesis or prove that the null hypothesis cannot be rejected, the trial will be terminated early. Otherwise, the trial will be continued and the final decision to accept or reject the null hypothesis will be made based on the data obtained from the full sample of patients. Since the objective of this trial is to demonstrate the superiority of the investigational product over the placebo drug, an asymmetric design was chosen in the planning of the trial. The cost function ("spendingfunction") for group sequential design was selected from the Hwang, Shihand De Cani family [2] with values $\gamma = -2$ and $\gamma = -4$ for the β- and α-cost functions, respectively, defining the lower and upper bounds of the acceptable range. The search for the required sample size and boundary conditions was performed using the gs Design module (v.2.4-01,2011, Anderson K.) of the statistical software package R v.3.5.2. Input data corresponded to a fixed sample size in a simple study with no interim analyses. Calculation of the sample size for the trial without interim analysis was done based on the following formula:

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

where Z_α and Z_β - critical values of the normal distribution corresponding to the established error levels α and β (α- and β-errors are 0.05 and 0.2, respectively); SD - standard deviation [3 - 5].
In estimating the sample size, the standard deviation was assumed to be 4.3 points. The specified value of the standard deviation is the maximum possible for the analysed performance indicator [6 - 8].
Assuming a difference in drug efficacy of at least 1 point, which corresponds to the minimum value of clinically significant differences [9, 10], the calculation based on the above values ($Z\alpha=1.96$, $Z^\beta=0.842$, $SD=4.3$, $\mu_m - \mu_\rho = 1$) resulted in a sample size providing statistical power of the trial of at least 80%, equal to 291 patients in each group (582 patients in total).

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

Asymmetric two-sided group sequential design with 80% power and 2.5% Type I Error.
Spending computations assume trial stops if a bound is crossed.

	---- Lower bounds ----		---- Upper bounds ----	
Analysis	N	Z	Nominal p	Spend+	Z	Nominal p	Spend++
1	150	0.40	0.6552	0.0538	2.75	0.0030	0.003
2	300	1.96	0.9751	0.1462	1.96	0.0249	0.022
Total				0.2000		0.0250	

+ lower bound beta spending (under H1):
Hwang-Shih-DeCani spending function with gamma = -2.
++ alpha spending:
Hwang-Shih-DeCani spending function with gamma = -4.

Boundary crossing probabilities and expected sample size assume any cross stops the trial

Upper boundary (power or Type I Error)

	Analysis			
Theta	1	2	Total	E {N}
0.0000	0.0030	0.0220	0.025	200.7
0.1642	0.2292	0.5708	0.800	256.8

Lower boundary (futility or Type II Error)

Analysis			
Theta	1	2	Total
0.0000	0.6552	0.3198	0.975
0.1642	0.0538	0.1462	0.200

Normal test statistics at bounds

	2.75
	0.4
	N=150
	1,96
	N=300
	Normal critical value
	Sample size
	Bound
	Lower
	Upper

For the intermediate analysis, the critical Z values will be 0.40 and 2.75, respectively. During the interim data analysis, Z is calculated from the current values of the effect size. If $|Z| \leq 0.40$, the trial will be stopped due to "futility" (futility: the effect of the drug is not strong enough according to the chosen endpoint, the null hypothesis could not be rejected). If $|Z| > 2.75$, the trial will be stopped due to "superiority" and the null hypothesis will be rejected (the drug will be considered superior to placebo in terms of efficacy). Otherwise, the trial will be continued, the null hypothesis will be tested for the value of 1.96 for the full sample size: if $|Z| > 1.96$, it will be concluded that the null hypothesis is rejected, if $|Z| \leq 1.96$, it will be concluded that the trial failed to reject the null hypothesis [11, 12].

8.3. Applied significance level

The probability of an error of the first kind is set at 5%.

8.4. Criteria for trial termination

Given that a two-stage adaptive design will be used, a decision on the need for a second stage will be made after an interim analysis of the results of the first stage. If the trial objective is achieved based on the results of the first phase, the second phase of the trial will not be conducted.

8.5. Procedures for recording missing, unanalysable and questionable data

Data on patients excluded from the trial due to protocol violations are not included in analyses of the PP population data, but are included in analyses of the ITT and safety populations.
If a protocol violation becomes known later, when the trial is already completed, the data of patients with protocol violations, if they fall under the list of violations that necessarily entail the exclusion of the patient from the trial, will be removed from the database, and they will not be included in the final statistical report, but the fact of data exclusion will be reflected in the report.

8.6.Procedures for reporting deviations from the initial analysis plan

A statistical plan will be prepared and agreed upon prior to the trial. All changes to the original statistical plan with their justification are reflected in the Clinical Study Report.
No changes will be made to the list of parameters to be evaluated.

8.7.Selection of subjects to be analysed

The following patient populations will be included in the statistical analyses:
Safety population: all patients who have taken at least one dose of the drug;
Intent-to-treat (ITT): all randomized patients for whom there is an estimate of efficacy parameters for at least one visit other than the randomization visit,
Per-protocol (PP): patients who completed the trial according to the clinical trial protocol.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

9.1.Access and verification of source data and records

All information contained in the original records and certified copies concerning clinical data, observations and other trial activities that is necessary for the reconstruction and evaluation of the trial is source data.
The investigator must ensure direct access to source data/documentation for trial-related monitoring, auditing, ethical review, and inspection by authorized bodies.
The Sponsor/Sponsor's Representative must ensure that each patient has given written consent for direct access to their original medical records for the purposes of monitoring, auditing, ethical review, and inspection by authorized bodies.

9.2.Provision of additional information

Upon request, the Investigator will provide the Sponsor with additional data regarding the trial, or copies of relevant source records after proper data processing to achieve anonymity of the trial participant's data. This is important if there are errors when writing data. In special cases or regulatory requests, it is also necessary to have access to full trial records, subject to patient confidentiality in accordance with applicable regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring will be carried out throughout the trial to ensure that:

- patient safety and rights are protected;
- data entered in the CRF correspond to the source documentation and are true, accurate and complete.
- trial is conducted in accordance with the approved latest version of the protocol and applicable protocol amendments (where applicable) and other trial documents.
- trial is conducted in accordance with ICH GCP principles and all applicable regulatory requirements of the Russian Federation.

