Multicenter double-blind placebo-controlled randomized parallel group clinical study of efficacy and safety of MMH-MAP in the treatment of cognitive disorders in patients with ischemic stroke in the carotid arteries

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-MAP-002**
Version date:	**June 11, 2019**
ClinicalTrials.gov Id:	**NCT04295681**

Protocol Summary

This document represents the protocol summary for the study on human subjects. The study will be carried out in accordance with ICH GCP, National Standard of the Russian Federation GOST 52379-2005 "Good Clinical Practice", World Medical Association Declaration of Helsinki, relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

Multicenter double-blind placebo-controlled randomized parallel group clinical study of efficacy and safety of MMH-MAP in the treatment of cognitive disorders in patients with ischemic stroke in the carotid arteries.

Phase: III

Sponsor: Company «MATERIA MEDICA HOLDING», Moscow, Russia

Protocol No. MMH-MAP-002

Purposes of the study

- To evaluate efficacy of MMH-MAP in the treatment of cognitive disorders in patients with ischemic stroke in the carotid arteries.
- To evaluate the safety of MMH-MAP in the treatment of cognitive disorders in patients with ischemic stroke in the carotid arteries.

Endpoints

Primary endpoint

1. Average MoCA score on treatment day 90.

Secondary endpoints

1. Changes in NIHSS score on treatment day 12, 90.
2. Percentage of patients with no major disability (mRs 0-1) after 90-day therapy.
3. Therapeutic and adverse effects, efficacy index according to clinical global impression scale (CGI-EI) after 90-day therapy.

Safety assessment

- Percentage of patients with sequelae of cerebral infarction (severe infections - hospital-acquired pneumonia, uroinfection; deep venous thrombosis, PATE; epileptic episodes) during IMP therapy.
- Frequency of all-cause mortality outcomes during IMP therapy.
- Percentage of patients with recurring cerebral infarction during IMP therapy.
- Occurrence and nature of adverse events (AEs) during the treatment, their intensity (severity), relation to the study drug, outcome.

- Changes in vital signs during IMP therapy.
- Percentage of patients with clinically relevant abnormal laboratory tests during IMP therapy.

Study design

Design: double-blind, randomized, parallel group placebo-controlled clinical study of efficacy and safety of MMH-MAP in the treatment of cognitive disorders in patients with ischemic stroke in the carotid arteries.

The study will enroll hospitalized subjects of either gender aged 40-75 years old with verified diagnosis of ischemic stroke in the carotid arteries within 72 hours post debut having moderate cognitive disorders, moderate neurological deficit.

At Visit 1 (day 1) the subject's complaints and medical history will be collected, objective examination, safety laboratory tests (hematology, serum chemistry, urinalysis) will be performed. The investigator will evaluate the patient's level of consciousness using The Glasgow Coma Scale, intensity of cognitive disorders using The Montreal Cognitive Assessment (MoCA), condition using National Institute of Health Stroke Scale (NIHSS) and The Modified Rankin Scale (mRs). Concomitant therapy will be recorded and changes in cerebral CT/MRI will be evaluated. If the subject meets inclusion criteria and has no exclusion criteria, he/she will be randomized to MMH-MAP or Placebo group. The first dose of the study product should be taken within 72 hours post stroke debut.

At Visit 2 (day 12±3, end of hospitalization period - the last day of hospitalization due to the current stroke) complaints will be collected, objective examination findings will be recorded, monitoring of the prescribed and concomitant therapy will be performed, treatment safety, compliance and stroke severity according to NIHSS will be evaluated.

By the end of hospital therapy the subject will be switched to outpatient therapy with continuation of IMP and medical assistance designed for the treatment of stroke and its sequelae.

At Visit 3 (day 45±7 days) the investigator will make a phone call to the subject evaluating the treatment safety.

At final Visit 4 (day 90±7 days) complaints will be collected, objective examination findings will be recorded, monitoring of the prescribed and concomitant therapy will be performed, treatment safety, compliance, condition according to NIHSS will be evaluated, mRs, Clinical Global Impression Efficacy Index (CGI-EI) will be filled. The investigator will perform MoCA testing. Safety laboratory tests (hematology, serum chemistry, urinalysis) will be carried out.

Throughout the study the patient will receive the treatment approved by the decree of the RF Ministry of Health dated 29.12.2012 No. 740n "On approval of standard of special care in

cerebral infarction" except for the products specified in section "Forbidden concomitant therapy".

