CLINICAL TRIAL PROTOCOL

A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA).

NCT Number: NCT06854601

Pharmasoft

October 15, 2019

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Protocol No. PHS-ADHD-002-MEX-TAB

Version: 4.0 dated 15.10.2019.

Development Phase: II-III

Sponsor: Limited Liability Company "Research and Production Company "PHARMASOFT" / RPC PHARMASOFT LLC Legal address: Russian Federation, 115407, Moscow, 41, Sudostroitelnaya St., floor 1, room 12

Postal address: Russian Federation, 109544, Moscow, Enthusiastov Boulevard, 2
Tel./fax: +7 (495) 626 47 55

CONFIDENTIAL INFORMATION

The information in this document is strictly confidential and can only be disclosed by investigators, potential investigators and Local Ethical Committees. The information contained in this document cannot be disclosed except to the extent necessary to obtain informed consent from potential trial subjects

TRIAL SPONSOR PROTOCOL APPROVAL PAGE

Trial Title	A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (Pharmasoft, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA).
Protocol	PHS-ADHD-002-MEX-TAB version 4.0 dated 15.10.2019.
Agreed by	Tatyana Anatolievna Mityushkina Medical Director RPC PHARMASOFT LLC Tel: +7 (495) 626 47 55 ext. 140 e-mail: mityushkina_t@pharmasoft.ru Date _____ Signature _____

CRO PROTOCOL APPROVAL PAGE

Trial Title	A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (Pharmasoft, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA).
Protocol	PHS-ADHD-002-MEX-TAB version 4.0 dated 15.10.2019.
Agreed by	Nikolay Olegovich Pozdnyakov Director ClinPharmDevelopment LLC Russia, 150031, Yaroslavl, Uglichskaya str. 68, office. 1. Tel: +7 (4852) 59-47-79, http://www.cphd.ru
	Date _____ Signature _____

Approval and signature of the Principal Investigator

(Name of principal investigator)

A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (Pharmasoft, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA).

Protocol version 4.0 dated 15.10.2019.

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical trial in accordance with this protocol, current principles of Good Clinical Practice, local laws and requirements.

I will ensure that all trial assistants and members of the trial team read and understand all aspects of the protocol.

I have received and read all the information provided to me relevant to the trial.

The objectives and contents of this protocol and the results obtained will be considered confidential and will not be made available to third parties without the prior consent of the Sponsor.

Site Name: .....

Principal Investigator: .....
FULL NAME

....
Signature *date*

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LIST OF ABBREVIATIONS

BD	blood pressure
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ULN	upper limit of normal
HIV	human immunodeficiency virus
GABA	gamma-aminobutyric acid
CI	Confidence Interval
BMI	Body Mass Index
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
LEC	Local Ethics Committee
mg	milligram
ICD-10	International Classification of Diseases, 10th revision
INN	international non-proprietary name
AE	Adverse Event
ADHD	Attention Deficit Hyperactivity Disorder
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	standard error of the mean
RR	respiratory rate
HR	heart rate
QPPV	Qualified Person Responsible for Pharmacovigilance
ADHD Rating Scale-IV	Attention Deficit Hyperactivity Disorder rating scale
CGI-ADHD-S	ADHD severity rating scale for overall clinical impression of ADHD severity
CGI-I	Clinical Global Impression-Improvement
CV	coefficient of variation
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV text revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IWRS	Interactive Web Response System

M	mean
mITT	modified intent-to-treat
PP	per protocol
SNAP-IV	Swanson, Nolan and Pelham Teacher and Parent Rating Scale
SCAS	Spence Children's Anxiety Scale
$TRR_{1/2}$	drug elimination half-life

1. GENERAL INFORMATION

1.1. Protocol summary

Trial Title:	A multicentre, double-blind, randomised, placebo-controlled clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC, Russia) in the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years under different dosing regimens (MEGA).
Estimated trial period	estimated trial start date: February 2019. estimated trial completion date: June 2020.
Trial purpose:	To evaluate the safety and efficacy of Mexidol® film-coated tablets, 125 mg (PRC Pharmasoft LLC, Russia) vs. placebo in children aged 6 to 12 years inclusive with attention deficit hyperactivity disorder (ADHD).
Trial objectives:	**Primary objective:** 1. To evaluate the efficacy of Mexidol® film-coated tablets, 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy in relation to the average change in the total score on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP-IV scale when administered at a dose of 125 mg OD. 2. To evaluate the efficacy of Mexidol® film-coated tablets, 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy in relation to the mean change in the total score on the "inattention", "hyperactivity/impulsivity" subscales of the SNAP-IV scale when administered at a dose of 125 mg BID. **Secondary objectives:** 1. To evaluate the efficacy of Mexidol® film-coated tablets 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy when administered at a dose of 125 mg OD and 125 mg BID on the basis of the following parameters: a. mean change on the SNAP-IV subscale - inattention; b. mean change on SNAP-IV subscale - hyperactivity/impulsivity; c. mean change on the SNAP-IV subscale - oppositional defiant disorder; d. mean change on the SNAP-IV subscale - Conners' clinical index; e. mean change on the Spence Children's Anxiety Scale (SCAS); f. mean change on ADHD Rating Scale-IV;

	g. mean change on the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale; h. assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores); i. The Clinical Global Impressions Scale - Improvement (CGI-I) score. 2. To evaluate the safety of Mexidol® film-coated tablets, 125 mg (RPC PHARMASOFT LLC, Russia) vs. placebo based on the assessment of frequency, severity and nature of adverse events.
Trial design:	A multicentre, prospective, double-blind, randomised in three parallel groups with a 1:1:1 ratio trial to evaluate the efficacy and safety of Mexidol® film-coated tablets, 125 mg using placebo controls.
Randomisation method	Patient randomisation will be performed at Visit 2 with a 1:1:1:1 patient allocation using the online IWRS (Interactive Web Response System). A patient randomisation number will be assigned to the trial subject in the order in which they access the IWRS system.
Planned number of patients:	The trial is planned to enrol 417 patients, from which 333 patients will be randomised, in order to obtain 300 completed cases (100 in each of the three groups).
Patient population:	Outpatients, boys and girls, aged 6 to 12 years (inclusive) with a diagnosis of attention deficit hyperactivity disorder, established according to the criteria of the 10th revision of the International Classification of Diseases (ICD-10) (F90.0) and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) by a psychiatrist or neurologist.
Trial duration:	The duration of treatment - 42 days and the duration of the follow-up period - 7 days. Screening and randomisation can be carried out on the same day provided all screening procedures are performed and results are available. The total minimum duration of patient participation in the trial will be 49 full days: a screening and therapy period of 42 days plus a follow-up period of 7 days. The total maximum duration of patient participation in the trial will be 67 days: a screening period of 14 days plus a therapy period of 42 days plus a follow-up period of 7 days, plus a window for the end-of-therapy visit (Visit 5) of 1 day and the follow-up visit (Visit 6) of 3 days.

