Multicenter double-blind placebo-controlled randomized clinical trial of efficacy and safety of Tenoten for children in the treatment of specific developmental disorders of scholastic skills in children

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-TD-005**
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ClinicalTrials.gov Id:	**NCT03159104**

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 randomized clinical trial of efficacy and safety of Tenoten for children in the treatment of specific developmental disorders of scholastic skills in children.

Phase: III

Sponsor: OOO «NPF «MATERIA MEDICA HOLDING», Moscow, Russia

Protocol No. MMH-TN-005

Objective of the study

- To evaluate efficacy and safety of Tenoten for children in the treatment of specific developmental disorders of scholastic skills in children.

Endpoints

Primary endpoint

1. Mean total scholastic skill score (reading, spelling and counting) in the groups after 12-week therapy compared to baseline.

Secondary endpoints

1. Mean score of “Reading skill test” in the groups after 12-week therapy compared to baseline.
2. Mean score of “Spelling skill test” in the groups after 12-week therapy compared to baseline.
3. Mean score of subtest No. 3 "Arithmetic" (of Wechsler Intelligence Scale for Children, WISC) in the groups after 12-week therapy compared to baseline.
4. Percentage of children with an increase in total scholastic skill score[1] (reading, spelling and counting) in the groups after 12-week therapy compared to baseline.
5. Efficacy Index according to Clinical Global Impression scaly by the end of therapy (CGI-EI).

[1] Improvement criterion – increased total scholastic skill score (reading, spelling and counting) by at least 5 points compared to baseline.

Safety assessment

- Occurrence and nature of adverse events (AE) during the treatment; AE severity, causal relationship to the study drug, and outcome.

Study design

A multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of the study treatment.

The study will enroll the school children (boys and girls) of grades 1, 2 and 3 of a regular school aged 7-9 years old (grade 1 school children will be enrolled at the beginning of the second half of the year) complaining of difficult learning classified according to ICD-10 as specific developmental disorders of scholastic skills (F81) including:

- specific reading disorder (F81.0);
- specific spelling disorder (F81.1);
- specific disorder of arithmetical skills (F81.2);
- mixed disorder of scholastic skills (F81.3);
- disorder simultaneously meeting criteria of F81.2+F81.0 or F81.2+F81.1, or F81.2+F81.0+F81.1.

The developmental disorders of scholastic skills will be verified by a doctor (either a neurologist or psychiatrist) according to reading, spelling, and counting tests. The children may have any concomitant diseases not considered as exclusion criteria and not requiring therapy during the following 12 weeks using the products specified in section "Forbidden concomitant therapy". Specific additional educational programs should not be performed within 12 weeks after enrollment either.

On signing information sheet (informed consent form) by the parent/adopter the patients will be examined by a neurologist or psychiatrist and tested for reading skills (method by L.A. Fotekova, T.V. Akhutina, 2002;), spelling skills (method by L.A. Fotekova, T.V. Akhutina, 2002) and counting skills (subtest No. 3 "Arithmetic" WISC test), and concomitant therapy will be recorded. If inclusion criteria are met and non-inclusion criteria are absent at Visit 1, the patient will be enrolled in the trial and randomized into one of the two groups: 1 tablet of Tenoten for children three times daily for 3 months (group 1) or the same dosing regimen of Placebo (group 2).

At Visit 1 the parents/adopters will receive the study product for 12-week treatment period and a diary to report any potential adverse events and cases of concomitant therapy.

Six weeks later (Week 6±3 days) a "Phone visit" (Visit 2) will be made in order to interview parents about the patient's condition, the presence / absence of concomitant diseases, adverse

events.

At Visit 3 (Week 12±3 days) repeated testing of reading, spelling and counting skills will be made, complaints, data on concomitant diseases, concomitant therapy, and adverse events will be collected. The investigator will evaluate the subject's compliance and fill in the Clinical Global Impression Scale to calculate Efficacy Index (CGI-EI).

The patients will be allowed to take symptomatic therapy and medications for their co-morbidities during the study, except for the medicines listed in “Forbidden concomitant therapy”.

