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", Helsinki Declaration of World Medical Association, relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

Multicenter double-blind placebo-controlled parallel-group randomized clinical study of efficacy and safety of Tenoten for children liquid dosage form therapy in infants with sequelae of perinatal brain injury.

Phase: III
Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia
Protocol No. MMH-TD-004

Study purposes

- To assess the clinical efficacy of Tenoten for children liquid dosage form therapy (10 oral drops per day for 12 weeks) in infants with sequelae of perinatal brain injury (mild-to-moderate cerebral hypoxia-ischemia and/or mild-to-moderate intracranial hemorrhage).
- To assess the safety of Tenoten for children liquid dosage form therapy (10 oral drops per day for 12 weeks) in infants with sequelae of perinatal brain injury (mild-to-moderate cerebral hypoxia-ischemia and/or mild-to-moderate intracranial hemorrhage).

Endpoints

Primary endpoint

1. Percentage of patients with a 4 and more point increase of the total score according to Jurba-Mastyukova psychomotor development scale by the end of the treatment course compared to baseline.

Secondary endpoints

1. Percentage of patients with normal psychomotor development (≥ 27 scores on Jurba-Mastyukova scale) by the end of the treatment course compared to baseline.
2. Mean Cognitive adaptive test/Clinical linguistic and auditory milestone scale (CAT/CLAMS) by the end of the treatment course compared to baseline.

3. Percentage of patients with normal psychomotor development (CATS/CLAMS + Gross motor developmental quotients score ≥ 75) by the end of the treatment course compared to baseline.
4. Clinical Global Impression scale - Efficacy Index (CGI-EI) score by the end of the treatment course.

Safety assessment

- Adverse events during the treatment, their severity, treatment relatedness, and outcomes.

Study design

Study design: multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical study to assess efficacy and safety of the study therapy.

The study will enroll children of both genders aged from 29 days (end of neonatal period) up to 9 months on outpatient neurologist's observation due to sequelae of perinatal brain injury (mild-to-moderate cerebral hypoxia-ischemia and/or mild-to-moderate intracranial hemorrhage). The subjects of the study are not to be scheduled for any other treatments besides the investigated therapy within 12 weeks of the trial.

After parent/adoptive parent has signed the patient information sheet (informed consent form) the subject’s medical history will be collected, physical examination will be performed, body weight, length, and head circumference will be measured. The infant neurological status will be assessed including psychomotor development according to Jurba-Mastyukova scale and Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone (CAT/CLAMS) scale. Concomitant therapy will be recorded. If the subject meets inclusion criteria and has no exclusion criteria he/she will be included in the study and randomized at Visit 1 into one of the two groups: group 1 will receive Tenoten for children (oral drops) 10 oral drops per day for 12 weeks; group 2 - Placebo 10 oral drops per day for 12 weeks.

The subject will be observed for 12 weeks during which he/she will be examined by neurologist every 4 weeks (Visits 2, 3 and 4) in order to evaluate changes in physical and neuropsychological development, changes in neurological status, and to record potential adverse events, study treatment compliance.

At the final visit (Visit 4, Week 12) the neurologist will evaluate motor and mental development, fill in Jurba-Mastyukova and CAT/CLAMS scales, record adverse events, and assess the therapy compliance. Then the Clinical Global Impression – Efficacy Index (CGI-EI) scale will be filled in.

Music therapy, herbal baths, gymnastics and tactile stimulation based on the child's age are allowed during the study.

If the prohibited medicines are required for patients they will be withdrawn from the study and it will be considered as the absence of efficacy.

Inclusion and exclusion criteria

Inclusion criteria

1. Full-term infants aged 29 days to 9 months[1].
2. Diagnosis of sequelae of perinatal brain injury (mild-to-moderate cerebral hypoxia-ischemia and/or mild-to-moderate intracranial hemorrhage).
3. Jurba-Mastyukova total score < 27 and > 12.
4. Physical development parameters within 25-27 centiles.
5. Neurologist's outpatient observation.
6. Information sheet (informed consent form) for parents/adoptive parents for participation in the clinical study signed by the child's parents/adoptive parents.