Diagnosis and basic selection criteria:	**Inclusion criteria:** 1. Signed written informed consent for participation in the trial from the patient's parents. 2. Patients are boys and girls, aged 6 to 12 years inclusive at the time of signing the informed consent. 3. Child is being raised by the father and/or mother. 4. Child's attendance at a mainstream pre-school or school. 5. Diagnosis of attention deficit hyperactivity disorder established according to ICD-10 and DSM-5 criteria by a psychiatrist or neurologist, namely: According to the DSM-5 a. 6 or more symptoms of inattention persisting for at least 6 months and/or; b. 6 or more symptoms of hyperactivity and impulsivity persisting for at least 6 months; c. symptoms are present in at least two areas of activity (preschool or school and home). and/or According to the ICD-10 d. at least 6 symptoms of attention deficit disorder; e. at least 3 symptoms of hyperactivity; f. at least 1 symptom of impulsivity; g. stable for at least 6 months. 6. Moderate severity of illness according to the General Clinical Impression of ADHD Severity Scale (CGI-ADHD-S), not requiring hospitalisation for treatment. 7. Presence of no more than two comorbid disorders that do not, in the opinion of the investigator, require additional pharmacotherapy at the time of the trial. **Non-inclusion criteria:** 1. Hypersensitivity to the active substance of the investigational product (ethylmethylhydroxypyridine succinate) and/or other components of the product. 2. Liver dysfunction: ALT and/or AST ≥2.5 upper limit of normal (ULN) by screening tests. 3. Renal function disorders: blood creatinine ≥1.5 ULN by screening tests. 4. Intracranial pathology (including but not limited to: intracranial haemorrhage, tumour, infection, history of head injury, excluding concussion). 5. Associated autism spectrum disorders, Asperger's syndrome. 6. Mental retardation of any degree. 7. Other mental illnesses, except behavioural disorders (ICD-10 code F91). 8. Failure to withdraw psychotropic medications used to treat

	ADHD. 9. Other somatic and/or neurological diseases, the treatment of which requires the use of drugs that may affect the efficacy of the Investigational product (including but not limited to: epilepsy, depression). 10. Administration of nootropics, vasoactive drugs, neuroprotectants, antioxidants, metabolic drugs for 7 days or 5 half-lives (whichever is longer) before randomisation. 11. Presence of any history of cancer within 5 years prior to the screening visit. 12. Participation in any other clinical trial of mrdicinal products and/or medical devices within 3 months prior to the screening visit and/or 5 half-lives, whichever is longer. 13. Inability or impossibility to follow the requirements of the protocol, including for physical, mental or social reasons, in the opinion of the investigator. 14. Lactose intolerance, lactase deficiency, glucose-galactose malabsorption. **Early termination criteria:** 1. Withdrawal of informed consent by parents of the patient. 2. Adverse events requiring cancellation of the investigational product. 3. Need for drugs that are prohibited under the terms of the protocol. 4. Continued participation in the trial is contrary to the patient's best interests. 5. Discontinuation of the trial by the Sponsor. 6. Discontinuation of the trial by regulatory authorities. 7. Loss of communication with the patient.
Trial procedures/frequency:	See the Schedule of Trial Visits and Procedures
Investigational product, dose and method of administration:	**Investigational product + Placebo (group 1)** Mexidol® (ethylmethylhydroxypyridine succinate) **film-coated tablets, 125 mg** (RPC PHARMASOFT LLC, Russia). ***Method of administration:*** the drug will be administered orally 1 tablet OD. Group 1 patients will additionally take 1 placebo tablet. The interval between doses of Mexidol and placebo - 12±1 hours. Thus, a single dosing regimen for all three groups - 1 tablet BID to maintain double-blinding of the prescribed therapy - will be followed. Duration of therapy: 42 days.

	Investigational product (group 2) Mexidol® (ethylmethylhydroxypyridine succinate) **film-coated tablets, 125 mg** (RPC PHARMASOFT LLC, Russia). ***Method of administration:*** the drug will be administered orally 1 tablet BID. Duration of therapy: 42 days.
Placebo, dose and method of administration:	**Placebo (group 3)** (RPC PHARMASOFT LLC, Russia). ***Method of administration:*** placebo will be administered orally 1 tablet BID. Duration of therapy: 42 days.
Prohibited therapy	1) neuroprotectants, antioxidants, metabolic drugs, vasoactive and nootropic agents, including but not limited to: actovegin, aminalon, biotredine, vasobral, gliatilin, glycine, dimefosfon, instenon, cohitum, cortexin, kudesan, minisem, noben, pantogam, picamilon, piracetam, tenoten for children, phenibut, cerebrolysin, cinnarizine, encephabol. 2) other agents affecting the central nervous system: ginkgo biloba leaf extract, atomoxetine, tranquillisers and antidepressants.
Efficacy evaluation:	Evaluation of the efficacy of therapy will be based on primary and secondary efficacy criteria. **Primary efficacy criterion:** 1. Mean change in the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline. **Secondary efficacy criteria:** 1. mean change on the SNAP-IV inattention subscale after 6 weeks of therapy vs. baseline 2. mean change on SNAP-IV subscale hyperactivity/impulsivity after 6 weeks of therapy vs. baseline 3. mean change on the SNAP-IV subscale, oppositional defiant disorder, after 6 weeks of therapy vs. baseline; 4. mean change on the SNAP-IV subscale - Conners' clinical index; 5. mean change on the Spence children's anxiety scale (SCAS) after 6 weeks of therapy vs. baseline; 6. mean change on ADHD Rating Scale-IV scores after 6 weeks