Inclusion and exclusion criteria

Inclusion criteria

1. Children of either gender aged 7 to 9 years old.
2. School children of grades 1-3 (grade 1 children will be enrolled at the beginning of the second half of the year) in regular schools with state accreditation with principal educational program of elementary general education in compliance with Federal State Educational Standard of the Russian Federation.
3. Beginning of the second half of the year (only for 1st grades).
4. Specific developmental disorder of scholastic skills such as:
    - specific reading disorder (F81.0);
    - specific spelling disorder (F81.1);
    - specific disorder of arithmetical skills (F81.2);
    - mixed disorder of scholastic skills (F81.3; i.e. meeting the criteria for one of the following combinations: F81.2+F81.0, F81.2+F81.1, or F81.2+F81.0+F81.1).
5. Reading score of 15 to 35 on the Reading Skills test (L.A. Fotekova, T.V. Akhutina, 2002).
6. Spelling score of 15 to 30 on the Spelling Skills test (L.A. Fotekova, T.V. Akhutina, 2002).
7. Counting score of 5 to 15 on the subtest No. 3 "Arithmetic" (of Wechsler Intelligence Scale for Children).
8. Availability of a patient information sheet (Informed Consent Form) signed by the parent/adopter to confirm the child's participation in the clinical trial.

Exclusion criteria

1. History of the diseases:

- Diseases of the nervous system, including:
  − inflammatory diseases of the central nervous system,
  − systemic atrophies,
  − extrapyramidal and movement disorders,
  − degenerative diseases of the nervous system,

  - demyelinating diseases of the central nervous system,
  - episodic and paroxysmal disorders,
  - polyneuropathies,
  - diseases of myoneural junction and muscle,
  - cerebral palsy.
- Congenital malformations of the nervous system (excl. Spina bifida without hydrocephalus).
- Diseases and congenital malformations of eye causing impairment of vision.
- Diseases and congenital malformations of ear causing impairment of hearing.
- Organic mental disorders.
- Mental retardation ranging from mild to profound.
- Stuttering (stammering).
- Obsessive-compulsive disorder.
- Pervasive developmental disorders including:
  - childhood autism,
  - atypical autism,
  - Rett syndrome,
  - overactive disorder associated with mental retardation and stereotyped movements,
  - Asperger syndrome.
- Phakomatoses (tuberous sclerosis, neurofibromatosis).
- Postconcussional syndrome.
- Hereditary metabolic diseases, including glycogen storage disease (glycogenosis), disorders of galactose metabolism (galactosaemia), other disorders of carbohydrate metabolism, disorders of glycosaminoglycan metabolism (mucopolysaccharidosis), disorders of aromatic amino-acid metabolism (phenylketonuria, tyrosinaemia etc.), disorders of branched-chain amino-acid metabolism and fatty-acid metabolism (maple-syrup-urine disease), mitochondrial myopathy.
- Chromosomal abnormalities.

2. Administration of the products specified in section “Forbidden concomitant therapy” within the previous 4 weeks.
3. Necessity in pharmacotherapy for underlying and/or concomitant disease during the following 12 weeks.
4. Acute infectious disease or exacerbation/decompensation of a disease affecting patient’s ability to participate in the trial.
5. Malignant neoplasm/suspected malignant neoplasm.
6. Allergy/drug intolerance to any of the components of medications used in the treatment.

7. Malabsorption syndrome, including congenital or acquired lactase deficiency (or any other disaccharidase deficiency) and galactosemia.
8. Mental disorders of patient's parent(s)/adopter(s).
9. Use of drugs or alcohol by the patient's parents/adopters at > 2 alcohol units[2] a day.
10. Participation in other clinical trials in the previous 3 months.
11. Patients whose parent(s)/adopter(s), from the investigator's point of view, will fail to comply with the observation requirements of the trial or with the dose regimen of the investigational drug.
12. Patients whose parent(s)/adopter(s) 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).
13. Patients whose parent(s)/adopter(s) work for OOO "NPF "MATERIA MEDICA HOLDING" (i.e., is the company's employee, temporary contract worker, or, designated officials responsible for carrying out the research or any immediate relatives of the aforementioned).