The sponsor and organisation conducting the trial is responsible for appointing Clinical Research Associates (CRAs) to carry out qualitative monitoring. The trial will be monitored regularly as planned.

Investigators are obliged to provide the CRA with direct access to all necessary documents for monitoring, and to enable the CRA to:

- visit the investigational site, have access to the rooms where the trial is conducted, the place where the trial documentation is stored, the place where the Investigational product is stored;
- meet with members of the trial staff;
- check the correctness of filling in the CRF and reconcile the CRF with the source medical documentation;
- reconcile drug records; monitor compliance of the trial with the protocol.

The purpose of the audit, conducted separately and independently from the routine monitoring and quality control functions, is to assess the compliance of the trial being conducted with the Protocol, SOPs, ICH GCP and regulatory requirements.

Protocol amendments

Changes to the clinical trial protocol are not permitted unless they are urgently necessary (e.g. changes to inclusion or non-inclusion criteria, if the number of patients is too low over a period of time, or if agreed criteria are too frequently violated). Any significant changes to the protocol require the issuance of protocol amendments.

Amendments are considered significant if they are likely to have an impact on:

- safety or the physical or mental integrity of patients;
- scientific value of the trial;
- trial conduction;
- quality or safety of any investigational product that is used in the trial.

Amendments to the clinical trial protocol must be submitted to the MoH RF and Local Ethics Committees for review and cannot be applied until written dated permission/approval is obtained from these organizations.

Once the amendment has been authorised/approved, all patients included in the trial must comply with the amended protocol or may withdraw their consent to participate in this trial.

11. ETHICS

11.1. General requirements

Investigators, as well as all the parties involved in the clinical trial, must conduct it in accordance with the ethical principles of the Declaration of Helsinki, the ICH GCP, and the current legislation of the Russian Federation. The Investigator and Sponsor must sign the protocol and trial agreement. The Investigator must not make any changes to the clinical trial protocol without the consent of the Sponsor and the approval of the Ethics Committee, except in cases where an immediate danger to the patient needs to be urgently addressed or where the changes relate only to supply or administrative issues.

11.2. Independent Ethics Committee

This clinical trial may not be initiated before written approval has been obtained from independent ethics committees (IECs), including local ethics committees.

The investigator, medical director or other responsible person should submit the required documentation to the local ethics committee in a timely manner for review. Documents submitted to the local ethics committee may vary from institution to institution, but must include the final version of the clinical trial protocol, patient information, Patient Information Sheet with Informed Consent Form, Investigator's Brochure with information about the investigational product, documents confirming the quality of the investigational product/placebo, insurance contract for patients participating in this trial, CV of the Principal Investigator, scales used in the trial, diaries.

Investigators must not make any changes to the trial or the conduct of the trial without IEC approval unless these changes are necessary to address obvious immediate threats to patient welfare. Corrections of minor inaccuracies in the protocol or changes to the trial design without ethical significance will be sent to the IEC for notification purposes.
The investigator must immediately report to the IEC any changes in the trial, unexpected problems, including risks to patients or others, and any deviations from the protocol to address immediate risks to patients. As part of the IEC's requirements for continued review of approved studies, the investigator must provide the IEC with a final report upon completion of the trial.

11.3. Informed consent

The patient's informed consent must be obtained and formalized in accordance with the requirements of the EAEC, the ICHGCP Guidelines and the ethical principles set out in the Declaration of Helsinki.
Prior to the trial, the patient is invited to the Investigational site. The investigator has a discussion with the patient about the upcoming trial and invites the patient to participate in the trial.
In selecting patients for participation in the trial, each potential trial subject must be adequately informed about the aims, methods, expected benefits of the trial and the risks and inconveniences associated with participation in the trial. Patients must be provided with comprehensive and accurate information regarding all aspects of the trial ("Patient Information Sheet and Informed Consent Form") prior to any procedures and activities related to the trial.
The following should be discussed with the patient at a level that is accessible to them:

- the trial is experimental in nature;
- objectives of the trial;
- the expected duration of the trial and the number of patients expected to be included in the trial;
- which pharmacological group the investigational product belongs to;
- routes of administration and dose;
- mechanism of action of the investigational product;
- indications and contraindications for the use of the investigational product;
- protocol procedures;
- protocol limitations;
- risks of adverse reactions and their manifestations;
- terms of insurance and remuneration;

- existence of a trial authorization;
- patient's responsibilities;
- patient confidentiality: name and other personal information will be kept confidential and may only be disclosed to the extent permitted by law and will not appear in publications;
- by signing the Informed Consent Form for participation in the trial, the patient is giving his or her *authorization for direct access to original medical records* to the CRA, auditor, IEC and regulatory authorities for the purpose of reviewing the clinical trial procedures and data, without compromising the confidentiality of his/her data;
- if new information becomes available that may affect the patient's willingness to continue in the trial, it will be provided in a timely manner, as will any additional information about the trial and the rights of participants, and contact details of people and organizations who can be contacted for further information and in the event of changes in well-being;
- possible circumstances and/or reasons why the patient's participation in the trial may be terminated.

The patient is warned to take adequate contraceptive measures throughout the trial. If pregnancy occurs in the patient or the patient's partner, the investigating physician is immediately notified, the resulting pregnancy is observed, if possible, until the outcome.
The patient is assured that qualified medical care will be provided if necessary, both during and after the trial (if the AE continues after the trial is completed) and that information about him/her obtained during the trial will be kept confidential.
The trial participant should be aware that they have the right to withdraw from participation in the clinical trial at any stage.
All information about the trial, benefits and possible risks is set out in the Patient Information Sheet with Informed Consent Form, which, if consenting to participate in the trial, is dated and signed personally by the patient and the investigator in 2 copies. One copy will be retained by the trial subject and another copy will be kept with the source documentation at the investigational site.
The potential trial subject should be given sufficient time to read the Patient Information Sheet with the Informed Consent Form, if necessary the patient can take it home to discuss the conditions of participation in the trial with relatives. The investigator should answer any questions about the trial that the patient has. The patient's consent to participate in the trial must be confirmed by signing an Informed Consent Form.