Exclusion criteria

1. Previously diagnosed lesions, diseases and conditions:
    1.1. Cerebral ischemia (grade III).
    1.2. Intraventricular hemorrhage (grade III).
    1.3. Metabolic and toxic disorders affecting central nervous system (persistent neonatal hypoglycemia, hyperbilirubinemia associated with elevated indirect bilirubin, and other severe conditions).
    1.4. Intracranial birth injury, focal impairments due to brain injuries (pareses and paralyses).
    1.5. Sequelae of birth injury to spinal cord, cranial nerves and peripheral nervous system (peripheral pareses and paralyses).
    1.6. Different types of hydrocephalus.
    1.7. Symptomatic epilepsy and epileptic syndromes.
    1.8. Sequelae of perinatal central nervous system (CNS) infectious diseases (injury to CNS caused by neonatal sepsis, encephalitis, meningitis, meningoencephalitis, ventriculitis).
    1.9. Infectious diseases including congenital diseases (cytomegalovirus infection, rubella, herpesvirus or enterovirus infection, toxoplasmosis, syphilis, HIV infection, etc.).

[1] Full-term neonates, i.e. born at gestation term of 38-42 weeks with birth weight > 2500 g.

1.10. Chronic respiratory diseases originating in the perinatal period, including bronchopulmonary dysplasia.

1.11. Hereditary metabolic diseases including glycogen storage disease (glycogenoses, E74.0), galactose metabolism disorders (galactosemia, E74.2), other carbohydrate metabolism disorders (E74), glucosaminoglycan metabolism disorders (mucopolysaccharidoses, E76), aromatic amino-acid metabolism disorders (phenylketonuria, tyrosinemia, etc, E70), branched-chain amino-acid and fatty-acid metabolism disorders (maple-syrup-urine disease, E71), mitochondrial myopathy (G71.3).

1.12. Neurogenerative diseases including Huntington disease (G10), copper metabolism disorder (Wilson disease, E83.0).

1.13. Chromosomal abnormalities.

1.14. Congenital anomalies [malformations] and deformities including congenital anomalies of nervous system and malformations of internal organs.

1.15. Congenital endocrine diseases (congenital hypothyroidism, hypoparathyroidism, adrenocortical dysfunction).

1.16. Malignant neoplasm / suspected malignant neoplasm.

2. Acute infectious disease, exacerbation / decompensation of diseases that may prevent the patients' participation in the clinical study.
3. Allergy/intolerance of any of the study treatment medications components.
4. Drug addiction, alcohol use in the volume over 2 alcohol units/day by the subject's parent(s)/adoptive parent(s).
5. Mental disorders of the patient's parent(s)/adoptive parent(s).
6. Participation in other clinical studies for a period prior to and during the course of this trial.
7. Other conditions complicating the subject's participation in the study (cannot make regular medical visits, moving, etc.).
8. Subjects whose parent(s)/adoptive parent(s), from the investigator's point of view, will not follow the study requirements or comply with the dosing regimen.
9. Patients whose parent(s)/adoptive parent(s) are related research staff of the clinical investigative site who are directly involved in the study or is a close relative of the investigator. Close relatives include spouse, parents, children or brothers (sisters) regardless of whether they are biological or adoptive ones.
10. Patients whose parent(s)/adoptive parent(s) is working in OOO "NPF "Materia Medica Holding", i.e. is the company official, temporary contract worker or an appointed official responsible for the study or their close relatives.

Discontinuation criteria

1. Inability or refusal of parent(s)/adoptive parent(s) to compliance the protocol.
2. Necessity in the products not allowed within the study.
3. Development of an adverse event requiring the product discontinuation.
4. Parents'/adoptive parents' wish to terminate the study early due to lack of therapeutic efficacy or for any other reason.
5. Cases not specified by the protocol when, according to the investigator, further subject's participation is dangerous.
6. Enrollment of an ineligible subject.

Number of subjects

Signing informed consent by the parent(s)/adoptive parent(s) of 184 patients is planned; this is supposed to assure completion of all protocol procedures by at least 144 subjects.