Inclusion and exclusion criteria

Inclusion criteria

1. Age between 40 and 75 years old inclusively.
2. Ischemic stroke in the carotid arteries (I 63) within 72 hours post debut.
3. Moderate cognitive disorders (MoCA < 26).
4. Normal consciousness (Glasgow score 15).
5. Stroke severity 8-12 according to NIHSS.
6. Disability mRs score 2-3.
7. Availability of cerebral CT/MRI within 72 hours post stroke debut.
8. Patients who agreed to use a reliable method of contraception during the study.
9. Patients who have signed the Participant Information Sheet and Informed Consent.

Exclusion criteria

1. Current or previous subarachnoidal/parenchymatous/ventricular hemorrhage, cerebral infarction, cerebral tumour.
2. Cerebral CT/MRI findings suggesting cerebral hemorrhage, tumour within 72 hours post stroke debut.
3. Scheduled or completed thrombolytic therapy for the treatment of the current cerebral infarction.
4. Central nervous system (CNS) diseases including:
    - Inflammatory diseases of the central nervous system (G00-G09);
    - Systemic atrophies primarily affecting the central nervous system (G10-G13);
    - Extrapyramidal and movement disorders (G20-G26);
    - Other degenerative diseases of the nervous system (G30-G32);
    - Demyelinating diseases of the CNS (G35-G37);
    - Episodic and paroxysmal disorders (G40-G47);
    - Polyneuropathies and other disorders of the peripheral nervous system (G60-64), with marked movement and/or sensory impairments that cause movement disorders;
    - Hydrocephalus (G91).
5. Head injuries (S00-S09) (including history), accompanied by impaired consciousness, brain contusion or open craniocerebral injuries.
6. Musculoskeletal disorders causing motor disturbances.
7. Presence (including history) (F00-F03).

8. Malignant neoplasms.
9. Patients previously diagnosed with class IV heart failure (1964 New York Heart Association functional classification), hypothyroidism, or poorly treated diabetes mellitus.
10. Patients having unstable angina or myocardial infarction in the past 6 months.
11. Allergy/ intolerance to any of the components of medications used in the treatment.
12. Malabsorption syndrome, including congenital or acquired lactase deficiency (or any other disaccharidase deficiency) and galactosemia.
13. Any conditions which, according to the investigator opinion, may interfere with the subject's participation in the study.
14. Prior history of non-adherence to a drug regimen, a psychiatric disorder, alcoholism or drug abuse, which, in the opinion of the investigator, can compromise compliance with study protocol.
15. Pregnancy, breast-feeding; childbirth less than 3 months prior to the inclusion in the trial, unwillingness to use contraceptive methods during the trial.
16. Participation in other clinical studies within 3 month prior to enrollment in the study.
17. Patients who are related to any of the on-site research personnel directly involved in the conduct of the trial or are an immediate relative of the study investigator. 'Immediate relative' means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
18. Patients who work for OOO "NPF "Materia Medica Holding" (i.e. the company's employees, temporary contract workers, designated officials responsible for carrying out the research or any immediate relatives of the aforementioned).

Criteria for Withdrawal or Termination

1. Screening failure.
2. Inability or patient’s refusal to comply with the protocol requirements.
3. Necessity in medications prohibited within the study.
4. An adverse event requiring discontinuation of the study drug.
5. Eligibility error.
6. Patient's desire to complete the study early for any reason.
7. Pregnancy.
8. Participation in any other clinical trial.
9. Cases not covered by the protocol where the investigator believes that the patient's continued participation in the study is harmful to him.

Number of subjects

It is planned to include 246 subjects, which is expected to yield at least 196 patients (98 x 2 groups - MMH-MAP and Placebo) completing all protocol procedures.

Interim analysis

The study included two interim analyses: on 15 and 30 percent of the recruited patients. Distribution of the first type error in accordance with the O'Brien–Fleming error waste function, of the second type – in accordance with the Pocock function. It is possible to stop the study early due to both acceptance and rejection of the null hypothesis. The interim analysis is based on the data obtained from the results of examination and treatment of the number of patients established by the protocol who completely completed participation in the study. Number of patients for the first interim analysis: 30 patients (MMN-MAP group - 15 patients, Placebo group - 15 patients). Number of patients for the second interim analysis: 60 patients (MMN-MAP group - 30 patients, Placebo group - 30 patients). Number of patients for the final analysis: 196 patients (MMN-MAP group - 98 patients, Placebo group - 98 patients).

Treatment

Group 1

Name of the medicinal product: MMH-MAP

Active ingredient: Modified affinity purified antibodies to S100 brain-specific protein - 0.006 g*.