Data on signed informed consents should be recorded in the Logbook of Included Patients.
No trial procedures, including screening procedures, may be performed with a patient until the patient has signed an Informed Consent Form.

12. DATA MANAGEMENT AND RECORD KEEPING

12.1. Clinical Trial documents

The Sponsoring Company/CRO shall provide the following key documents and materials to the investigational site:

- Trial protocol (and amendments to it, if any).
- Investigator's Brochure.
- CRF.
- Patient information Sheet with Informed Consent Form
- Investigator Site File.
- Investigational/comparator products.
- Copy of the insurance contract and original insurance policies for patients.
- Trial Agreement.
- Copy of the regulatory authority's approval.
- Documents required for submission to the Local Ethics Committee (LEC).

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

- Letter of direction to the LEC (if there is a LEC).
- Signed confidentiality agreement.
- Signed agreement by the researcher to the terms and conditions of the protocol.
- Signed Trial Agreement.
- Approval of the trial and trial documents by the LEC (if LEC is available).
- List of LEC members (if there is a LEC), SOPs and LEC regulations.
- Updated CVs *(Curriculum Vitae) of* all investigators and co-investigators (signed and dated).
- Laboratory norms with signature and date of the responsible officer from the laboratory (if using a local laboratory), scientific CV of the head of the laboratory.
- Certificates for medical/laboratory equipment used in the trial.

The Investigator must retain all documentation related to the conduct of the clinical trial, including source documentation, copies of the CRF, and the Investigator Site File for 15 years after completion of the trial or until written notification by the Trial Sponsor.

12.2. Provision (supply) of trial materials and documents

All deliveries to the site and collection of trial materials from the site will be documented using the Transfer/Return of Trial Materials forms.

12.3. Source documentation

The availability of source documentation at the investigational site is necessary to confirm the existence of patients and to confirm the validity of the information collected. Source documentation includes original documents that are relevant to the trial, treatment, history and description of the patient's condition. For example, such documents include medical history and extracts (printouts) with the results of laboratory/instrumental examinations, including those kept at the medical institution where the patient is being treated/staying.
The source medical record must contain all pertinent information about the trial, including:

- Demographic data
- Information regarding inclusion and non-inclusion criteria.
- The fact of participation in the trial, indicating the trial number and patient number.
- The date of all visits.
- History and physical examination findings.
- Adverse events
- Prior therapy and concomitant treatment.
- Results of instrumental examinations.
- Lab results.
- Information on the use of the Investigational product.
- Reason for early termination of participation in the trial (when applicable).

12.4. Data collection: Case Report Forms

CRFs serve multiple purposes:

- ensure that data are collected in accordance with the Protocol;
- ensure that the requirements of the control and licensing authorities for the collection of information are met;
- facilitate efficient and complete data processing, analysis and reporting of results; facilitate the sharing of safety data among the project team and other parts of the organization.

The investigator should ensure that data entry into the CRF is correct, complete and timely.
The data in the CRF should be consistent with the source documentation from which it is transferred. Any discrepancies should be explained.

All observed AEs (changes in laboratory parameters, physical examination data, vital signs and ECG parameters), including those that are clinically insignificant, are recorded in the CRF.
The CRA should check the information entered into the CRF against the source documentation to confirm that there are no discrepancies in the various documents when recording data. If the CRA finds discrepancies, the necessary changes will be made in the CRF. If discrepancies are identified, the CRA should discuss the issue with the investigator to ensure that appropriate changes to the CRF are made in a timely manner.
The CRA shall monitor the completeness and correctness of the CRF. The CRA is not authorized to personally make corrections to the CRF.
The investigator or other person authorized to complete the CRF should enter data into the CRF during or immediately after each visit, according to the source documentation.

12.5. Data processing and changes to the CRF

All information for each patient that is recorded according to the protocol must be entered in a timely manner into the CRF that is developed according to this protocol.
In order to ensure the most efficient data collection and transfer process, the investigator or authorized investigational site staff member should enter information into the CRF at or shortly after the patient visit. The CRF and other documents (e.g., source documentation) should be available for inspection by the CRA.
Any changes or corrections to the CRF will reflect all necessary information about the correction made - original value, date and details of the person who made the correction. If it is necessary to make changes to the CRF data after the source records have been verified, requests for data clarification will be addressed to the person who entered the data of the record being corrected.

12.6. Confidentiality of patient data

The patient's personal health information obtained during the trial is considered confidential and may not be disclosed to persons not authorized to see the information. This information may be shared with the patient's treating doctor or other health care provider responsible for the patient's health after the patient's consent.
Each patient will be assigned an identification number that will be used in place of the patient's last name to maintain patient confidentiality when communicating information about AEs or other data related to the trial being conducted.
This information should be kept confidential. To this end, the investigational site will complete and maintain a Patient Identification Log, which contains information about the patient and the randomization code assigned. The identification log or a copy of it will not be given to the Sponsor and will be kept on file at the investigational site after completion of the trial. This log will provide identification of coded information about the trial participant with their individual data and outpatient record.

The Investigator must provide access to source documentation to the CRA, Sponsor, and regulatory authorities to enable verification.
All those involved in the research process should ensure that patient confidentiality is respected by not allowing the use of any information that could identify the patient (e.g. their name or address).

12.7. Investigator Site File.

The investigator must keep all records to ensure complete documentation of the progress of the trial, in accordance with GCP, EAEC and other regulations in force at the time of the trial. The investigator must retain all required documentation of the trial for 15 years, unless otherwise specified in the contract. The investigator should take steps to prevent accidental or premature destruction of these documents.
The investigator is required to maintain a Patient Identification Log, which provides a unique link between the source records in which the name appears and the anonymised CRF data for the Sponsor. The investigator must arrange for this Identification Log to be kept for at least 15 years after completion or termination of the trial.
Trial documents may not be destroyed without the written permission of the Sponsor. If the investigator wishes to transfer the trial documentation to another party, or move them to another location, the Sponsor must agree to this action.
The Investigator Site File includes the necessary documents required for detailed review, including:

- Investigator's Brochure.
- Clinical Trial Protocol
- Patient Information Sheet and Informed Consent Form.
- Reports on the progress of the Clinical Trial.
- CRF.
- A form of assignment of responsibilities.
- Patient Identification Logbook.
- Investigational product accounting/dispensing
- Screening and patient randomization record forms.