Treatment

Group 1

Name: Tenoten for children

Active ingredient (per 1.0 mL): affinity purified antibodies to brain-specific S-100 protein - 0.006 g*

** administered as a mixture of three active water dilutions of the substance diluted respectively 100^{12}, 100^{30}, 100^{50} times*

Excipients: Maltitol − 0.06 g; glycerol − 0.03 g; potassium sorbate − 0.00165 g; citric acid anhydrous – 0.0002 g; purified water − up to 1.0 mL

Dosage: Per os. 10 drops (0.5 mL) once daily 15 min prior to morning feeding approximately at the same time. Prior to administration the drops may be diluted in small amount (1-5 mL) of boiled water of room temperature

Dosage form: Oral drops

Description: Colourless or almost colourless clear fluid

Storage conditions: Store protected from light at temperature below 25°C. Keep out of the reach of children. Do not freeze

Group 2

Name: Placebo

Active ingredient (per 1.0 mL): NA

Excipients: Maltitol − 0.06 g; glycerol − 0.03 g; potassium sorbate − 0.00165 g; citric acid anhydrous – 0.0002 g; purified water − up to 1.0 mL

Dosage: Placebo using Tenoten for children scheme.

Dosage form: Oral drops

Description: Colourless or almost colourless clear fluid

Storage conditions: Store protected from light at temperature below 25°C. Keep out of the reach of children. Do not freeze

Treatment period

Tenoten for children/Placebo treatment period is 12 weeks.

Basic therapy

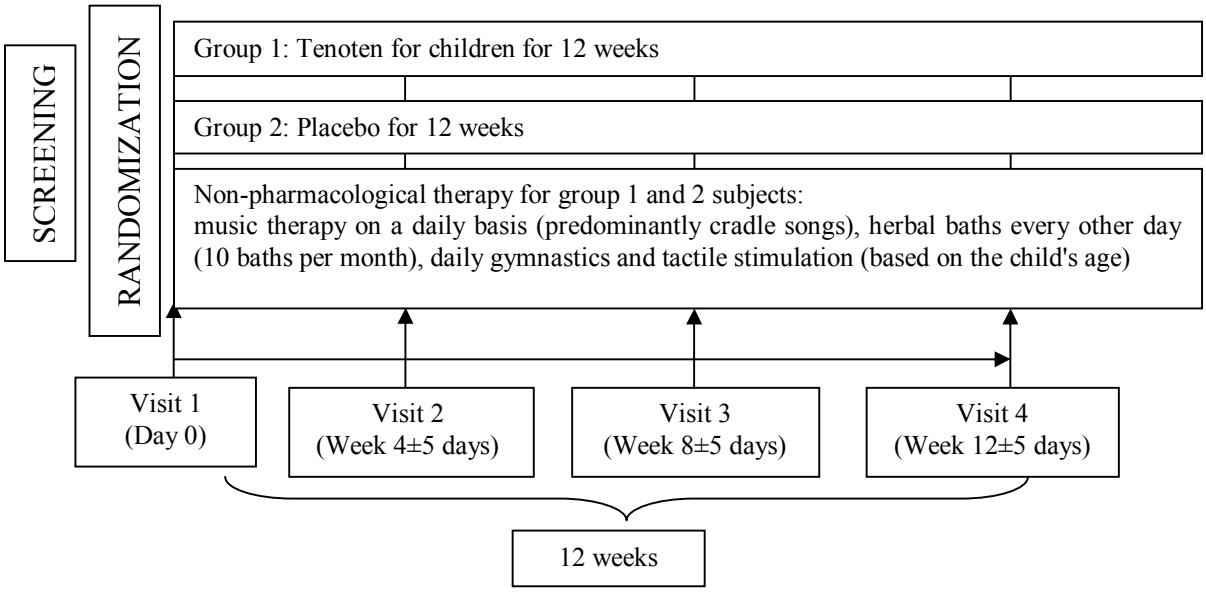
All subjects participating in the study will receive non-drug therapy in home conditions: music therapy, herbal baths, gymnastics and tactile stimulation based on the child's age.