	of therapy vs. baseline; 7. clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale score after 6 weeks of therapy vs. baseline; 8. assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores); 9. Clinical Global Impressions Scale - Improvement (CGI-I) score after 6 weeks of therapy vs. baseline.
Safety evaluation:	The safety of investigational product administration will be evaluated using the following criteria: 1. Number of adverse events (AEs) and serious AEs (SAEs). 2. Frequency and severity of AE/SAE associated with investigational product/placebo. Safety assessment will be based on patient and/or patient's parents interview, physical examination findings (including assessment of vital signs: BP, HR, RR), data from the Patient Diary and results of laboratory and instrumental examination (clinical and biochemical blood tests).
Statistical methods:	**Statistical analysis** Statistical analysis populations: 1) the safety population will include all randomised patients who have taken at least one dose of Investigational product; 2) the full analysis set (FAS) population will include all randomised patients who have taken at least one dose of Investigational product and who have an assessment of response to therapy after 6 weeks of therapy. This will be the main population for efficacy analyses; 3) PP (per protocol population) is a subgroup of the FAS population that will include patients in the absence of significant protocol deviations with respect to inclusion/exclusion criteria, adherence to therapy, and use of concomitant therapy. This will be an additional population used for efficacy analyses. Descriptive statistics for data whose distribution follows the law of normal distribution will be presented using the arithmetic mean and standard deviation. For otherwise distributed data, descriptive statistics will be presented using non-parametric measures (median/mode, quartiles). Two-sided confidence intervals will be used to assess treatment efficacy (primary and secondary efficacy criteria). A conclusion on

	superiority can be made if the upper bound of the two-sided 95% confidence interval for the difference in mean changes in SNAP scores of Mexidol® vs. placebo is negative. For primary and secondary efficacy criteria, differences will be considered statistically significant at the p-value level of <0.05. The χ-square test or Fisher's exact test will be used to assess differences in event rates. The χ-square test or Fisher's exact test will also be used to assess differences in patient adherence. Safety parameters will be tabulated for all patients who received investigational medicinal product. Comparisons of safety profiles between trial groups will be made using the χ-square test (for qualitative data) and the t-test for data whose distribution follows the law of normal distribution, or its non-parametric analogue (for data whose distribution does not follow the law of normal distribution). AEs will be coded per MedDRA and categorised using Organ System Classes and preferred term. The protocol provides for the recording of all AEs that occur to the patient after the first administration of the trial therapy and until the end of the patient's participation in the trial. During screening, information about medical adverse events will be attributed to the patient's medical history (pre-existing/concomitant conditions). The planned trial will record all deviations in the health status of patients (based on the results of physical examination, laboratory and instrumental methods of investigation) from the data obtained at the Screening and from the accepted reference values. After obtaining the necessary information, the investigating physician will categorise the patient's condition as 'normal', 'clinically insignificant abnormalities' or 'clinically significant abnormalities'. In case the abnormalities detected during the trial have not been previously reported, or there is an aggravation of the patient's condition vs. the data staffobtained at Screening, the detected abnormalities will be classified as AEs.

1.2. Schedule of trial visits and procedures

Procedures		Visits				
			Therapy			Follow-up
	Screening	Initiation of therapy	Telephone contact[1]	Telephone contact[2]	End of therapy	
Day	-14-1	1	14±2	28±2	43+1	50+3
Visit number	1	2	3	4	5	6
Informed consent	X					
Demographic data and history	X					
Measurement of height, body weight, BMI calculation	X					
Registration of previous therapy	X					
Registration of previous pathology	X					
Registration of comorbidities	X					
Registration of concomitant therapy	X	X	X	X	X	X
Inclusion / non-inclusion criteria	X	X				
Exclusion criteria		X			X	
Physical examination with measurement of BP, HR, and RR	X				X	X
Complete Blood Count[3]	X				X	
Biochemical blood test[4]	X				X	

[1] During telephone contact, the investigator should obtain information about the general tolerability of treatment, the occurrence of AEs, prescribed concomitant medications, and remind about compliance with the therapy regimen
[2] During the telephone contact, the investigator should obtain information about general tolerability of treatment, occurrence of NSAIDs, prescribed concomitant medications, ADHD Rating Scale IV score, and remind about adherence to the therapy regimen
[3] Haemoglobin; haematocrit; red blood cell count; platelet count; white blood cell count and complete white blood cell count; ESR
[4] Total protein; albumin; glucose; ALT; AST; total bilirubin, alkaline phosphatase (ALP), amylase, creatinine

Procedures		Visits				
			Therapy			Follow-up
	Screening	Initiation of therapy	Telephone contact[1]	Telephone contact[2]	End of therapy	
Day	-14-1	1	14±2	28±2	43+1	50+3
Visit number	1	2	3	4	5	6
Clinical urinalysis[5]	X				X	
AE registration		X	X	X	X	X
Neurological status	X				X	X
SNAP-IV score	X	X			X	
Randomization		X				
SCAS score		X			X	
ADHD Rating Scale IV score		X		X	X	
CGI-ADHD-S score	X	X			X	
CGI-I score					X	
PedMIDAS questionnaire score[6]		X			X	
Completion of an assessment card for a child/adolescent with headache[7]		X			X	
Dispensing and/or record keeping of medications		X			X	
Assessment of adherence to therapy					X	

[5] Colour, transparency, pH, specific gravity, protein, glucose, leucocytes, red blood cells, bacteria, cylinders, salts

[6,7] If the patient has headache complaints, at Visit 2, to be completed for the previous 3 months; if the patient has headache complaints identified at Visit 2, to be completed at Visit 5, to be completed for the last 1.5 months (6 weeks)

