Multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of MMH-MAP in the treatment of mild cognitive impairment in subjects in early rehabilitation period of ischemic stroke

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-MAP-001**
Version date:	**August 29, 2018**
ClinicalTrials.gov Id:	**NCT03815292**

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 mild cognitive impairment in subjects in early rehabilitation period of ischemic stroke.

Phase: III

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

Protocol No. MMH-MAP-001

Objective of the study

- To evaluate efficacy of MMH-MAP in the treatment of mild cognitive impairment in subjects in early rehabilitation period of ischemic stroke.
- To evaluate the safety of MMH-MAP in the treatment of mild cognitive impairment in subjects in early rehabilitation period of ischemic stroke.

Endpoints

Primary endpoint

1. Proportion of subjects with improved cognitive functions (MoCA ≥ +1) after 24-week therapy compared to baseline.

Secondary endpoints

1. Change in MoCA scores after 24 weeks of treatment.
2. Percentage of patients with improved performance in activities of daily living (total Barthel Index score + 5 or more) after 24 weeks of treatment.
3. Changes in Barthel index for activities of daily living after 24 weeks of treatment.
4. Change in SS-QOL total score after 24 weeks of therapy.
5. Therapeutic effect and adverse event values and CGI-EI scores after 24 weeks of treatment.
6. Changes in intensity of cognitive disorders (MoCA) in follow-up period (24–28 weeks).
7. Changes in Barthel index for activities of daily living in follow-up period (24−28 weeks).
8. Changes in SS-QOL in follow-up period (24−28 weeks).

Safety assessment

- Presence and nature of adverse events during the therapy, their intensity (severity), relation to the product, outcome.
- Changes in vital signs.
- Percentage of patients with clinically relevant laboratory abnormalities.

Study design

Design – multicenter double blind placebo-controlled randomized parallel-group clinical study.

The study patients are subjects of either gender, aged 45-80 years old, after an ischemic stroke within 3-6 months prior to enrollment and confirmed by neuroimaging, having mild cognitive impairment.

After the patients provide signed Participant Information Sheet and Informed Consent, they will be interviewed for complaints and medical history and undergo physical examination and laboratory tests. The doctor will rate the severity of patients' cognitive impairments on the Mini Mental State Examination (MMSE) scale and Montreal Cognitive Assessment (MoCA) scale, assess their performance in activities of daily living on the Barthel Index scale, and administer the Stroke Specific Quality of Life Scale (SS-QOL) questionnaire. Eligible participants will have to have moderate cognitive impairments (MMSE score - at least 21 and MoCA - less than 26). Therapy received by patients for their co-morbidities and primary diagnosis will be recorded. All women of childbearing potential will be administered pregnancy tests.

If a patient meets all inclusion criteria and does not have any exclusion criteria at Visit 1, he/she is randomized to one of the two groups: group 1 will receive MMH-MAP at 2 tablets twice daily; group 2 will receive Placebo using the study product dosing regimen. The total duration of follow-up and treatment will be 28 weeks, which will include 5 additional visits.

At Visit 2 (Week 4±7 days), the doctor records patients' complaints and physical examination data, reviews the progress of study and basic and concomitant therapy, and assesses treatment safety and patient compliance with treatment.

At Visit 3 (Week 8±7 days), Visit 4 (Week 16±7 days), and Visit 5 (Week 24±7 days), the doctor assesses patients' cognitive impairments (MoCA) and performance in activities of daily living (the Barthel Index). The patients complete the SS-QOL questionnaire.

At Visit 5 (Week 24±7 days), the doctor will additionally complete the Clinical Global Impression Efficacy Index (CGI-EI) scale and collect samples for laboratory testing. The patient stops taking the study drug.

After four weeks following the end of study therapy patients complete a follow-up visit –Visit 6 (Week 28±7 days). The patients are interviewed for complaints and undergo physical

examination, with a check on their concomitant and primary therapies as well as on the safety of study treatment. The doctor assesses patients' cognitive impairments (MoCA) and performance in activities of daily living (the Barthel Index) and administers the SS-QOL questionnaire.

The total length of the observation period will be 28 weeks.

During the study, symptomatic therapy and therapy for underlying chronic conditions are allowed with the exception of the drugs indicated in the section “Prohibited Concomitant Treatment”.

