Multicenter double-blind placebo-controlled randomized parallel-group clinical study of efficacy and safety of Prospekta in the treatment of attention deficit/hyperactivity disorder in children

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-MAP-004**
Version date:	**April 07, 2020**
ClinicalTrials.gov Id:	**NCT04569357**

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 Prospekta in the treatment of attention deficit/hyperactivity disorder in children.

Phase: III

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

Protocol No. MMH-MAP-004

Objective of the study

- To evaluate efficacy of Prospekta in the treatment of attention deficit/hyperactivity disorder in children.
- To evaluate the safety of Prospekta in the treatment of attention deficit/hyperactivity disorder in children.

Endpoints

Primary endpoint

1. Proportion of subjects with total ADHD-RS-V reduction ≥25% after 8 weeks of therapy.

Secondary endpoints

1. Change in total ADHD-RS-V score vs. baseline after 8-week therapy.
2. Change in total ADHD-RS-V score (attention deficit subscale) vs. baseline after 8-week therapy.
3. Change in total ADHD-RS-V score (hyperactivity/impulsivity subscale) vs. baseline after 8-week therapy.
4. CGI-EI therapeutic effect, adverse event values and efficacy score after 8 weeks of treatment.
5. Occurrence and type of adverse events (AE) during the treatment; AE severity, relation to the study drug, and outcome.

Safety assessment

- Presence and nature of adverse events during the therapy, their intensity (severity), relation to the study drug, outcome.
- Changes in vital signs during the study therapy.

- Percentage of patients with clinically relevant laboratory abnormalities during the treatment with the study drug.

Study design

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

The study will enroll children of either gender, age from 7 to 12 years old with diagnosis of attention deficit/hyperactivity disorder (ADHD) verified by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Association» [DSM-V].

After signing patient information sheet and informed consent form by the patient's parent/adoptive parent collection of complaints, examination of the children, filling Attention Deficit Hyperactivity Disorder-Rating Scale-V [ADHD-RS-V] scale by the parent/adoptive parent (for children aged 7-10 years old, for teenagers aged 11-12 years old) will be performed, concomitant therapy will be recorded and laboratory tests will be carried out.

The study will enroll children with a total score ADHD-RS-V $\geq$ 22.

If the inclusion criteria were met and there were no exclusion criteria (Day 1), the patient is randomized to one of the two groups: group 1 will receive Prospekta at 1 tablets twice daily; group 2 will receive Placebo using the study drug dosing regimen.

Treatment period is 8 weeks, the main stages of the examination (collection of complaints, registration of objective examination data, re-filling of the ADHD-RS-V scale by the parent/adoptive parent) are made at Visit 1 (Day 1), then 4 weeks later (Visit 2) and 8 weeks later (Visit 3). Each visit to the investigational site is made by the patient is accompanied by his/her parent/adoptive parent. Two weeks later (Visit 1.1, week 2±3 days) after randomization and initiation of the study therapy and between Visits 2 and 3 (Visits 2.2, week 6±3 days) the investigator checks the patient's clinical condition during «phone visits»: based on the collection of complaints, control of prescribed therapy, evaluates the safety of treatment. At Visit 2 (week 4±3 days) and Visit 3 (week 8±3 days) the investigator collects complaints, registers objective examination data, controls re-filling by the patient's parent/adoptive parent of the ADHD-RS-V scale, the prescribed and concomitant therapy, assesses the safety of the treatment and the degree of adherence of the patient to the study therapy (compliance). Additionally, at Visit 3 the investigator completes the Clinical Global Impression Efficacy Index [CGI-EI] scale and collect samples for laboratory testing. The patient stops taking the study drug.

The total duration of the observation period is 8 weeks.

During the study the treatment for underlying conditions is allowed with the exception of the drugs indicated in the section «Prohibited Concomitant Treatment».

Inclusion and exclusion criteria

Inclusion criteria

1. Male and female children aged 7-12 years old inclusive.
2. Children with verified diagnosis of ADHD.
3. Presence of all ADHD criteria according to DSM-V:

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1) Attention deficit: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

- Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
- Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
- Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
- Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework).
- Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, eyeglasses).
- Is often easily distracted by extraneous stimuli.
- Is often forgetful in daily activities (e.g., doing chores, running errands).