Procedures		Visits				
			Therapy			Follow-up
	Screening	Initiation of therapy	Telephone contact[1]	Telephone contact[2]	End of therapy	
Day	-14-1	1	14±2	28±2	43+1	50+3
Visit number	1	2	3	4	5	6
Issuance of the Patient Diary and instructions on how to complete it		X				
Collecting the Patient Diary and monitoring its completion					X	

1.3. Trial Sponsor

Sponsor:	**RPC PHARMASOFT LTD** Legal address: Russian Federation, 115407, Moscow, 41, Sudostroitelnaya St., floor 1, room. 12 Postal address: Russian Federation, 109544, Moscow, Enthusiastov Boulevard, 2 Tel./fax: +7 (495) 626 47 55
Sponsor's Responsible Representative:	**Tatyana Anatolievna Mityushkina** Medical Director RPC PHARMASOFT LLC Tel: +7 (495) 626 47 55 ext. 140 e-mail: mityushkina_t@pharmasoft.ru
In case of serious adverse events, notify:	**Qualified Person Responsible for Pharmacovigilance (QPPV): Irina Vladimirovna Medvedeva** RPC PHARMASOFT LLC tel.: +7 (495) 626 47 55 ext. 162 e-mail: pv@pharmasoft.ru

1.4. Organizer of the trial

Organizer:	**ClinPharmDevelopment LLC** Russia, 150031, Yaroslavl, Uglichskaya str. 68, office. 1. Tel: +7 (4852) 59-47-79, http://www.cphd.ru
Organizer's Responsible Representative:	Nikolay Olegovich Pozdnyakov Director Address: Russia, 150031, Yaroslavl, Uglichskaya str. 68, office. 1. Tel: +7 (4852) 59-47-79 E-mail: no_pozdnyakov@cphd.ru

1.5. Clinical Research Associate (CRA)

ClinPharmDevelopment LLC

Russia, 150031, Yaroslavl, Uglichskaya str. 68, office. 1.

Tel: +7 (4852) 59-47-79, http://www.cphd.ru

1.6. Person authorised by the Sponsor to sign the protocol and amendments

thereto

Tatyana Anatolievna Mityushkina

Medical Director

RPC PHARMASOFT LLC

tel.: +7 (495) 626 47 55 ext. 140

e-mail: mityushkina_t@pharmasoft.ru

1.7. Clinical laboratories and other organizations relevant to the trial

The Clinical Central Laboratory will not be involved in this trial.

1.8. Investigators and Investigational sites

The list of investigators and Investigational sites will be provided in a separate document.

2. TRIAL RATIONALE

Attention deficit hyperactivity disorder (ADHD) is characterised by a triad of symptoms: attention deficit disorder, hyperactivity and impulsivity (coded as F90.0 in the International Classification of Diseases 10th revision)[1]. ADHD is the most common behavioural disorder in children: according to various authors, the prevalence in the paediatric population ranges from 2 to 12% (average 3-7%). The high prevalence and social maladaptation resulting from ADHD represent a major social problem[1-7].

The etiology of ADHD remains controversial to date. Several concepts of the origin of this syndrome have been proposed, one of which is genetic, according to which ADHD is a polygenic disorder and its development is determined by multiple genes. Neurobiological and neurophysiological concepts link the emergence of ADHD with a decrease in local cerebral blood flow in the frontal cortex and subcortical nodes, deficit of inhibition in the sensorimotor system both at the level of cortical structures (frontal lobe) and at the level of subcortical formations (caudate nucleus) causing activation of sensorimotor cortex[1,6.] The existing hypotheses do not exclude each other, but describe disturbances in different systems[6]. The results of biochemical studies have shown that the major neurotransmitter systems of the brain - dopaminergic, noradrenergic and serotoninergic - play an important role in pathogenesis. It was found that there are fundamental differences in monoamine metabolism in this pathology[6]. Several studies have shown reduced blood flow and low neuronal activity in striatal and prefrontal orbital areas, whereas increased blood flow has been reported in primary sensory and sensorimotor areas[6].

Currently, the diagnosis of ADHD is based on clinical criteria[7]. Uniform criteria for the diagnosis of ADHD are represented by two major international classifications: DSM-5 (until 2013 the DSM- IV-TR version was used) and ICD-10. There are no fundamental differences in the approach to diagnosis between these classifications. Diagnosis is made on the basis of qualitative criteria that are descriptive or based on the presence of a number of standard behavioural patterns that occur at a certain age and lead to impaired social adaptation[8]. In general, both classifications use the same set of symptoms, but there are some fairly important differences. The DSM-5 identifies the following subtypes of ADHD:

a) with predominant symptoms of inattention;
b) with predominant symptoms of hyperactivity and impulsivity;
c) mixed type.

Symptoms of inattention: inability to focus on details and making mistakes due to inattention in school, work or other activities; difficulty maintaining attention on tasks or in play activities; lack of attention to spoken language; difficulty following instructions and inability to complete lessons, homework or workplace duties (not due to oppositional behaviour or inability to understand instructions); impaired organization of tasks and activities; avoidance or dissatisfaction, resistance to involvement in tasks that require prolonged mental effort; loss of things necessary for the performance of any work; increased distractibility by external stimuli, forgetfulness in everyday situations[7].

Symptoms of hyperactivity and impulsivity: restless inappropriate movements of hands and feet; inability to sit still; inadequate noisy activity in games, difficulty in quiet leisure time; constant movement; talkativeness; impatience; difficulty waiting in queues; interrupting conversations, games, other people's work[7].

ICD-10 does not distinguish forms and subtypes of ADHD, but hyperkinetic behaviour disorder (F90.1) is distinguished along with ADHD (F90.0), which are grouped under the general heading of hyperkinetic disorders (F90)[7,8.]