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of either sex, aged 45 to 80 years old inclusively.
2. Patients with a history of one stroke sustained 3 to 6 months prior to study entry and confirmed by neuroimaging.
3. Patients with cognitive impairment (MoCA score < 26).
4. Patients with moderate performance in activities of daily living (Barthel score = 61-80).
5. Agreement to use a reliable method of birth control for the duration of the study (men and women of reproductive potential)
6. Availability of signed patient information sheet (Informed Consent form) for participation in the clinical trial.

Exclusion criteria

1. Patients with a history of subarachnoid/parenchymatous/ventricular hemorrhage, brain neoplasm, or any other condition which has caused neurological dysfunction.
2. History of central nervous system (CNS) disorders, including:
   - inflammatory diseases of the CNS (G00-G09)
   - systemic atrophies primarily affecting the CNS (G10-G13)
   - extrapyramidal and movement disorders (G20-G26)
   - other degenerative diseases of the nervous system (G30-G32)
   - demyelinating diseases of the CNS (G35-G37)
   - epilepsy (G40–41)
   - polyneuropathies and other disorders of the peripheral nervous system (G60-64), with marked movement and/or sensory impairments that cause movement disorders
   - diseases of neuromuscular junction and muscle (G70-73)
   - hydrocephalus (G91)
   - compression of brain (G93.5).
3. Dementia (20 or less on the MMSE score).

4. Speech disorders affecting investigator-patient communication.
5. Prior diagnosis of heart failure defined by the New York Heart Association classification (1964) as IV Functional Classification or poorly treated hypothyroidism or diabetes mellitus.
6. Patients having unstable angina or myocardial infarction in the past 6 months.
7. History/suspicion of oncology of any location (except for benign neoplasms).
8. Any other co-morbidity which, in the opinion of the investigator, may affect patient participation in the clinical trial.
9. Patients allergic to/intolerant of any components of the study treatment.
10. Patients with hereditary lactose intolerance.
11. Malabsorption syndrome, including congenital or acquired lactase deficiency (or any other disaccharidase deficiency) and galactosemia.
12. Pregnancy, breast-feeding or unwillingness to use birth control during the study.
13. Patients who, from the investigator's point of view, will not comply with the observation requirements of the study or adhere to study drug dosing regimens.
14. Patients with a history of non-adherence to medication; mental disorder (except for cognitive deficits); or alcoholism or abuse of psychoactive substances, which, in the investigator's opinion, will compromise compliance with study procedures.
15. Patients who have used medications listed in 'Prohibited Concomitant Treatment' in the past week.
16. Participation in other clinical trials in the previous 3 months.
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 MATERIA MEDICA HOLDING (i.e. the company's employees, temporary contract workers, appointed officials responsible for carrying out the research or 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 product.
5. Eligibility error.
6. Pregnancy.

7. Patient's decision to complete the study ahead of schedule due to lack of the therapy efficacy or any reasons.
8. Enrollment of the subject into another clinical study.
9. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.
10. Unblinding.

Number of subjects

It is planned to include 276 subjects, which is expected to yield at least 220 patients completing all protocol procedures.

Interim analysis

Two interim analyses are scheduled in the study: involving 15% and 30% subjects recruited. Type 1 error distribution is in accordance with O'Brien-Fleming alpha spending function, type II - according to Pocock test. Early study termination is possible both due to acceptance and rejection of null hypothesis.

Treatment

Group 1

Name of the medicinal product: MMH-MAP

Active ingredient: Affinity purified antibodies to S-100 brain protein – 0.006 g, modified. C200 dilution.

Excipients: Lactose monohydrate - 0.267g
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.

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.

Storage conditions: At temperature ≤ 25 ºC.

Treatment duration

MMH-MAP/Placebo treatment duration is 24 weeks.

Observation period

The total length of patient observation is 28 weeks (screening + randomization – up to 1 day, treatment – 24 weeks, follow-up – 4 weeks).

Symptomatic (Standard) treatment

Throughout the study the subject will receive therapy for the underlying disease including therapy designed for secondary prevention of stroke and other vascular events except for the medicinal products referred to in "Prohibited concomitant therapy".

1. Antihypertensive products.
2. Angiotensin-converting enzyme (ACE) inhibitors.
3. Angiotensin II receptor antagonists.
4. β-adrenoblockers or α- and β-adrenoblockers.
5. Calcium antagonists (except for nimodipine).
6. Diurectics (thiazide, aldosterone receptor antagonist).
7. Antiplatelets (acetylsalicylic acid, clopidogrel, dipyridamol, ticlopidine, ticagrelor).
8. Anticoagulants.
9. Statins.
10. Antidiabetic drugs.
11. Other agents except for those referred to as prohibited ones.