12.8. Archival data storage

Documentation relevant to the trial, the Patient Identification Log and the PIS with ICF must be retained by the investigator for 15 years.

In the event of relocation, investigator's retirement, or other changes related to the retention of the records archive for the time named (15 years), the Sponsor must be notified of who will be responsible for the storage of the CRF and other trial documentation. An inventory of the stored data will be maintained by the investigator and a copy will be provided to the Sponsor.
The investigator should inform the CRO/Sponsor representative of the location where key documents are stored, and contact the CRO/Sponsor representative for his/her approval before destroying any of them. The investigator should take measures to prevent the accidental destruction of these documents before the required time.

13. FINANCING AND INSURANCE

The trial will be funded by RPC PHARMASOFT LLC, Russia. The contract research organisation will be ClinPharmDevelopment LLC, Russia.
The Sponsor will provide insurance for patients and investigators during the conduct of this trial in accordance with applicable Russian law.
In accordance with the Rules of Compulsory Life and Health Insurance for Patients Participating in Clinical Trials of a Medicinal Product approved by the Russian Government Decree No. 714 dated 13 September 2010 (including amendments dated 18 May 2011), the Trial Sponsor concludes a contract of compulsory life and health insurance for patients participating in a clinical trial with Ingosstrakh.
In order to conclude the contract, the policyholder sends a written application to the insurer for the conclusion of the contract specifying the maximum number of patients participating in the clinical trial, the name of the medicinal product undergoing the clinical trial, the purpose of the clinical trial, and the name of the Clinical Trial Protocol.
The contract shall be deemed concluded from the day of its signing and shall enter into force from the day the insurer receives information about the inclusion of the first patient in the trial, provided that the insurance premium has been paid before the date of entry into force of the contract.
The register(s) of individual patient identification codes is an integral part of the contract and attached to it, will be provided to the insurance company as patients are included in the trial.
Establishment of an individual patient identification code is performed by the Sponsor after the Sponsor has received approval from the Ministry of Health of Russia to conduct the clinical trial.
The investigator must inform the patient about the conclusion of a compulsory insurance contract and explain to the patient that other treatments and concomitant therapies in the course of the trial (except for emergency medical treatment) are only possible with the permission of the investigator.

The insurance covers harm to the life and health of patients resulting from the following events:

- deficiencies and/or defects in the medical equipment used in the conduct of the clinical trial;
- errors and omissions in the provision of medical care and patient care;
- violations of the Clinical Trial Protocol;
- other errors and omissions made during the clinical trial of a medicinal product;
- deficiencies of the investigational product;
- insufficient information about the medicinal product, resulting in adverse events, as well as unexpected side effect of the medicinal product.

The beneficiaries (persons in favour of whom the insurance contract has been concluded) are:

- in case of harm to health - patients participating in the clinical trial, according to the approved Clinical Trial Protocol;
- in case of death of the patient - persons who have suffered property and (or) moral damage as a result of the patient's death.

14. PUBLICATION POLICY

The results of this trial, including all data obtained during the trial, remain the property of RPC PHARMASOFT LLC, Russia. However, the investigator may request permission from the Sponsor to publish the results. The release of unpublished data by the investigator to third parties without the written permission of the Sponsor is prohibited.

15. *APPENDIX 1.* LIST OF TRIAL PROCEDURES

Procedures/Trial period	Screening	Period of parenteral therapy		Period of oral therapy			Unscheduled visit[1]	Early withdrawal visit
Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		
Day	Day -7- 0	Day 1	Day 14	Day 28±2 (telephone visit)	Day 44±2	Day 75+2		
Signing informed consent	+							
Physical examination	+	+	+		+	+		+
Collection of the patient's subjective complaints	+	+	+	+	+	+		+
Collection of demographic and anthropometric data	+							
Collection of medical and pharmacotherapeutic history	+							
Measurement of BP, HR, RR, body t°	+	+	+		+	+		+
12-lead ECG	+		+			+		+
Urine pregnancy test with test strips (for women with preserved reproductive potential)	+		+		+	+		+
Complete Blood Count[2]	+		+			+		+

[1] any of the procedures may be carried out at the visit as decided by the investigator
[2] haemoglobin, erythrocytes, platelets, leukocytes, haematocrit, leukocyte count, ECR.

Procedures/Trial period	Screening	Period of parenteral therapy		Period of oral therapy			Unscheduled visit[1]	Early withdrawal visit
Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		
Day	Day -7- 0	Day 1	Day 14	Day 28±2 (telephone visit)	Day 44±2	Day 75+2		
Biochemical blood test[3]	+		+			+		+
Determination of the glomerular filtration rate (Cockcroft-Gault formula)	+							
Clinical urinalysis[4]	+		+			+		+
Blood tests for HIV, syphilis, hepatitis B and C	+							
Head MRI/CT[5]	+							
Evaluation of scales and indices:	+	+	+		+	+		+
MoCA	+	+	+		+	+		+
DSM-5	+							
HDRS	+							
SF-36		+	+		+	+		+
MFI-20		+	+		+	+		+
Beck Anxiety Rating Scale		+	+		+	+		+
Wein questionnaire		+	+		+	+		+
Tinetti test		+	+		+	+		+

[3] glucose, creatinine, urea, ALT, AST, eGFR.
[4]pH, protein, glucose, ketone bodies, red and white blood cells, epithelium
[5]is carried out in case of absence of results for the last 12 months