A DSM-5 diagnosis of ADHD requires the presence of 6 (or more) of the listed symptoms of inattention and 6 (or more) of the listed symptoms of hyperactivity and impulsivity that are persistent for at least 6 months or more[7]; with several symptoms of inattention and hyperactivity-impulsivity present before age 12 years, occurring in two or more types of settings, clear evidence that the symptoms are having a significant impact by reducing the quality of performance, symptoms are not associated with anincrease in the quality of activity, and symptoms are not associated with a decrease in the quality of activity. To diagnose attention deficit hyperactivity disorder, the ICD-10 research criteria require at least 6 symptoms of inattention out of 9, three symptoms of hyperactivity out of 5, and at least 1 symptom of impulsivity out of 4[8].

Compared to DSM-IV and ICD-10, DSM-5 includes the same 18 leading symptoms of ADHD, but the new version contains the following major changes: age of onset is defined up to 12 years (under ICD-10 and DSM-IV - up to 7 years); the requirement for the cross-situational nature of symptoms is strengthened - the patient must have more than one symptom confirmed in each type of setting; the description of symptoms is supplemented with typical examples illustrating their manifestations at different age periods; autistic disorders are not mentioned as an exclusion criterion; a threshold number of ADHD symptoms for adult patients (older than 17 years) is given for the first time: at least 5 (rather than 6 as in children) symptoms of one or two sections of the diagnostic criteria must be confirmed[7].

Since clinical psychopathological criteria in both the DSM and the ICD are standardised but not ranked in terms of severity, specially developed assessment scales are used for scoring symptoms, which allow to evaluate the quantitative manifestations of symptoms, the degree of their severity, as well as the dynamics of the patient's condition in the process of therapeutic measures and social rehabilitation[6,8.]

Treatment of ADHD should be comprehensive and include methods of behavioural correction,

psychotherapy, and neuropsychological correction[7]. Psychological and pedagogical correction is considered as one of the main methods of therapy[1]. Pharmacotherapy is prescribed on an individual basis when cognitive and behavioural disorders cannot be overcome by behavioural therapy, psycho-educational correction and psychotherapy[6]. Drug therapy requires sufficient duration, as the improvement should not only extend to the main symptoms but also to the socio-psychological side of patients' lives[7]. The programme of medication treatment of ADHD consists in the sequential prescription of complexes of drugs of different pharmacological groups. Approaches to drug therapy for ADHD vary around the world[7]. Most ADHD drugs used in the West are either not registered in Russia (amphetamine, dextroamphetamine, methylphenidate) or are not approved for use in ADHD and are not used in paediatric practice (clonidine, guanfacine, bupropion, imipramine)[1]. In Russia, ADHD therapy traditionally includes gamma-aminobutyric acid, nootropic and neurometabolic drugs, as well as some tranquilisers, atypical neuroleptics, antidepressants and amoxetine. At the same time, the issue of the efficacy of medication methods for ADHD correction is still debatable[1]. It should be noted that in children without pronounced attention disorders, the use of nootropic drugs, which are most often used in the treatment of ADHD in Russia[7], is not always justified due to the possibility of such side effects as agitation and sleep disturbances.

Mexidol® is an inhibitor of free-radical processes, a membrane-protector with antihypoxic, stress-protective, nootropic, anticonvulsant and anxiolytic action. Anti-stressor effect is manifested in normalisation of post-stress behaviour, somatovegetative disorders, restoration of sleep-wake cycles, disturbed learning and memory processes, reduction of dystrophic and morphological changes in various brain structures. Thus, Mexidol® may potentially act favourably on the neurobiological and neurophysiological mechanisms of ADHD development, allowing to reduce the severity of symptoms[9].

There are no studies of safety and efficacy of Mexidol® in adults for the proposed indication, which is due to the fact that this pathology is characteristic of childhood and practically does not occur in the adult population. While the present trial is planned to include the age group of children from 6 to 12 years inclusive.

In this regard, the Sponsor has planned a multi-centre prospective, double-blind, placebo-controlled, randomised clinical trial in three parallel groups to study the safety and efficacy of Mexidol® in the treatment of attention deficit hyperactivity disorder in children 6-12 years of age.

2.1. Name and description of the trial products

2.1.1. Investigational product:

Name: Mexidol®

Group name: Ethylmethylhydroxypyridine succinate

Dosage form: film-coated tablets

Composition:

Active substance: ethylmethylhydroxypyridine succinate (2-ethyl-6methyl-3-hydroxypyridine succinate) - 125 mg.

Excipients: lactose monohydrate - 97.5 mg, povidone 25.0 mg, magnesium stearate - 2.50 mg.

Film coating: opadray II white 33G28435 - 7.5 mg (hypromellose -3.0 mg, titanium dioxide - 1.875 mg, lactose monohydrate - 1.575 mg, polyethylene glycol (macrogol) - 0.6 mg, triacetin - 0.45 mg).

Description: round, biconvex, film-coated tablets, from white to white with a creamy tinge colour.

Pharmacotherapeutic group: antioxidant agent.

ATC code: N07XX

Pharmacodynamics:

Mexidol® is an inhibitor of free-radical processes, a membrane-protector with antihypoxic, stress-protective, nootropic, anticonvulsant and anxiolytic action. The drug increases the body's resistance to various damaging factors (shock, hypoxia and ischaemia, cerebral circulatory disorders, intoxication with alcohol and antipsychotic drugs (neuroleptics)).

Mechanism of action of Mexidol® is due to its antioxidant, antihypoxant and membrane-protective action. It inhibits lipid peroxidation, increases superoxide dismutase activity, increases the lipid-protein ratio, decreases membrane viscosity, and increases membrane fluidity. Mexilol® modulates the activity of membrane-bound enzymes (calcium independent phosphodiesterase, adenylate cyclase, acetylcholinesterase), receptor complexes (benzodiazepine, GABA, acetylcholine), which enhances their ability to bind to ligands, contributes to the preservation of structural and functional organisation of biomembranes, transport of neurotransmitters and improvement of synaptic transmission. Mexidol® increases the content of dopamine in the brain. It causes enhancement of compensatory activation of aerobic glycolysis and reduction of the degree of inhibition of oxidative processes in the Krebs cycle under hypoxia with an increase in the content of ATP and creatine phosphate, activation of energy-synthesising functions of mitochondria, stabilisation of cell membranes.