2) Hyperactivity/impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities.

Note. The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions.

- Often fidgets with or taps hands or feet or squirms in seat.

- Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
- Often runs about or climbs in situations where it is inappropriate.
- Often unable to play or take part in leisure activities quietly.
- Is often "on the go" acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time).
- Often talks excessively.
- Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
- Often has trouble waiting his/her turn (e.g., while waiting in line).
- Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission).

Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings, (e.g., at home, school or work; with friends or relatives).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

4. ADHD-RS-V $\geq$ 22.
5. Availability of signed information sheet and informed consent form for the parents/adoptive parents for the subject's participation in the clinical trial.

Exclusion criteria

1. History of central nervous system (CNS) diseases including:
   - Inflammatory diseases of the central nervous system (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)
- Hydrocephalus (G91).

2. Childhood autism (F84.0), atypical autism (F84.1).
3. Mental retardation (F70-79).
4. Disorders of psychological development (F80–F89).
5. History of hyperthyroidism (thyrotoxicosis).
6. History/suspicion of oncology of any location (except for benign neoplasms).
7. Any other co-morbidity which, in the opinion of the investigator, may affect patient participation in the clinical trial.
8. Patients allergic to/intolerant of any components of the study treatment.
9. Hereditary lactose intolerance, malabsorption due to lactose intolerance including congenital or acquired lactase (or other disaccharide) deficiency, galactosemia.
10. Patients whose parents/adoptive parents will not fulfill the requirements during the study or follow the order of administration of the study drug (SD) products, from the Investigator's point of view.
11. History of treatment noncompliance, mental diseases, alcoholism or drug abuse in parents/adoptive parents which, according to the investigator, will prevent from following the study procedures.
12. Administration of the products outlined in section "Prohibited concomitant therapy" within 1 month prior to enrollment.
13. Patients who have participated in other clinical trials in the past 3 months.
14. The patient’s parent/adoptive parent is a study specialist of the center and is directly involved in the study, or is an immediate family member of the Investigator. Spouses, parents, children, or siblings, regardless of whether they are siblings or adopted are considered immediate family members.
15. The patient's parent/adoptive parent works at OOO "NPF "MATERIA MEDICA HOLDING", i.e. they are employees of the Company, temporary employees on a contract basis or appointed officials responsible for conduction of the study or their immediate family members.

Criteria for Withdrawal or Termination

1. Screening failure.
2. Parent’s/adoptive parent’s failure or unwillingness 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. Parent's/adoptive parent's wish to terminate the study early for any reason.
7. Enrollment of the subject into another clinical study.
8. Cases not specified by the protocol when, according to the investigator's opinion, further participation in the study harms the patient.
9. Pregnancy.
10. Unblinding.

Number of subjects

It is planned to include 366 subjects, which is expected to yield at least 292 (146 in Prospekta and Placebo groups) patients completing all protocol procedures.

Interim analysis

There are no interim unblinded analyses are planned during the study. However, at the sponsor's request, a blinded interim analysis may be carried out to specify population parameters and potential adjustment of sample size (increasing only).

Treatment

Group 1

Name of the medicinal product: Prospekta

Active ingredient: Affinity purified antibodies to brain-specific protein S-100, modified – 10 000 UMA*

** UMA – Units of Modifying Activity*

Excipients: Lactose monohydrate - 0.267g
Microcrystalline cellulose - 0.030 g
Magnesium stearate - 0.003 g

Method of administration: Per os. One tablet per intake 2 times a day (approximately at the same time), outside of meal (between meals or 15 minutes prior to meal or drinking). The tablet should be held in mouth until completely dissolved.

Dosage form: Tablets.

Description: Flat cylinder-shaped scored beveled edge white to off-white tablets with smooth even 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: Per os. One tablet per intake 2 times a day (approximately at the same time), outside of meal (between meals or 15 minutes prior to meal or drinking). The tablet should be held in mouth until completely dissolved.

Dosage form: Tablets.

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

Storage conditions: At temperature ≤ 25 ºC.

Treatment duration

Treatment period – 8 weeks.

Observation period

Duration of the observation period shall be 8 weeks (screening + randomisation – up to 1 days, study therapy – 8 weeks).