** applied onto lactose monohydrate as a water-alcohol mixture containing no more than 10^{-391} ng/g active form of the API*

Excipients: Lactose monohydrate - 0.267 g

Microcrystalline cellulose - 0.030 g

Magnesium stearate - 0.003 g

Method of administration: Tablet for oral use. 2 tablets twice daily (approximately at the same time), outside the meal (between meals or 15 minutes before meals or fluids). Keep the tablets in mouth until completely dissolved.

Dosage form: Tablets.

Description: Flat cylinder-shaped scored beveled edge white to off-white tablets with a smooth, uniform surface.

Storage conditions: At temperature ≤ 25 ºC.

Group 2

Name of the medicinal product: Placebo

Active ingredient: No

Excipients: Lactose monohydrate - 0.267 g

Microcrystalline cellulose - 0.030 g

Magnesium stearate - 0.003 g

Method of administration: Tablet for oral use. Dose per administration: 2 tablets. 2 tablets twice daily (4 tablets/day). The tablets should be held in mouth without chewing until complete dissolution.

Dosage form: Tablets.

Description: Flat cylinder-shaped scored beveled edge white to off-white tablets with a smooth, uniform surface.

Storage conditions: Store at a temperature not exceeding 25 ° C.

Treatment duration

MMH-MAP/Placebo treatment duration is 90 days.

Observation period

In total the patients will be monitored for 90 days.

Hospital stage – 12 days;

Outpatient stage – 78 days.

Symptomatic (Standard) treatment

During the study, patients can receive basic therapy approved by order No. 1740n of the Ministry of Health of the Russian Federation dated December 29, 2012 “On approval of the standard of specialized care for cerebral infarction.”

Basic therapy is selected for each patient individually and may include: antihypertensive drugs, ACE inhibitors, angiotensin II receptor antagonists, β-blockers or α- and β-blockers, calcium antagonists, diuretics (thiazide, aldosterone receptor antagonist), antiplatelet agents (acetylsalicylic acid, clopidogrel , dipyridamole, ticlopidine, etc.), statins and their combinations, as well as a complex of rehabilitation measures.

Patients are allowed to receive medications used to treat concurrent diseases except for the products listed in section "Forbidden concomitant therapy".

During the study, the patient may receive therapy for concomitant diseases and conditions, except for the medicines specified in the section "Prohibited concomitant treatment."

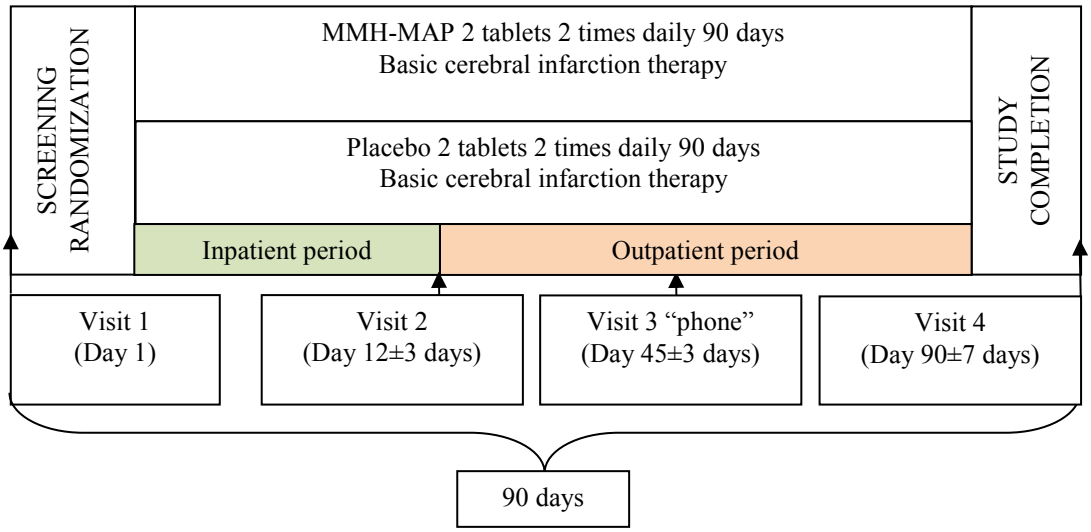
Prohibited concomitant therapy

During the study (after signing patient information sheet and informed consent form) the following medications are prohibited (ATC group is specified in brackets):

1. Nicotinic acid and its derivatives; purines (xanthinol nicotinate, pentoxifylline), ergot alkaloids (nicergoline, alpha-dihydroergocryptine+caffeine), other vasodilators (vincamine, bencyclan, naftidrofuryl), papaverine, etamivan+etophylline+hexobendine.