The drug improves metabolism and blood supply to the brain, improves microcirculation and rheological properties of blood, reduces platelet aggregation. Stabilises membrane structures of blood cells (erythrocytes and platelets) during haemolysis. It has hypolipidemic action, reduces the content of total cholesterol and low-density lipoproteins.

Anti-stressor effect is manifested in normalisation of post-stress behaviour, somatovegetative disorders, restoration of sleep-wake cycles, disturbed learning and memory processes, reduction of dystrophic and morphological changes in various brain structures.

Mexidol® has a pronounced antitoxic effect in withdrawal syndrome. It eliminates neurological and neurotoxic manifestations of acute alcohol intoxication, restores behavioural disorders, autonomic functions, and is also able to relieve cognitive impairment caused by long-term ethanol intake and its withdrawal. Under the influence of Mexidol® enhances the effect of tranquilising, neuroleptic, antidepressant, antidepressant, sleeping and anticonvulsant drugs, which allows to reduce their doses and side effects. Mexidol® improves the functional state of ischaemic myocardium. In conditions of coronary insufficiency increases collateral blood supply of ischaemic myocardium, promotes preservation of integrity

of cardiomyocytes and maintenance of their functional activity. It effectively restores myocardial contractility in reversible cardiac dysfunction.

Pharmacokinetics

It is rapidly absorbed when taken orally. The maximum concentration at doses of 400500 mg is 3.5-4.0 μg/ml. It is rapidly distributed in organs and tissues. The average retention time of the drug in the body when administered orally is 4.9-5.2 h. It is metabolised in the liver by glucuronidation. Five metabolites have been identified: 3-oxypyridine phosphate - formed in the liver and broken down into phosphoric acid and 3-oxypyridine with the participation of alkaline phosphatase; the 2nd metabolite - pharmacologically active, formed in large quantities and detected in the urine 1-2 days after administration; the 3rd - excreted in large quantities with urine; the 4th and 5th - glucuronconjugates. T1/2 at ingestion is 2.0-2.6 h. It is rapidly excreted with urine mainly in the form of metabolites and in an insignificant amount - in unchanged form. It is most intensively excreted during the first 4 hours after taking the drug. Urinary excretion rates of unchanged drug and metabolites have individual variability.

Indications for use:

- Consequences of acute cerebral circulatory disorders, including after transient ischaemic attacks, in the phase of subcompensation as prophylactic courses;
- Mild head injury, consequences of head injuries;
- Encephalopathies of various genesis (dyscirculatory, dysmetabolic, post-traumatic, mixed);
- Autonomic dystonia syndrome;
- Mild cognitive disorders of atherosclerotic genesis;
- Anxiety disorders in neurotic and neurosis-like states;
- Ischaemic heart disease as part of complex therapy;
- Coping with withdrawal syndrome in alcoholism with predominance of neurosis-like and vegetative-vascular disorders, post-abstinence disorders;
- Condition after acute intoxication with antipsychotic drugs;
- Asthenic conditions, as well as for the prevention of somatic diseases under the influence of extreme factors and loads;
- Exposure to extreme (stressor) factors.

Contraindications

- acute liver and/or renal dysfunction;
- hypersensitivity to the drug and its components;
- infancy (due to insufficiently studied effect of the drug);
- pregnancy, breastfeeding (due to insufficient study of the drug action);
- lactose intolerance, lactase deficiency, glucose-galactose malabsorption.

Use in pregnancy and during breastfeeding:

Mexidol® is contraindicated in pregnancy and during breastfeeding.

Method of administration and doses

For adults: orally, 125-250 mg TID; maximum daily dose - 800 mg (6 tablets). Duration of treatment 2-6 weeks; for alcohol withdrawal - 5-7 days. Treatment is discontinued gradually, reducing the dose over 2-3 days.

The initial dose is 125-250 mg (1-2 tablets) 1-2 times a day with gradual increase until therapeutic effect is obtained; maximum daily dose - 800 mg (6 tablets)[1].

Duration of the course of therapy in patients with ischaemic heart disease is not less than 1.5-2 months. Repeated courses (on the doctor's recommendation) should preferably be carried out in the spring and autumn periods.

Side effects

The frequency of side effects was determined according to the World Health Organisation (WHO) classification: very frequent (≥10%); common (≥1%, but <10%); uncommon (≥0.1%, but <1%); rare (≥0.01%, but <0.1%); very rare (<0.01%); frequency unknown (frequency cannot be determined from available data).

Immune system disorders: very rare - angioedema, urticaria.

Mental disorders: very rare - somnolence.

Nervous system disorders: very rare - headache.

Gastrointestinal disorders: very rare - dry mouth, nausea, pain, burning and discomfort in the epigastric region, heartburn, flatulence, diarrhoea.

Skin and subcutaneous tissue disorders: very rare - rash, pruritus, hyperaemia.

Interaction with other drugs:

Mexidol® is combined with all drugs used for the treatment of somatic diseases. It enhances the effect of benzodiazepine drugs, antidepressants, anxiolytics, anticonvulsants and antiparkinsonian drugs. It reduces the toxic effects of ethyl alcohol.

Overdose

Symptoms: drowsiness, insomnia.

Treatment: due to low toxicity, overdose is unlikely. Treatment is usually not required - symptoms disappear on their own within 24 hours. In severe manifestations, supportive and symptomatic treatment is carried out.

Effect of the drug on the ability to drive vehicles or operate mechanisms:

[1] When administered intravenously, the maximum daily dose of Mexidol® is 2000 mg.

During the period of drug administration, caution should be exercised in work requiring quick psychophysical reactions (driving vehicles, mechanisms, etc.).

Pharmaceutical form: Film-coated tablets, 125 mg. 10 tablets each in a PVC/Alu blister. 1, 2, 3, 4, 5 blisters together with instructions for use in a carton pack.

Storage conditions

Store in a dry place, protected from light, at a temperature not exceeding 25°C. Keep out of reach of children.

Shelf life

3 years. Do not use after the expiry date indicated on the pack.