Prohibited concomitant therapy

Within 1 week prior to enrollment and during the study (beginning from signing patient information sheet and informed consent form and initiation of screening) subjects are not allowed to receive any medications that may affect mental and emotional status (parenthesized is the ATC group):

1. Peripheral vasodilators (ATC group – C04) including nicotinic acid and its derivatives; purines (xantinol nicotinate, pentoxifylline), ergot alkaloids (nicergoline, alpha-

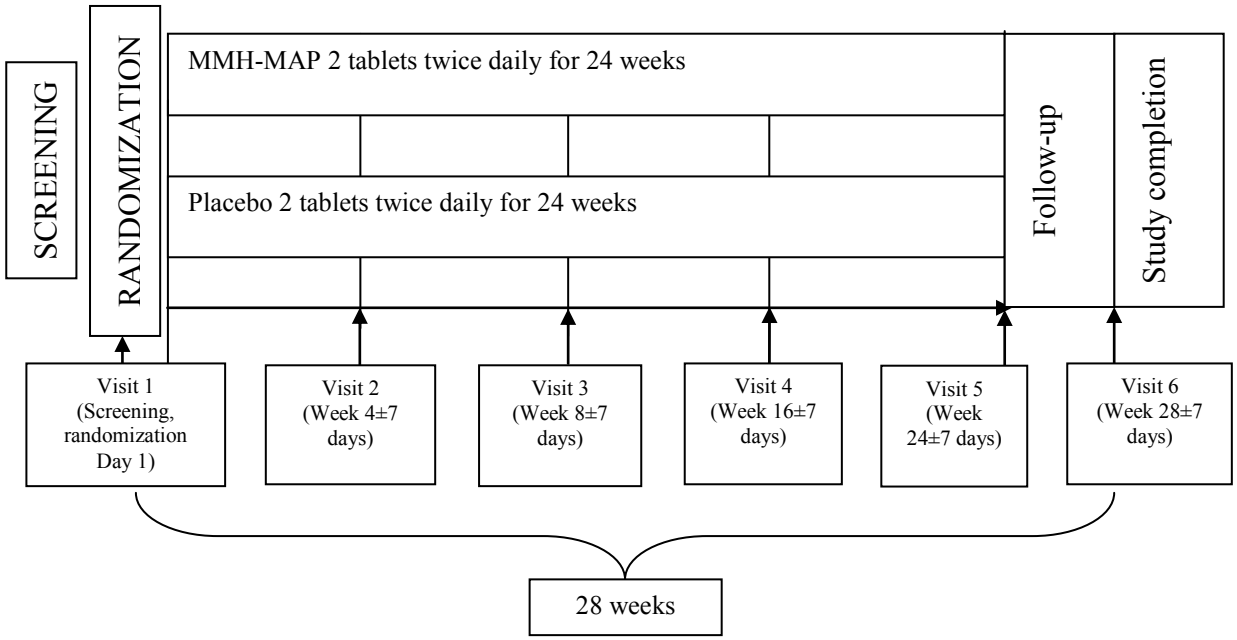
dihidroergocryptine + caffeine), other vasodilators (vincamine, bencyclane, naftidrofuryl), papaverine, etamivan+etophylline+hexobendine.

2. Calcium channel blockers − nimodipine (C08CA06), instenon (C01EX).
3. Muscle relaxants (M03).
4. Anticholinergic agents (N04A).
5. Dopaminergic agents (N04B).
6. Actovegin (B06).
7. Psycholeptics (N05), including anxiolytics (tranquilizers), hypnotics and sedatives.
8. Psychoanaleptics (N06), including antidepressants, psychostimulants and nootropics including:
   - pyrrolidine derivatives (racetams) – piracetam, etiracetam, aniracetam, etc.;
   - dimethylaminoethanol derivatives (acetylcholine precursors) - deanol aceglumate, meclofenoxate;
   - pyridoxine derivatives - pyritinol, biotredin;
   - GABA derivatives and analogues – gamma-aminobutyric acid, nicotinoyl gamma-aminobutyric acid, gamma-amino-beta-phenylbutyric acid hydrochloride, hopantenic acid, calcium gamma-hydroxybutirate;
   - gingko biloba;
   - neuropeptides and their analogues - methionyl-glutamyl-histidyl-phenylalanyl-propyl-glycyl-proline;
   - aminoacids and substances affecting excitatory amino acid system – glycine, pyrodoxine+threonine;
   - derivatives of 2-mercantobenzimidazole – ethylthiobenzymidazole hydrobromide;
   - idebenon;
   - vinpocetine;
   - polypeptides and organic composites - bovine cortical polypeptides, cerebrolysin;
   - memantine (N06DX01).
9. Other nervous system drugs (N07) including:
   - parasympathomimetics (N07A);
   - antivertigo preparations (N07C);
   - other nervous system drugs (N07X).
10. Substances of other pharmacological group with a nootropic ingredient including:
    - general tonic agents and adaptogens – ginseng, melatonin, lecithin, acetylaminosuccinic acid etc.;