2. Antiepileptic agents (N03A).
3. Anchicnolonergic agents (N04A).
4. Dopaminergic agents (N04B).
5. Actovegin.
6. Pyrrolidine derivatives (racetams: piracetam, etiracetam, aniracetam, etc.); idebenone; pyridoxine derivatives (pyritinol, biotredin, etc.); dimethylaminoethanol derivatives (acetylcholine precursors: deanol aceglumate, meclofenoxate etc.).
7. Other anti-dementia agents (N06DX): ginkgo biloba, memantine, etc.
8. General restoraive agents and adaptogens (A13A): ginseng, melatonin, etc.
9. Any unregistered medicinal product and/or vaccine.
10. Drugs that previously caused allergic reactions in patient.

Study design scheme



Schedule of study procedures

Procedure/Visit	*Visit 1 Screening, Randomization (Day 1)*	*Visit 2* (Day 12±3 days)*	*Visit 3 «phone visit» (Day 45±3 days)*	*Visit 4** (Day 90±7 days)*
Informed consent	+			
Registration patient in IVRS and assignment of a personal code	+			
Collection of complaints	+	+	+	+
Medical history	+			
Concomitant conditions and diseases	+			

Physical examination	+	+		+
Evaluation of vital signs (HR, RR, BP) ***	+	+		+
Recording therapy for concomitant diseases	+	+	+	+
Filling MoCA scale	+			+
Filling Glasgow scale	+			
Filling NIHSS scale	+	+		+
Filling mRs scale	+			+
Pregnancy test	+			
Safety laboratory tests	+			+
Inclusion/exclusion criteria	+			
Randomization	+			
Dispensing of study drug	+	+		
Study drug accountability and return		+		+
Treatment compliance		+		+
Evaluation of study treatment safety	+	+	+	+
Filling CGI-EI scale				+
Visit completion	+	+	+	+
Study completion				+

* *The end of the inpatient period is the last day of hospitalization for the current stroke*
** *Study completion*
*** *HR - heart rate; RR - respiration rate; BP - blood pressure*

Statistical Analyses

Samples

Total set includes all the subjects who have signed ICF. This sample will consider all adverse events (AEs) throughout the study, including those occurred prior to the study therapy.

The sample including all patients who received at least one dose of the study drug to be used for ***analysis of the study treatment safety and tolerability*** (*Safety population*), as all AEs identified after the study drug administration will be recorded.

Full Analysis Set This sample will consist of all enrolled patients, except for those who met at least one of the following criteria:

1) non-compliance with inclusion/exclusion criteria;
2) patient did not take any dose of study drug;
3) absence of any patient data after administration of study drug.

This was the best set for the Intention-to-treat method, so it will be used in the ***Intention-to-treat efficacy analysis (ITT-analysis) of the study therapy.***

Per Protocol set. This sample includes all patients who received full protocol therapy and completed all scheduled visits. This set will be used for ***Per Protocol analysis (PP analysis) of efficacy of study therapy***. *Per Protocol set* will not include the patients whose data are fully or partially invalid for analysis due to a protocol deviation.

Protocol deviations resulting in full or partial data invalidity:

1. Violation of visit schedule.
2. Inappropriate distribution/issue of the study drug.
3. Prescription of prohibited therapy.
4. Increase or decrease of 25% or more in the amount of study therapy received.
5. Inability to assess patient's objective compliance (adherence to therapy) according to the formula (e.g. loss of packaging).
6. Gross inconsistencies between source documents and CRF detected during monitoring or other authorized inspection.
7. Violations of the Informed consent procedure.
8. Non-compliance with the clinical study protocol procedures.
9. Inability to collect all patient's data used for evaluation of the study endpoints (e.g. lack of entries in source documents required for verification of inclusion/exclusion criteria, safety and efficacy criteria).
10. Other protocol deviations resulting in full or partial data invalidity.

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software.[1]

Evaluation of sample size

The sample size was assessed in accordance with the following rules and assumptions:

1. Statistical assumptions:
   - 1.1 the power of statistical tests 'P = (1 − β)' is 80% (the probability of correct rejection of the null hypothesis is 0.8)
   - 1.2 the probability of type 1 error 'a' is less that 5% (the probability of false acceptance of the alternative hypothesis is less than 0.05)
   - 1.3 statistical criteria of intergroup comparisons are two-sided, unless otherwise stated
   - 1.4 calculation of sample size will be based on the assumptions on the expected effect declared in the primary efficacy criterion of the protocol

[1] Holder of license: OOO "NPF "Materia Medica Holding", No. 70100045.