Manufacturer:

ZiO-Zdorovye CJSC, Russia, 142103, Moscow region, Podolsk, Zheleznodorozhnaya St., 2

Tel: +7(495)642-05-42
Fax: +7(495)642-05-43

Marketing Authorization Holder/ Claims Receiving Organisation:

RPC PHARMASOFT LLC, Russia, 115407, Moscow, 41, Sudostroitelnaya St., floor 1, room. 12
Tel./fax: +7(495)626-47-55

2.1.2. Placebo

Name: placebo

INN or group name: not applicable

Dosage form: film-coated tablets

Composition: lactose monohydrate - 222.50 mg, povidone 25.0 mg, magnesium stearate - 2.50 mg.

Film coating: opadray II white 33G28435 - 7.5 mg (hypromellose - 3.0 mg, titanium dioxide - 1.875 mg, lactose monohydrate - 1.575 mg, polyethylene glycol (macrogol) - 0.6 mg, triacetin - 0.45 mg).

Description: round, biconvex, film-coated tablets, from white to white with a creamy tinge colour.

Pharmacotherapeutic group: not applicable

ATC code: not applicable

Manufacturer:

ZiO-Zdorovye CJSC, Russia, 142103, Moscow region, Podolsk, Zheleznodorozhnaya St., 2

Tel: +7(495)642-05-42
Fax: +7(495)642-05-43

2.2. Summary of results of preclinical and clinical studies

2-ethyl-6-methyl-3-oxypyridine succinate (under the code SOP-1) was synthesised in the 1980s by L.D. Smirnov and V.I. Kuzmin. Smirnov and V.I. Kuzmin. In the same years, under the direction of Professor T.A. Voronina, Doctor of Medical Sciences, it was first shown that for SOP-1 (Mexidol), which combines the properties of a tranquiliser and nootropic, anxiolytic and anti-stressor effects are dominant in the spectrum of psychotropic action, and SOP-1 is superior to piracetam and piritinol in its anti-amnesic action. From this point onwards, numerous studies

have revealed other pharmacological effects peculiar to this substance, in particular antioxidant, membranotropic, antihypoxic, radioprotective, geroprotective, antitoxic, etc.

Mexidol® is the first preparation of ethylmethylhydroxypyridine succinate included in the Order of the Ministry of Health of the Russian Federation dated 31 December 1996 No. 432 "On Approval of Medical Use" (in the dosage form of solution for intramuscular and intravenous administration). Mexidol® in the pharmaceutical form of film-coated tablets, 125 mg is approved for medical use in accordance with the Order of the Ministry of Health of the Russian Federation No. 21 dated 26 January 1998. In accordance with Federal Law No. 61-FZ "On Circulation of Medicines" dated 12.04.2010, Mexidol® (film-coated tablets, solution for intravenous and intramuscular administration) is recognised by FSBI NCESMP of the Ministry of Health of Russia as a reference (original) drug (letter of the Ministry of Health of Russia No. 20-3/1262 dated 19.09.2016, letter of FSBI NCESMP of the Ministry of Health of Russia dated 09.09.2016).

According to the data of numerous preclinical studies it was shown antihypoxic, anti-ischaemic (including myocardial infarction) action, antioxidant and membranoprotective effects, anxiolytic and anti-stressor effects, positive effects in experimental alcoholism and drug addiction, the presence of antiarrhythmic activity, positive effect in dyslipoproteidaemia, anti-atherogenic effect, hypolipidemic, anti-allergic action.

The potential efficacy of Mexidol® against ADHD has been demonstrated in animal experiments. In a model of hyperactivity in rats with spontaneous hypertension of the SHR line, behavioural functions were studied in an open-field test (study of vertical and horizontal activity). Efficacy was evaluated against the paediatric ADHD drug, Strattera (INN: atomoxetine), at two dose levels equivalent to a daily dose of 125 and 250 mg for humans. Administration of Mexidol® in SHR rats at a dose of 75 mg/kg (equivalent to 250 mg/day for humans) statistically significantly reduced hyperactivity and this effect was comparable to Strattera® and was maintained over the following two weeks.

Another experiment in Wistar rats examined one of the cognitive functions (attention) and general impulsivity, which is an integral component of ADHD, in the 5-CSRTT (reaction time when choosing among 5 possibilities) test. Wistar rats are initially highly impulsive, as manifested in the 5-CSRTT test as a "premature response," i.e., the number of times the nose was inserted into one of the five holes between attempts or during a timeout (no illumination for 5 seconds). The attention index was quantified as the number of correct attempts. Putting the nose through the illuminated hole within 18 seconds of the start of the attempt was taken as a correct attempt, which was reinforced by providing the rat with a pellet of food. It was demonstrated that administration of Mexidol® in rats at a dose of 75 mg/kg (equivalent to 250 mg/day for humans) statistically significantly leads to an improvement in attention performance (increase in the proportion of correct attempts) and reduces the impulsivity index (decrease in the proportion of premature attempts) and this effect was comparable to Strattera®.

As part of the development of the drug for a new indication for use in paediatric practice, preclinical toxicological studies were conducted on two species of immature animals in the whole age range of development.

According to the results of the study of acute toxicity and determination of maximum tolerated dose of Mexidol® at a single injection into the stomach by probe to male and female SD rats at

the age of 2 weeks it was found that the maximum tolerated dose for males was 1700 mg/kg, for females - 1500 mg/kg, the LD_{50} value for male rats was 2010±101 mg/kg, for females - 1957±104 mg/kg.

As a result of acute toxicity study and determination of the maximum tolerated dose of Mexidol® when administered once in the stomach to male and female Sprague-Dawley (SD) rats at the age of 4 weeks, it was found that the maximum tolerated dose for males and females was 5000 mg/kg, the LD_{50} value for male rats was 6328±207 mg/kg, for females - 6098±192 mg/kg.

According to the results of the study of acute toxicity and determination of maximum tolerated dose of the medicinal product Mexidol® at a single injection into the stomach by probe to male and female SD rats at the age of 7.5 weeks it was found that the maximum tolerated dose for male and female rats is 5000 mg/kg, the LD_{50} value for male rats was 6328±207 mg/kg, for females - 6098±192 mg/kg.