Procedures/Trial period	Screening	Period of parenteral therapy		Period of oral therapy			Unscheduled visit[1]	Early withdrawal visit
Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		
Day	Day -7- 0	Day 1	Day 14	Day 28±2 (telephone visit)	Day 44±2	Day 75+2		
Clinical Global Impressions Scale		+	+			+		
Digit Symbol Substitution Test		+	+		+	+		+
Assessment of inclusion/non-inclusion criteria;	+	+						
Randomization		+						
Issuing a patient diary		+						
Checking the patient's diary			+		+	+		+
Return of the patient diary						+		+
Intravenous IP administration		+	+					
Dispensing of oral medication			+		+			
IP take-back and compliance assessment					+	+		+
Evaluation of concomitant therapy		+	+	+	+	+		+
Evaluation of exclusion criteria;		+	+	+	+	+		+
Evaluation of AEs		+	+	+	+	+		+

16. *APPENDIX 2.* MONTREAL COGNITIVE FUNCTION ASSESSMENT SCALE

Montreal Cognitive Function Assessment Scale **NAME:**

Education: **Date of birth:**

Gender **DATE:**

	Visual-constructional/performance skills		Serial subtraction by 7 from 100.
	Copy the cube		4-5 correct answers: 3 points, 2-3 correct answers...: 2 points, 1 correct answer..: 1 point, 0 correct answers...: 0 points.
	E A B C D		**SPEECH**
	End		Repeat: All I know is that Ivan is the one who can help me today. [ ] The cat always hid under the couch when the dogs were in the room. [ ]
	Start		Speech fluency/in one minute, name the maximum number of words beginning with the letter L [ ] (N ≥ 11 WORDS)
	[ ]		**ABSTRACTION**
	Draw a WATCH (Ten minutes past twelve) (3 points)		What do words like banana-apple = fruit have in common, for example
	POINTS		[ ] train - bicycle
	Contour		[ ] watch - ruler
	Figures		**DELAYED PLAYBACK**
	Arrows		You have to say the words without prompting
	NAME		PERSON [ ]
	MEMORY		BARHAT [ ]
	Read the list of words, the subject must repeat them. Make 2 attempts, Ask him/her to repeat the words after 5 minutes.		CHURCH [ ]
	Attempt 1		VIOLET [ ]
	Attempt 2		RED [ ]
	FACE		Points only for words WITHOUT clues
	VELVET		**OPTIONALLY**
	CHURCH		Category hint
	VIOLET		Multiple choice
	RED		**ORIENTATION**
	no points		[ ] Date [ ] Month [ ] Year [ ] Day of Week [ ] Place [ ] City
	ATTENTION		© **Z.Nasreddine MD** Version 7.1
	Read the list of digits (1 digit/sec).		Performed:
	The testee must repeat them in direct order.		**www.mocatest.org**
	The testee must repeat them in reverse order.		The norm is 26/30
	Read a letter row. The testee must clap his/her hand on each letter A. No points for > 2 errors.		translation: Posokhina O. V, Smirnova A. Yu.
	[ ] F B A B A N M N A A G L B A F A D E A A G A G A M O F A B A G A B		NUMBER OF POINTS ___/30
			Add 1 point if education ≤ 12

Montreal Cognitive Assessment Scale (MoCA)

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-4-D-5-E, 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 on the space below the drawing".*

Evaluation: One point is awarded when the drawing is accurately executed:
- The drawing should be three-dimensional;
- All 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 candy-like 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, 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. Granted: 1 point 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 tools, 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: fabric type multiple choice: denim, cotton, velvet
CHURCH categorical clue: building type multiple choice: church, school, hospital
VIOLET categorical clue: flower type multiple choice: rose, tulip, violet
RED categorical cue: 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.

Translation: O.V. Posokhina
A.YU. Smirnova

17. APPENDIX 3. SF-36. QUALITY OF LIFE QUESTIONNAIRE

SF-36. Quality of Life Questionnaire

INSTRUCTIONS
This questionnaire contains questions about patient views on his/her health. The information you provide will help keep track of how you are feeling and how well you are doing with your regular activities. Answer each question by marking your chosen answer as indicated. If you are not sure how to answer a question, please choose the answer that most accurately reflects your opinion.

1. Overall, you would rate your health status as (circle one number):
Excellent 1
Very good 2
Good 3
Satisfactory.....4
Bad 5

2. How would you rate your health now compared to a year ago? (circle one number)
Much better than a year ago 1
Somewhat better than a year ago 2
About the same as a year ago 3
Somewhat worse than a year ago 4
Much worse than a year ago 5

3. The following questions are about physical activities that you may encounter during your typical day. Does your current health condition limit you from doing any of the following physical activities? If yes, to what extent? (circle one digit in each row)

	Type of physical activity	Yes, significantly restricts	Yes, restricts a little	No, it doesn't restrict it at all
A	Heavy physical activity, such as running, lifting weights, weightlifting, strength sports	1	2	3
B	Moderate physical activity such as moving a table, vacuuming, picking mushrooms or berries	1	2	3
C	Lift or carry a grocery bag	1	2	3
D	Walk up a few flights of stairs on foot	1	2	3
E	Walk up one flight of stairs on foot	1	2	3
F	Bend over, kneel down, squat down	1	2	3
G	Walk a distance of more than one kilometre	1	2	3
3	Walk a distance of a few blocks	1	2	3
H	Walk a distance of one block	1	2	3
I	Washing and dressing on your own	1	2	3

4. In the past 4 weeks, has your physical condition caused you difficulty in your work or other normal daily activities because of (circle one number in each row):

		Yes	No
A	Had to reduce the amount of time spent on work or other activities	1	2
B	You did less than wanted to	1	2
C	You have been restricted from doing any particular type of work or other activity	1	2
D	There were difficulties in doing your job or other things (e.g., they required extra effort)	1	2

5. In the past 4 weeks, has your emotional state caused difficulties in your work or other normal daily activities because of (circle one number in each row):

		Yes	No
A	Had to reduce the amount of time spent on work or other activities	1	2
B	You did less than wanted to	1	2
C	You did not do your work or other chores as neatly as usual	1	2

6. During the past 4 weeks, how much has your physical or emotional condition prevented you from spending time with your family, friends, neighbours, or co-workers? (circle one number)
Didn't interfere at all 1
A little 2
Moderately 3
Considerably.....4
Very considerably.....5

7. How much physical pain have you experienced in the past 4 weeks? (circle one number)
Not experienced at all 1
Very weak 2
Weak 3
Moderate 4
Severe.....5

A very severe.....b

8. During the past 4 weeks, to what extent has pain prevented you from doing your normal work, including work outside the home and housework? (circle one number)

Didn't interfere at all 1
A little 2
Moderately 3
Considerably.....4
Very considerably.....5

9. The following questions are about how you have been feeling and what your mood has been like during the recent 4 weeks Please give one answer to each question that most closely matches how you feel.