Criteria for Withdrawal or Termination

1. Failure or refusal of parents/adopters to follow the protocol requirements.
2. Necessity for prescribing medications not permitted during the study.
3. An adverse event requiring discontinuation of the study drug.
4. Parent /adopter's decision to withdraw early for lack of efficacy or other reasons.
5. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.
6. Eligibility error.

Number of subjects

It is planned to include 264 subjects, which is expected to yield at least 184 patients (92 x 2 groups) patients completing all protocol procedures.

Interim analysis

An interim analysis is planned for potential adjustment of sample size.

[2] 1 unit of alcohol is equivalent to 0.33 L of lager/150 mL of unfortified wine, or 40 mL of Ethyl Alcohol.

Treatment

Group 1

Name of the medicinal product: Tenoten for cildren

Active ingredient: Affinity purified antibodies to brain-specific S-100 protein - 0.003 g*

** added to lactose monohydrate powder as a water-ethanol mixture containing not more than 10-16 ng/g of an activated form of the active substance.*

Excipients: Lactose monohydrate - 0.267g
Microcrystalline cellulose - 0.03 g
Magnesium stearate - 0.003 g

Method of administration: Tablet for oral use. Dose per administration: 1 tablet. 1 tablet three times daily (3 tablets per day). The tablets should be held in the mouth until complete dissolution, without meal.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store below 25ºC. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: Lactose monohydrate - 0.267 g
Microcrystalline cellulose - 0.03 g
Magnesium stearate - 0.003 g

Method of administration: Tablet for oral use. Dose per administration: 1 tablet. 1 tablet three times daily (3 tablets/day). The tablets should be held in the mouth until complete dissolution, without meal.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store below 25ºC. Keep out of the reach of children.

Treatment duration

Tenoten/Placebo treatment duration is 12 weeks.

Observation period

In total the patients will be monitored for 12 weeks.

Symptomatic (Standard) treatment

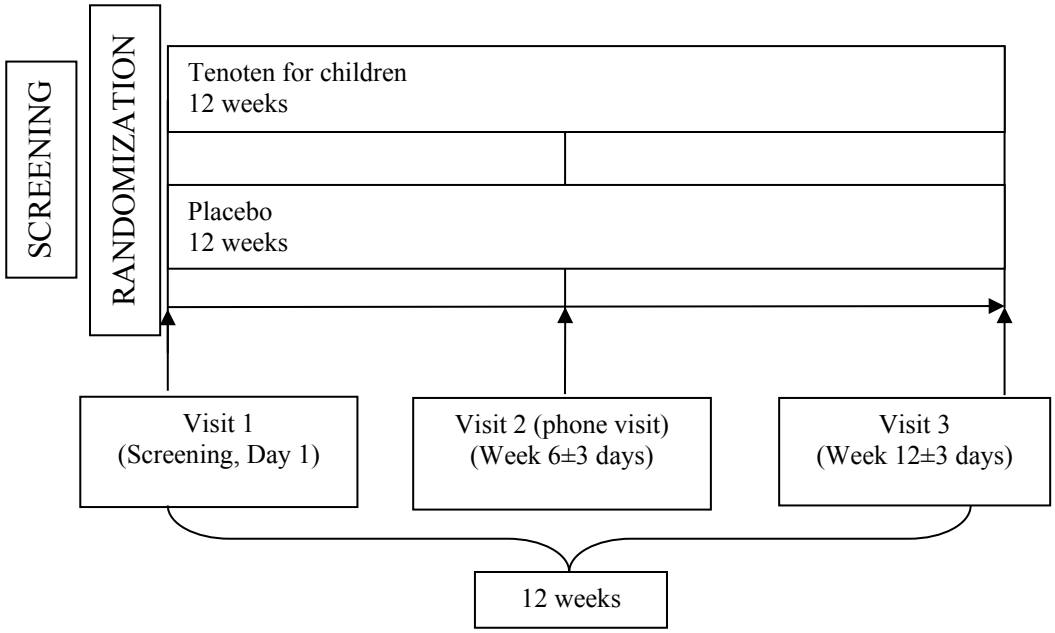
Medicinal products and procedures required for the subjects including for the treatment of underlying and concomitant diseases except for the product included into section "Forbidden concomitant therapy".