Symptomatic (Standard) treatment

Throughout the study patients may receive therapy for the underlying disease except for the medicinal products indicated in the section “Prohibited concomitant therapy”.

The data on therapy for concomitant diseases and conditions should be described in source documents.

Prohibited concomitant therapy

Within 1 month prior to enrollment and during the study (after signing patient information sheet and informed consent form by the patient’s parent/adoptive parent for participation in the clinical study and initiation of screening) no therapy used for ADHD treatment (psychostimulants, central sympathomimetics, antidepressants, nootropes, etc.) and capable of affecting the patient's neurological status will be allowed (the brackets show ATC code)):

1. Antiepiletics (N03A).
2. Muscle relaxants (M03).
3. Anticholinergic agents (N04A).
4. Dopaminergic agents (N04A).
5. Actovegin (B06).
6. Psycholeptics (N05), including anxiolytics (tranquilizers), hypnotics and sedatives.

7. Psychoanaleptics (N06) including antidepressants, psychostimulants, nootropic drugs and atomoxetine.

8. Parasympathomimetics (N07A).

9. 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.;
    - metabolic agents.

11. Herbal sedative drugs.

12. Vitamins B (A11EA).

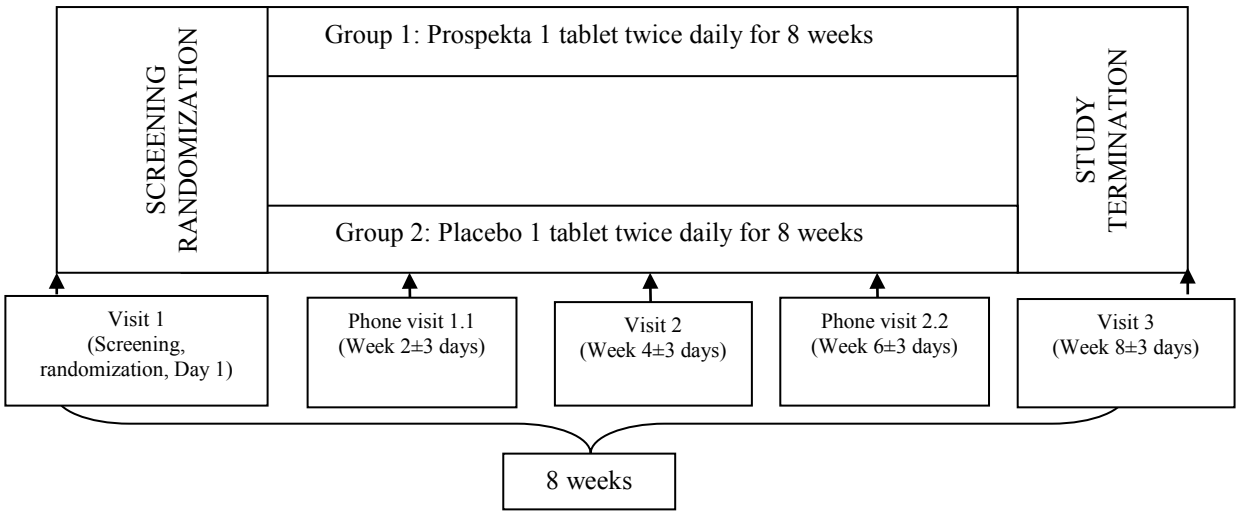
13. Homeopathic drug products.

14. Any unauthorized product and/or vaccine.

15. Drugs that previously caused allergic reactions in patient.

16. Psychotherapy, psychological and pedagogical correction (holding therapy, logopedic treatment) aimed at the underlying disease.

Study design scheme



Schedule of study procedures

Procedure/Visit	***Visit 1 Screening, Randomization (Day 1)***	***Phone visit 1.1 (Week 2±3 days)***	***Visit 2 (Week 4±3 days)***	***Visit 2.2 (Week 6±3 days)***	***Visit 3 (Week 8±3 days)***
Informed consent	+				
Registration patient in IVRS and assignment of a personal code	+				
Collection of demographic data	+				
Collection of complaints	+	+	+	+	+
Medical history	+				
Concomitant conditions and diseases	+				
Physical examination	+		+		+
Evaluation of vital signs (HR, RR, BP)	+		+		+
Recording therapy for concomitant diseases	+	+	+	+	+
Matching ADHD diagnosis with diagnostic DSM-V criteria	+				
Filling ADHD-RS-V	+		+		+
Pregnancy test[1]	+				
Inclusion/exclusion criteria	+				
Randomization	+				
Laboratory tests	+				+
Study drug supply	+		+		
Study drug accountability and return, compliance assessment			+		+
Clinical Global Impression assessment (CGI-EI)					+
Evaluation of treatment safety	+	+	+	+	+
Visit completion	+	+	+	+	+
Suggested duration of the patient's participation in the study					+