How often in the last 4 weeks (circle one number in each row):

		All the time	Most of the time	Often	Sometimes	Rarely	Not once
A	Did you feel awake?	1	2	3	4	5	6
B	Were you very nervous?	1	2	3	4	5	6
C	Did you feel so depressed that nothing could cheer you up?	1	2	3	4	5	6
D	Did you feel calm and peaceful?	1	2	3	4	5	6
	Did you feel full of vigour and energy?	1	2	3	4	5	6
F	Did you feel down in spirit and sad?	1	2	3	4	5	6
G	Did you feel exhausted?	1	2	3	4	5	6
3	Did you feel happy?	1	2	3	4	5	6
h	Did you feel tired?	1	2	3	4	5	6

10. In the last 4 weeks, how often has your physical or emotional condition prevented you from actively interacting with people? For example, visiting relatives, friends, etc. (circle one digit)

All the time 1
Most of the time 2
Sometimes 3
Rarely 4
Not once 5

11. How true or false each of the following statements seems to you?
(circle one number in each row)

		Definitely true	Basically true	I don't know	Basically false	Definitely false
A	I think I'm more prone to illness than others	1	2	3	4	5
B	My health is as good as most people I know	1	2	3	4	5
C	I expect my health to deteriorate	1	2	3	4	5
D	I'm in excellent health	1	2	3	4	5

18. APPENDIX 4. HAMILTON DEPRESSION RATING SCALE (HDRS) [52]

1. Low mood (feelings of sadness, hopelessness, helplessness, worthlessness)
4 - the patient spontaneously expresses only these feelings when communicating verbally and non-verbally
3 - the patient expresses his/her affective experiences in a non-verbal way (facial expressions, voice, readiness to cry, etc.)
2 - spontaneously communicates his/her experiences verbally (talks about them)
1 - reports his/her experiences only when questioned
0 - absent
Evaluation _____

2. Guilt
4 - hears voices of accusatory or humiliating content, experiences threatening visual hallucinations
3 - sees his/her painful condition as a punishment, has delusions of persecution
2 - ideas of guilt and punishment for past mistakes and sinful behaviour
1 - ideas of self-humiliation, self-deprecation, has a feeling of being the cause of other people's suffering
0 - absent
Evaluation _____

3. Suicidal tendencies
4 - suicide attempt (any serious suicide attempt is scored 4)
3 - suicidal thoughts or gestures
2 - expresses thoughts about his/her death or any other ideas about not wanting to live
1 - expresses thoughts about the meaninglessness, low value of life
0 - absent
Evaluation _____

4. Difficulty falling asleep
2 - daily complaints of difficulty in falling asleep
1 - occasional complaints of difficulty in falling asleep 0 - none
Evaluation _____

5. Insomnia
2 - does not sleep during the night (any getting out of bed during the night, except for going to the toilet, is rated 2 points)
1 - complains of agitation and restlessness during the night
0 - absent
Evaluation _____

6. Early awakenings
2 - unable to fall asleep again upon awakening
1 - wakes up early but goes back to sleep again
0 - absent
Evaluation _____

7. Work and activities
4 - unable to work due to a present illness
3 - significant decrease in activity and productivity
2 - loss of interest in professional activities, work and entertainment
1 - thoughts and feelings of fatigue, weakness and inability to function
0 - no difficulties
Evaluation _____

8. Sluggishness (slowness of thinking and speech, difficulty concentrating, decreased motor activity)
4 - unable to work due to a present illness
3 - significant decrease in activity and productivity
2 - loss of interest in professional activities, work and entertainment
1 - thoughts and feelings of fatigue, weakness and inability to function
0 - no difficulties
Evaluation _____

9. Excitement
2 - wringing hands, biting nails, biting lips, tearing hair out
1 - motor restlessness, "playing with hands, hair"
0 - absent
Evaluation _____

10. Mental Anxiety
4 - spontaneously articulates or anxious fears
3 - signs of particular anxiety in facial expressions and speech
2 - worries for minor reasons

1 - thoughts and feelings of fatigue, weakness and inability to function
0 - absent
Evaluation _____

11. Somatic anxiety (physiological signs)
3 - very severe, up to functional failure
2 - heavy
1 - medium
0 - absent
Evaluation _____

12. Gastrointestinal somatic disorders
2 - has difficulty eating without staff assistance, needs to be prescribed laxatives and other medications to aid normal digestion
1 - complains of lack of appetite, but eats independently without compulsion, has a feeling of heaviness in the stomach
0 - absent
Evaluation _____

13. Generalised symptoms
2 - distinct expression of any somatic symptom is estimated at 2 points
1 - feeling of heaviness and fatigue in limbs, back, head, back pain, head pain, muscle pain 0 - absent
Evaluation _____

14. Sexual dysfunction
2 - distinct severity of decreased libido
1 - mild degree of decreased libido
0 - absent
Evaluation _____

15. Hypochondriacal disorders
4 - hypochondriacal delusions
3 - frequent complaints, calls for help
2 - particular concern for health
1 - increased interest in own body
0 - absent
Evaluation _____

16. Weight loss (for items A and B)
A. Assessment is based on anamnestic data
2 - weight loss of 3 or more kg
1 - weight loss between 1 and 2.5 kg
0 - no weight loss
Evaluation _____
B. Evaluation is done weekly based on weigh-in readings
1 - weight loss less than 0.5kg per week
0 - weight loss less than 0.5kg per week
Evaluation _____

17. Attitude towards the disease
2 - does not consider him/herself sick
1 - admits to being ill but attributes the causes of illness to food, climate, overwork, viral infection, etc.
0 - considers him/herself to be suffering from depression
Evaluation _____

Overall assessment _____
The total score is determined from the first 17 items. The last four items of the Hamilton scale (18 to 21) are used to assess additional symptoms of depression and identify subtypes of depressive disorder and are not included in the calculation of the Hamilton scale total score, which determines the severity of depressive disorder.