Prohibited concomitant therapy

Within 4 weeks prior to enrollment and throughout the study the subjects are not allowed to use any of the following medications (ATC group is specified in brackets):

1. Psycholeptic drugs (ATC group - N05) including anxiolytics (tranquilizers), hypnotics and sedatives.
2. Psychoanaleptics (ATC group – N06) including psychostimulants and nootropic drugs including:
   - 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-hydroxybutyrate;
   - Ginkgo biloba;
   - neuropeptides and their analogues – methionyl-glutamyl-hidtidyl-phenylalanyl-prolyl-glycyl-proline;
   - amino acids and substances affecting excitatory amino acid system – glycine, pyridoxine+threonine;
   - Polypeptides and organic composites - bovine cerebral cortical polypeptides, cerebrolysin;
   - substances from other pharmacological groups with nootropic effect (general tonic drugs and adaptogens – acetylaminosuccinic acid, melatonin, lecithin, etc.).
3. Antiepileptic drugs (ATC group – N03A).
4. Anticholinergic drugs (ATC group − N04A).
5. Dopaminergic drugs (ATC group − N04B).
6. Antihypoxic and antioxidant drugs (ethylmethylhydroxypyridine succinate, citicoline, etc.).
7. Agents improving metabolism and energy supply to tissues, reducing tissue hypoxia (cytoflavin, corylip, eltacin, inosie, etc.).
8. Homeopathic remedies.
9. Drugs known to have caused allergic reactions.
10. Specific additional educational programs (forbidden during the study).

Study design scheme



Schedule of study procedures

Procedure	Visit 1 (Screening, Day 1)	Visit 2 Phone visit (Week 6 ±3 days)	Visit 3 (Week 12 ±3 days)
Informed consent	+		
Collection of complaints	+	+	+
Medical history	+		
Physical examination	+		+
Concomitant therapy	+	+	+
Examination of reading skills (method by L.A. Fotekova, T.V. Akhutina, 2002)	+		+
Examination of spelling skills (method by L.A. Fotekova, T.V. Akhutina, 2002)	+		+
Examination of counting skills ("Arithmetic" subtest No. 3 of WISC)	+		+
Inclusion/exclusion criteria	+		
Randomization and prescription of study therapy	+		
Study drug supply	+		
Study drug accountability, compliance assessment			+
Distribution of diaries	+		
Evaluation of correct diary filling			+
Diary return			+
CGI-EI scale filling			+
Evaluation of treatment safety	+	+	+

Statistical Analyses

Samples

Total set includes all the subjects who have signed ICF. This sample will consider all adverse events 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 adverse events 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) failure to meet inclusion/non-inclusion criteria;
2) subject failing to take any dose of the study drug;
3) absence of any data on the subject after randomization.

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

Per Protocol set. This sample includes all subjects who completed the therapy as per the study protocol, without any missing visits or major protocol deviations. This set will be used in the ***Per Protocol efficacy analysis of the test therapy.***

Mean value of the total set for the relevant day will be used to fill lacking/missing data.

Data treatment and all statistical calculations under the protocol will be made using SAS-9.3 statistical software.[3]

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 is 80% (the probability of correct rejection of the null hypothesis is 0.8)
   - 1.2 the probability of type 1 error 'α' is less than 0.05 (the probability of false acceptance of the alternative hypothesis)
   - 1.3 statistical criteria used are two-sided
   - 1.4 value of clinically relevant "δ" difference is taken as equal to 5 (i.e. Tenoten for children effect is supposed to be clinically relevant compared to placebo effect if the effect in the study group exceeds the one in control group by at least 5 points)
   - 1.5 statistical null and alternative hypotheses will be as follows:

[3] Holder of license: OOO "NPF "MATERIA MEDICA HOLDING", No. 70100045.

$$H_0: : m_1-m_2 \leq \delta$$

$$H_1: m_1-m_2 > \delta,$$

where m_1 - mean total scholastic skill score in Tenoten for children group

m_2 – mean total scholastic skill score in placebo group

δ – clinically relevant difference value.