Prohibited concomitant therapy

The following products (ATC group is specified in brackets) are not allowed 15 days prior to enrollment and throughout the study:

1. Psycholeptics (ATC group N05) including anxiolytics (tranquilizers), hypnotics and sedative products.
2. Psychoanaleptics (ATC group N06) including psychostimulants and nootropic agents:
   - pyrrolidine derivatives (racemates) – piracetam, etiracetam, aniracetam, etc.;
   - 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-hydrobutyrate;
   - ginkgo biloba;
   - neuropeptides and their analogues - methionyl-glutamyl-histidyl-phenylalanyl-prolyl-glycyl-proline;
   - amino acids and substances affecting excitatory amino acid system - glycine, pyridoxine + threonine;
   - polypeptides and organic composites - live stock cerebral cortical polypeptides, cerebrolysin;
   - substances from other pharmacological groups with nootropic effect (general tonic agents and adaptogenes - acetylasparaginic acid, melatonin, lecithin, etc.).
3. Antiepileptic drugs (ATC group N03A).
4. Anticholinergic drugs (ATC group N04A).
5. Dopaminergic drugs (ATC group N04B).
6. Muscle relaxants (ATC group M03).
7. Antihypoxants and antioxidants (ethylmethylhydroxypyridine succinate, citicoline, etc.).
8. Agents improving metabolism and energy supply to tissues reducing tissue hypoxia (cytoflavin, corylip, eltacin, inosine, etc.).
9. Homeopathic products.
10. Vitamins and vitamin-like agents (ATC groups A11E, A11D, A11HA) − thiamine (vitamin B_1), pyridoxine (vitamin B_6), pyridoxal phosphate, nicotinic acid (vitamin PP), pantothenic (vitamin B_5) and pangamic (vitamin B_{15}) acids.
11. Products previously causing allergic reactions in the subjects.

Study design scheme



Schedule of study procedures

Procedure/visit	Visit 1 (Screening, Day 0)	Visit 2 (Week 4±5 days)	Visit 3 (Week 8±5 days)	Visit 4 (Week 12±5 days)
Signing patient information sheet	+			
Collection of complaints	+	+	+	+
Collection of medical history	+			
Objective examination	+	+	+	+
Neurological status	+	+	+	+
Body weight measurement	+			+
Body length measurement	+			+
Head circumference measurement	+			+
Evaluation of physical development by centile tables	+			+
Evaluation of psychomotor development using Jurba-Mastyukova scale	+	+	+	+
Evaluation of psychomotor development using CAT/CLAMS scale	+	+	+	+
Recording concomitant therapy	+	+	+	+
Evaluation of compliance with inclusion/exclusion criteria	+			
Randomization and prescription of the study therapy	+			
Drug issue	+	+	+	
Accounting and return of the product, determination of compliance		+	+	+
CGI score				+
Therapeutic safety evaluation		+	+	+

Statistical Analyses

The following rules and assumptions were taking into account when calculating the sample size: power of statistical criteria is equal to 80% (probability of non-missing the effect is equal to 0.8); probability of error of the first kind is < 5% (probability of erroneous decision on the effect presence < 0.05). The statistical criteria used are two-sided, sample size is based on the assumption of the expected effects according to the primary outcome measure claimed in the protocol.

It is supposed that the difference between proportions of subjects with increased Jurba-Mastyukova total score ≥ 4 scores by the end of the treatment course in Tenoten for children group compared to equivalent proportion of subjects in Placebo group is no less than 22% in favour of Tenoten for children.

Given the statistical terms mentioned above, the size of each group will be 72 subjects (PP analysis, total = 144).

Supposing potential withdrawal of at least 22% subjects at screening and during the study for various reasons, at least 92 subjects in each group (184 in total) will be required to be recruited with their parents/adoptive parents signing informed consent form.

Safety and tolerability analysis of the study therapy will be based on the data from all randomized subjects who have received at least one dose of the study product/placebo. Efficacy analysis will be based on the two samples - FAS (Full Analysis Set) and PP (Per Protocol set): ITT-analysis and PP-analysis, respectively.

SAS-9.4 software will be used for statistical analysis including various parametric and nonparametric tests.