[1] Sexually active teenagers - at the parent's/adoptive parent's disposal

Statistical Analyses

Samples

Total set includes all enrolled patients' parents/adoptive parents 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 failing to take any dose of the study drug;
3) lack of any data on the subject after the study drug administration.

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 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.

The list of deviations which may result in complete or partial invalidity of data is developed by a medical expert jointly with a biostatistician according to the study design.

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. ≥ 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.

Based on the subject's age the study may use various versions of ADHD-RS-V. The following is suggested to monitor the scale impact on the results (unless the manufacturer provides another method of result unification): in all statistical analysis associated with ADHD-RS-V (both as a dependent variable and as independent variable) the statistical model should consider the factor of the scale used (children/teenagers).

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 criteria "P=(1−β)" will be taken as being equal to 80% (probability of correct rejection of the null hypothesis is 0.8);
   - 1.2 the probability of a type I error "α" will be allowed to be less than 5% (the probability of the erroneous acceptance of an alternative hypothesis was less than 0.05);
   - 1.3 statistical criteria of intergroup comparisons will be two-sided unless otherwise specified;
   - 1.4 calculation of sample size will be based on the assumptions on the expected effect declared in the primary efficacy endpoint of the protocol;
   - 1.5 ratio between sample sizes in Prospekta and Placebo group will be 1:1;
   - 1.6 statistical hypotheses - null and alternative hypotheses on the difference between test product and placebo under the dosing regimen used:

     a) primary endpoint:

     $$H_0: \Theta_1 - \Theta_2 = 0$$

     $$H_a: \Theta_1 - \Theta_2 \neq 0$$

     where Θ_1 is proportion of events in Prospekta group,

     Θ_2 is proportion of events in Placebo group;
   - 1.7 calculation of sample size for statistical criteria was made using the following formula:

     $$n_2 = kn_1$$

     $$n_1 = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 * (\Theta_1 * (1 - \Theta_1) + \Theta_2 * (1 - \Theta_2))}{\varepsilon^2}$$

     where n_1, n_2 is sample size of Prospekta and Placebo group, respectively,

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

$\varepsilon = \Theta_1 - \Theta_2$ is expected differences between frequencies of events in Prospekta and Placebo group;

k – coefficient of sample ratio between Prospekta and Placebo (1:1);

$z_{\omega/2}$ – tabular value of two-sided z-test for **α**;

z_{β} – tabular value for one-sided z-test for **β.**

1.8 final sample size will be determined using the formula:

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

where N_T – final sample size;

N_{PP} – result of calculation in cl. 1.7 – cl.1.8, i.e. scheduled number of subjects completing the study per protocol;

R_w – withdrawal rate.

A priori estimates for parameter variables in the groups:

Primary endpoint:

Proportion of subjects with an event in Prospekta group will be at least 66%, proportion of subjects in Placebo group will be no more than 50%[3].

Therefore based on cl. 1.7, 146 subjects per group will be needed. Given withdrawal rate (Rw=0.2) and based on cl. 1.8, 366 subjects will be needed (n=183 per group).

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, etc.).

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 assess the dynamics of the compared values – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.
3. In case of multiple comparisons between the groups variety of corrections for multiplicity will be used (Dunnett, Tukey, Scheffe, Holm adaptive test), etc.

[3] Based on TD1061511-01.18.P study.

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 – analysis of Generalized Linear Models for studying temporal dynamics (ANOVA, ANCOVA)
- GENMOD – analysis of Generalized Linear Models
- MIXED – analysis of Mixed Linear Models.

Non-parametric criteria

Below are potential types of comparisons with relevant criteria:

1. To assess the dynamics of the compared indicators – Friedman test, non-parametric analogue of analysis of variance with repeated measures.
2. 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).
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.