- antihypoxants and antioxidants – ethylmethylhydroxypyridine succinate, citicoline, vitamin E, etc.;
- metabolic agents.

11. Any unauthorized product and/or vaccine.
12. 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 (Week 4±7 days)*	*Visit 3 (Week 8±7 days)*	*Visit 4 (Week 16±7 days)*	*Visit 5 (Week 24±7 days)*	*Visit 6 (Week 28±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	+	+	+	+	+	+

Recording basic therapy	+	+	+	+	+	+
Inclusion/exclusion criteria	+					
Randomization	+					
Filling MMSE	+					
Filling MoCA	+		+	+	+	+
Filling Barthel scale	+		+	+	+	+
Filling SS-QOL	+		+	+	+	+
Laboratory tests[1]	+				+	
Pregnancy test	+					
Drug issue	+	+	+	+		
Study drug accountability, compliance assessment		+	+	+	+	
Clinical Global Impression assessment (CGI-EI)					+	
Evaluation of treatment safety	+	+	+	+	+	+
Visit completion	+	+	+	+	+	+
Suggested duration of the subject's participation in the study						+

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

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

1) non-compliance with inclusion/exclusion criteria;
2) subject failing to take any dose of the study drug;
3) lack of any data on the subject after the study drug administration.

[1] Laboratory tests will be performed in central laboratory in subjects signing the relevant PIS and ICF.

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 test therapy.***

Per Protocol set. This set will comprise all the subjects receiving per protocol therapy in full and completing all the scheduled visits. This set will be used for ***efficacy Per Protocol analysis***. *Per Protocol set* will not include the subjects 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 product.
3. Prescription of prohibited therapy.
4. ≥ 25% increase or reduction in the amount of the study therapy administered.
5. Inability to assess the subject's compliance using the formula (e.g. loss of pack with the product).
6. Major discrepancies between source documents and CRF detected during monitoring or another authorized check.
7. Violation of the procedure for obtaining Informed consent.
8. Non-compliance with the clinical study protocol procedures.
9. Inability to collect all subject'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.[2]

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 will be two-sided, equivalence criterion - one-sided;

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

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;

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

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

$$\mathbf{H_0: \Theta_1 - \Theta_2 = 0}$$

$$\mathbf{H_a: \Theta_1 - \Theta_2 \neq 0}$$

where $\mathbf{\Theta_1}$ is frequency of the claimed event in MMH-MAP group, a $\mathbf{\Theta_2}$ is frequency of the claimed event 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 = twosamplefreq (test = PROP nullprop = 0.4 prop = 0.6)
Run;
```

1.8 terminal sample size will be determined using the formula:

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

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

2. Assumptions on expected clinical study effects:

Proportion of subjects with improved cognitive function (MoCA ≥ +1) after 24-week therapy with MMH-MAP is expected to be no less than 60%, Placebo – no more than 40%.

Therefore, group size needed to compare test product and placebo will be **110** subjects for each group. Given potential withdrawal of at least 20% subjects (**Rw=0.2)** during the study for various reasons, at least **276** subjects will be required to sign informed consent, with **138** subjects 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 parameters and approaches are to be used:

1. To evaluate the differences in continuous variables obtained in one group at two different visits – Student's test for matched samples.
2. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or modified repeated measures covariance (ANCOVA).
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 analysis of time changes (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, nonparametric analogue of repeated measures analysis of variance.
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 test.

Safety parameters

Adverse events recorded during the study will be grouped into frequency tables by severity, seriousness and relationship with the study drug. At least 138 subjects evenly distributed to the study groups will participate in blood and urine sampling for adequate assessment of laboratory values.

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.