18. Daily state fluctuations (for items A and B)
A. Note when there is a worsening of the condition
2 - in the evening
1 - in the morning
0 - the state does not change
Evaluation _____
B. If there are fluctuations, clarify their severity
2 - pronounced
1 - weak
0 - the state does not change
Evaluation _____

19. Depersonalization and derealization
4 - fully embrace the consciousness of the patient
3 - strongly pronounced
2 - moderately pronounced
1 - increased interest in own body
0 - absent
Evaluation _____

20. Delusional disorders
3 - delusions of reference and persecution
2 - ideas of reference
1 - heightened suspicion
0 - absent
Evaluation _____

21. Obsessive-compulsive disorders
2 - strongly pronounced
1 - weak
0 - absent

Evaluation _____

The total score of the first 17 items-

0-7 - norm
8-13 - mild depressive disorder -
14-18 - moderate depressive disorder -
19-22 - major depressive disorder -
More than 23 is an extremely severe depressive disorder

19. *APPENDIX 5.* MULTIDIMENSIONAL FATIGUE INVENTORY (MFI-20)

No.	Statement	Yes, it is						No, it is not
1	I feel healthy		□ 1	□ 2	□ 3	□ 4	□ 5	
2	Physically, there's not much I can do		□ 5	□ 4	□ 3	□ 2	□ 1	
3	I'm feeling very active		□ 1	□ 2	□ 3	□ 4	□ 5	
4	Everything I do gives me pleasure		□ 1	□ 2	□ 3	□ 4	□ 5	
5	I feel tired		□ 5	□ 4	□ 3	□ 2	□ 1	
6	I feel like I get a lot done in a day		□ 1	□ 2	□ 3	□ 4	□ 5	
7	When I'm doing something, I can concentrate on it		□ 1	□ 2	□ 3	□ 4	□ 5	
8	Physically, I'm capable of a lot of things		□ 1	□ 2	□ 3	□ 4	□ 5	

9	I'm afraid of the things I have to do		□ 5	□ 4	□ 3	□ 2	□ 1	
10	I think I get very few things done in a day		□ 5	□ 4	□ 3	□ 2	□ 1	
11	I can concentrate well		□ 1	□ 2	□ 3	□ 4	□ 5	
12	I feel rested		□ 1	□ 2	□ 3	□ 4	□ 5	
13	It takes a lot of effort for me to concentrate		□ 5	□ 4	□ 3	□ 2	□ 1	
14	Physically, I feel like I'm in bad shape		□ 5	□ 4	□ 3	□ 2	□ 1	
15	I've got a lot of plans		□ 1	□ 2	□ 3	□ 4	□ 5	
16	I get tired quickly		□ 5	□ 4	□ 3	□ 2	□ 1	
17	There's very little I have time to do		□ 5	□ 4	□ 3	□ 2	□ 1	
18	I feel like I'm not doing anything		□	□	□	□	□	

			5	4	3	2	1	
19	My thoughts are easily dispelled		□ 5	□ 4	□ 3	□ 2	□ 1	
20	Physically, I feel in great condition		□ 1	□ 2	□ 3	□ 4	□ 5	

Fill-in example

No.	Approval	Yes, it is						No, it is not
1	I feel healthy		☒ 1	□ 2	□ 3	□ 4	□ 5	

The score for this answer is 1 point

No.	Approval	Yes, it is						No, it is not
2	Physically, there is not much I can do		☒ 5	□ 4	□ 3	□ 2	□ 1	

The score for this answer is 5 points

20. APPENDIX 6. QUESTIONNAIRE FOR DETECTING SIGNS OF VEGETATIVE CHANGES (A.M. VEIN, 1998)

Patient_____Date_____

	Yes	Points	No
1. Do you notice (with any excitement) a tendency to:			
(a) facial redness	Yes	3	No
b) facial pallor	Yes	3	No
2. Do you experience numbness or coldness in:			
(a) fingers, toes, feet	Yes	3	No
b) whole hands, feet	Yes	4	No
3. Do you have any colour changes (pale, redness, lividity):			
(a) fingers, toes, feet	Yes	5	No
b) whole hands, feet	Yes	5	No
4. Do you experience excessive sweating? If the answer is "yes", underline the word "constant" or "when excited".	Yes	4	No
5. Do you have frequent feelings of palpitations, "freezing", "cardiac arrest"?	Yes	7	No
6. Do you often experience breathing difficulties: shortness of breath, rapid breathing? If the answer is "yes", specify: in excitement, in a stuffy room (underline the word).	**Yes**	7	No
7. Is your gastrointestinal tract dysfunction characteristic of you: tendency to constipation, diarrhoea, abdominal "bloating", pain?	Yes	6	No
8. Do you have fainting spells (sudden loss of consciousness or the feeling that you might lose consciousness)? If yes, specify the conditions: stuffy room, excitement, length of time in an upright position (underline the appropriate word).	Yes	7	No
9. Do you have episodic headaches? If "yes", specify: diffuse or only half of the head, "whole head", compressive or throbbing (underline as appropriate).	**Yes**	7	No
10. Do you currently experience a decrease in performance, rapid fatigue?	**Yes**	5	No
11. Do you notice any sleep disturbances? If the answer is "yes", specify: a) difficulty falling asleep; b) shallow, shallow sleep with frequent awakenings: c) feeling of sleeplessness, fatigue when waking up.	Yes	5	No

If the total score is equal to or greater than 15, autonomic dystonia syndrome is suspected.

21. *APPENDIX 7.* BECK ANXIETY SCALE

	Didn't bother me at all (0)	**Slightly** Didn't bother me too much (1)	**Moderately** It was unpleasant, but I could bear it (2)	**Very much** I could hardly stand it**.** (3)
1. A feeling of numbness or tingling in the body				
2. Feeling hot				
3. Shivering in my legs				
4. Inability to relax				
5. Fear that the worst will happen				
6. Dizziness or a feeling of lightness in the head				
7. Rapid heartbeat				
8. Unsteadiness				
9. Sense of dread				
10. Nervousness				
11. Shivering in my hands				
12. Feeling of suffocation				
13. Shaky gait				
14. Fear of loss of control				

15. Shortness of breath				
16. Fear of death				
17. Fright				
18. Gastrointestinal disorders				
19. Fainting spells				
20. Rush of blood to the face				
21. Increased sweating (not heat related)				

Counting the results:

Each column is assigned a specific score.