1.5 ratio between sample sizes of MMH-MAP and Placebo sample sizes is 1:1 (1 MMH-MAP patient per 1 Placebo patient)

1.6 statistical hypotheses - null and alternative hypotheses on the difference between study drug and placebo under the dosing regimen used:

$$\mathbf{H_0: \mu_1 - \mu_2 = 0}$$

$$\mathbf{H_a: \mu_1 - \mu_2 \neq 0}$$

where μ_1 - change in mean MoCA summary score in MMH-MAP group, μ_2 - change in mean MoCA summary score in Placebo group

1.7 calculation of sample size for statistical criteria was made using the following program code:

Proc seqdesign errspend
Design nstages = 3
Info = cum (0.15,0.3,1)
Method (alpha) = UNI (rho = 0.5 tau = 0)
Method (beta) = UNI (rho = 0 tau = 0)
Stop = both
Alpha = 0.05
Beta = 0.2
Samplesize model = twosamplemean (meandiff = 1.3 stddev = 3.0)
Run

1.8 terminal sample size will be determined using the formula:

$$N_T = N_{PP}/(1 - K_B)$$

where N_T – terminal sample size; N_{PP} – result of calculation in c. 1.7 i.e. scheduled number of patients completing the study per protocol; K_B – withdrawal rate.

2. Assumptions on expected clinical study effects.

It is assumed that the difference between the changes in the mean total MoCA score in the Study Drug and Placebo groups on Day 90 of treatment will be at least 1.3 points with a standard deviation of at least 3.0 points.

Therefore, group size needed to compare Study Drug and Placebo will be **98** patients for each group. Given potential withdrawal of at least 20% patients ($K_B = 0.2$) during the study for various reasons, at least **246** patients will be required to sign informed consent, with **123** patients per group (see cl. 1.8).

Statistical criteria

All statistical calculations will be made using two groups of statistical criteria:

- parametric - to obtain effective estimates for random parameters in case the relevant conditions of method/model applicability are not violated (e.g. sphericity, normality, risk proportionality, etc.)
- nonparametric – in all other cases.

Parametric criteria

The application of parametric criteria will be accompanied by a check of models for applicability (e.g. Kolmogorov-Smirnov test, Shapiro-Wilk test).

The following parametric methods and approaches are supposed to be used:

1. To evaluate the differences in continuous variables obtained in one group at two different visits – Student t-test for paired samples.
2. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or covariance (ANCOVA) modified with repeated measures.
3. In case of multiple comparisons of the groups various corrections for multiplicity will be used, e.g. Dunnett, Tukey, Scheffe, Holm adapted test, etc.
4. Generalized Linear Models and/or Mixed Linear Models will be used in case of abnormal data distribution.
5. Selection of the type of distribution, specification of factor and covariance structures of the model will be made using fit-statistics such as AIC (Akaike information criterion).

The following SAS software programs are supposed to be applied to the above listed tests and techniques:

- UNIVARIATE – normality verification of the distributions under comparison
- CORR, MEANS – calculation of descriptive statistics
- TTEST – Student's test with all modifications
- GLM – generalized linear models for studying temporal dynamics (ANOVA, ANCOVA)
- GENMOD – generalized linear models
- MIXED – mixed linear models.

Non-parametric criteria

Below are potential types of comparisons with relevant criteria:

1. To evaluate time changes in the parameters compared – Friedman test, non-parametric analogue of analysis of variance with repeated measures.
2. For frequency analysis of contingency tables 2×2 – $\chi2$ (if the frequency under comparison > 5) or exact Fisher's test (if one of the frequencies under comparison < 5).

3. Cochran-Mantel-Haenszel test (modified $\chi 2$ test for multiple comparisons) – to perform frequency analysis based on independent strata.
4. For frequency analysis of data on presence/absence of an event or outcome during repeated measurements (contingency tables with dependent strata) – survival analysis.

To perform the above-mentioned nonparametric statistical analysis the following SAS procedures are to be used:

- FREQ – Friedman test, $\chi 2$ test and/or exact Fisher's test; Cochran-Mantel-Haenszel test
- LIFETEST, PHREG – survival analysis
- NPAR1WAY - Mann-Whitney U-test

Safety parameters

Adverse events recorded during the study will be grouped into frequency tables by severity, seriousness and relationship with the study drug.

Data presentation

Descriptive statistics will be provided for each study continuous / interval variable. Numerical data will be presented by mean, standard deviation, min and max values. Comparisons suggesting statistical conclusion will have the relevant confidence intervals. Outliers will be analyzed individually. The data will be grouped by visits. The categorical variables will be presented as frequency tables by visits.