1.6 an interim analysis is planned for potential adjustment of sample size:

a. calculations will be made using O'Brien-Fleming boundary;

b. proportions of the subjects completing the study and yielding the results for interim and final analyses, will be taken as 0.5 and 1.0 (i.e. interim analysis will be made after recruitment of half of the planned number of the clinical study subjects.

1.7 therefore, sample size will be calculated taking into account:

a. interim analysis;

b. assumption on expected effects declared in the main efficacy criterion of the protocol.

1.8 calculation of sample size in groups 1 and 2 for two-sided test for interim and final analysis will be made using the formula defining sample size (i.e. for the variant without interim analysis):

$$N_1=N_2=(\sigma_1^2 + \sigma_2^2)\, I,$$

where N_1 and N_2 are sample sizes in Tenoten for children and placebo groups

σ_1 and σ_2 – expected standard deviations in these groups

I – Fisher information determined using the formula:

$$I=(F^{-1}(1-\alpha)+F^{-1}(1-\beta))^2/\theta_1^2,$$

where $F^{-1}(1-\alpha)$ and $F^{-1}(1-\beta)$ are tabular z-test values for α and β, a $\theta_1 = (m_1-m_2)$.

1.9 final sample size will be determined using the formula:

$$N_F = N_{PP} / (1 - C_w),$$

where N_F – final sample size;

N_{PP} – result of calculation in cl. 1.8, i.e. scheduled number of subjects completing the study per protocol;

C_w – withdrawal coefficient.

2. Assumptions on expected clinical study effects:

The difference between Tenoten for children effect consisting in increased mean total scholastic skill score by the end of therapy and effect in placebo group is supposed to be at least 10 points with standard deviation of at least 12 points.

Given the statistical terms and assumptions above each group size will be:

a) at interim analysis - 46 subjects

b) at final analysis - 92 subjects.

Therefore, total PP set will include 184 subjects.

Taking into account that potential withdrawal of 30% subjects at the screening and during the study for various reasons, at least **132** subjects in each group will be required to sign informed consent (in total **264** subjects).

Statistical criteria

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

- parametric - to evaluate continuous and interval random values;
- nonparametric – to obtain:
  - evaluations of equality/inequality of proportions of the subjects upon their comparison for various visits,
  - analysis of frequencies of the features compared,

  and
  - evaluation of continuous and interval random values in case of non-compliance with normal random distribution.

The following SAS procedures are suggested for interim analysis:

- SEQDESIGN, SEQTEST – design and performance of interim analysis;
- The terms of early termination of the study will be set using O'Brien-Fleming stopping boundary.

Parametric criteria

Prior to analysis using parametric statistics, data samples under comparison will be tested for normality (the Kolmogorov-Smirnov test).

The following parameters and approaches are to be used:

1. To evaluate the differences in continuous variables from two different (independent) groups – Student's test for independent samples.
2. To evaluate differences in continuous variables in one group at two different visits - Student's test for paired samples.
3. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or modified repeated measures covariance (ANCOVA).
4. In case of multiple comparisons of the groups various corrections for multiplicity will be used, e.g. Dunnett, Tukey, Scheffe, Holm adapted test, etc.
5. Generalized Linear Models will be used in case of abnormal data distribution.

6. 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 difference in continuous variables obtained in two different (independent) groups – Mann-Whitney test.
2. To evaluate time changes in the parameters compared – Friedman test, nonparametric analogue of repeated measures analysis of variance.
3. For frequency analysis of contingency tables 2×2 – $\chi 2$ (if the frequency under comparison > 5) or exact Fisher's test (if one of the frequencies under comparison < 5).
4. Cochran-Mantel-Haenszel test (modified $\chi 2$ test for multiple comparisons) – to perform frequency analysis based on independent strata.
5. 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 – 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.

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. Outliers will be analyzed

individually. The data will be grouped by visits. The categorical variables will be presented as frequency tables by visits.