Didn't bother me at all - **0 points**

Slightly**-1 point**

Moderate - **2 points**

Very strong - **3 points**

The total amount of points is calculated:

0 to 9 - no alarm (normal state)

10 to 18 - degree of anxiety from mild to moderate

19 to 29 - degree of anxiety from moderate to severe

30 or more points - severe anxiety.

22. APPENDIX 8. DIGIT SYMBOL SUBSTITUTION TEST.

Digit	1	2	3	4	5	**6**	7	8	9	Total Score
Symbol	⎯⎯	⊥	]	└	U	O	∧	X	=	

Samples

2	**1**	**3**	**7**	**2**	**4**	**8**	**1**	**5**	**4**		**2**	**1**	**3**	**2**	**1**	**4**	**2**	**3**	**5**	**2**	**3**	**1**	**4**	**6**	**3**

1	**5**	**4**	**2**	**7**	**6**	**3**	**5**	**7**	**2**		**8**	**5**	**4**	**6**	**3**	**7**	**2**	**8**	**1**	**9**	**5**	**8**	**4**	**7**	**3**

6	**2**	**5**	**1**	**9**	**2**	**8**	**3**	**7**	**4**		**6**	**5**	**9**	**4**	**8**	**3**	**7**	**2**	**6**	**1**	**5**	**4**	**6**	**3**	**7**

9	**2**	**8**	**1**	**7**	**9**	**4**	**6**	**8**	**5**		**9**	**7**	**1**	**8**	**5**	**2**	**9**	**4**	**8**	**6**	**3**	**7**	**9**	**8**	**6**

23. *APPENDIX 9.* TINETTI TEST [54, 55].

General Resilience Scale

- The maximum number of points is 24.
- Sitting stability (0 - 1 point);
- Stability when attempting to stand up (0-2 points);
- Getting up from the supine position (0 - 2 points);
- Stability for 5 sec after standing up (0 - 2 points);
- Duration of standing (relative to standing for less than one minute) (0 - 2 points);
- Standing on one leg (right) for 5 sec (0 - 1 point);
- Standing on one leg (left) for 5 sec (0 - 1 point);
- Stability when standing with eyes closed (0 - 1 point);
- Chest thrust stability (0 - 2 points);
- Stepping over while turning 360 degrees (0 - 1 point);
- Stability when turning 360 degrees (0 - 1 point);
- Stability when performing back bends (0 - 2 points);
- When reaching upwards (0 - 2 points);
- Stability when performing a downward bend (0 - 2 points);
- When sitting down on a chair (0 - 2 points).

Degree of sustainability disruption:

- significant - 0 - 10 points;
- moderate - 11 to 20 points;
- light - 21 to 22 points;
- the norm is 23 to 24 points.

Gait scale

- Beginning of movement (0 - 1 point);
- Step symmetry (0 - 1 point);
- Continuity of walking (0 - 1 point);
- Step length of the left foot (0 - 1 point);
- Step length of the right foot (0 - 1 point);
- Deviation from the line of travel (0 - 2 points);
- Stability when walking (0 - 1 point);
- Degree of torso sway (0 - 2 points);
- Rotations (0 - 2 points);
- Arbitrary increase in walking speed (0 - 2 points);
- Step height of the right foot (0 - 1 point);
- Step height of the left foot (0 - 1 point).

The degree of gait disturbance:

- significant - 0 - 10 points;

- moderate - 11 to 13 points;
- light - 14 to 15 points;
- norm - 16 points.

Degree of impairment of general **motor activity** (degree of impairment of stability + degree of impairment of gait):

- significant - 0 - 20 points;
- moderate - 21 - 33 points;
- light - 34 - 38 points;
- norm - 39 - 40 points.

24. *APPENDIX 10.* THE CLINICAL GLOBAL IMPRESSIONS SCALE

Overall clinical impression

1. QSORRES disease severity at QSTESTCD = CGI0101

Given your general clinical experience with a specific population group, would you assess the patient's mental state at this time?

0 = Not assessed
1 = Normal, not ill
2 = Condition bordering on "mentally ill"
3 = Mildly ill
4 = Moderately ill
5 = Ill to a great extent
6 = Severely ill
7 - Refers to patients with an extremely severe condition

2. Overall Improvement: Give an assessment, in your opinion, of whether the overall improvement is related to drug therapy or not.

How much has the patient's condition improved compared to the condition at the beginning of participation in the project? **QSORRES at QSTESTCD = CGI0102**

0 = Not assessed
1 = Very much improved
2 = Strongly improved
3 = Slightly improved
4 = No change
5 = Deteriorated slightly
6 = Severely deteriorated
7 = Very badly deteriorated

3. Efficacy indicator: Evaluate this item based on the **action of the medication. QSORRES at QSTESTCD = CGI0103**

Select the terms that best describe the degree of therapeutic effect, and side effects, and record the number in the cell where the two numbers overlap.

EXAMPLE: The therapeutic effects were rated as "Moderate" and adverse events were rated as "No significant effect on patient's activities of daily living".

Therapeutic effects		**Side effects**			
		Absent	*No significant impact on the patient's patient functioning*	*Have a significant impact on patient functioning*	*Beyond therapeutic effect*
To a large extent	Strong improvement. Complete or almost complete remission of all symptoms.	01	02	03	04
Moderately	Tangible improvement. Partial remission of symptoms.	05	06	07	08
To a small extent	Minor improvement that does not affect the patient's treatment status.	09	10	11	12
No change or deterioration		13	14	15	16

Not assessed = 00

Reproduced from Assessment Manual for Psychopharmacology, ed. Guy W., 1976, Rockville, Maryland, U.S. Department of Health, Education and Welfare.

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