To assess subchronic toxicity, a study of Mexidol® film-coated tablets 125 mg was conducted during multiple intragastric administration to immature rats and rabbits with assessment of possible delayed action. Within the framework of the conducted study on immature animals it was shown that the investigated Mexidol® film-coated tablets, 125 mg (RPC Pharmasoft LLC., Russia) is a low-toxic substance. At doses of 50 mg/kg for rats and 25 mg/kg for rabbits, which approximate the maximum therapeutic doses for adult humans, the drug did not cause toxic disorders. At doses of 600 mg/kg in rats and 200 mg/kg in rabbits (greater than the maximum therapeutic doses by a factor of 12 and 8, respectively, per animal), the drug also did not cause toxic changes. The doses of Mexidol® coated tablets that do not cause adverse effects in immature rats and in immature rabbits are in the dose range of 600 - 1200 mg/kg and 200 - 400 mg/kg, respectively.

These studies concluded that it was feasible to conduct clinical studies involving children.

Indications for prescribing Mexidol® in adults are the following conditions and diseases:

- Consequences of acute cerebral circulatory disorders, including after transient ischaemic attacks, in the phase of subcompensation as prophylactic courses;
- Mild head injury, consequences of head injuries;
- Encephalopathies of various genesis (dyscirculatory, dysmetabolic, post-traumatic, mixed);
- Autonomic dystonia syndrome;
- Mild cognitive disorders of atherosclerotic genesis;
- Anxiety disorders in neurotic and neurosis-like states;
- Ischaemic heart disease as part of complex therapy;
- Coping with withdrawal syndrome in alcoholism with predominance of neurosis-like and vegetative-vascular disorders, post-abstinence disorders;
- Condition after acute intoxication with antipsychotic drugs;
- Asthenic conditions, as well as for the prevention of somatic diseases under the

influence of extreme factors and loads;

- Exposure to extreme (stressor) factors.

Previously, clinical studies to register the drug for use in children have not been conducted. However, there are a number of publications investigating the effects of the drug in neurology in a paediatric population. According to the results of these studies, the efficacy of Mexidol® film-coated tablets 125 mg for school adaptation in children with attention deficit hyperactivity disorder, posthypoxic encephalopathy, correction of autonomic dysregulation syndrome and autonomic status, posttraumatic epilepsy was shown. However, the authors did not note any safety concerns with the use of the drug in children. Individual adverse reactions may occur when using the drug. The safety profile of the drug in children is not expected to be significantly different from the safety profile in the adult population.

For more details, all information on the results of the preclinical studies, please refer to the Investigator Brochure.

2.3. Summary of known and potential risks and benefits to patients

The Trial Sponsor, RPC PHARMASOFT LLC, Russia, is planning to conduct a multicentre prospective, double-blind, placebo-controlled randomised clinical trial in three parallel groups to evaluate the safety and efficacy of Mexidol® film-coated tablets 125 mg in the treatment of attention deficit hyperactivity disorder in children 6-12 years old with different dosing regimen.

Mexidol® is registered in the Russian Federation for use in adults for various indications and currently the positive benefit/risk ratio of its use is beyond doubt.

Currently, psychological and pedagogical correction is considered as the main method of ADHD therapy, the question of the effectiveness of medication methods remains debatable[1], so the use of placebo against the background of psychological and pedagogical correction in one of the therapy groups will not bring additional risks for patients.

There are virtually no risks associated with the tests and examinations required under the terms of this protocol for patients. Blood sampling is required for the examinations required by this protocol and there is an unlikely risk of hematoma formation at the puncture site and infection, which can be eliminated by skilled performance of the procedure by professional staff at the participating clinical sites. Mild painful sensations may occur during the blood sampling procedure, which pass on their own and do not require additional therapeutic interventions. Dizziness and/or weakness may occur during or shortly after the blood sampling procedure.

The investigator will closely monitor the patients' condition throughout the clinical trial.

Patients will receive reliable information about their health status as a result of the examination and follow-up conducted as part of their examinations.

A detailed description of possible side effects of the investigational product as well as special instructions for its use are given in section 2.1. of this protocol.

2.4. Description and justification of the method of administration, dosage, regimen and course of treatment

Investigational product:

Mexidol® (ethylmethylhydroxypyridine succinate) film-coated tablets, 125 mg (RPC PHARMASOFT LLC, Russia).

Method of administration:

In Group 1, the drug will be administered orally 1 tablet OD. To maintain double-blinding and a uniform dosing regimen of the prescribed therapy, patients will take 1 placebo tablet. The interval between doses should be 12±1 hours.

In Group 2, the drug will be administered orally 1 tablet BID, morning and evening with an interval between doses of 12±1 hours.

Duration of therapy: 42 days.

Placebo

Placebo film-coated tablets (RPC PHARMASOFT LLC, Russia).

Method of administration: placebo will be administered orally 1 tablet BID, morning and evening with an interval between doses of 12±1 hours.

Duration of therapy: 42 days.

According to the results of the study of general toxic properties in acute and subchronic experiments on immature animals, the doses that do not cause adverse effects were determined: in immature rats the dose interval was 600 - 1200 mg/kg, in immature rabbits - 200 - 400 mg/kg, respectively.

To assess the safety of the selected dosage, the maximum recommended initial dose (MRID) was calculated according to the preclinical study guidelines[1].

In accordance with the guidelines, the highest dose levels that did not cause a significant increase in adverse effects compared to the control group were selected as the dose with no observed adverse effect (NOEL) in animals. In a subchronic toxicity study, the NOEL in rats was 1200 mg/kg and in rabbits 400 mg/kg. The human equivalent dose (HED) calculated using the formula provided in the guidance is then:

HED = NOEL for rats 1200 mg/kg / 6.0 = 200 mg/kg;

HED = NOEL for rabbits 400 mg/kg / 3.2 = 125 mg/kg.

For further calculations, the minimum resulting HED was used.

MRID = HED / safety factor (SF).

Standard SF = 10.

Then, MRID = 125 mg/kg / 10 = 12.5 mg/kg, which, taking into account the body weight of an "average" child of age 6 years, equal to 20 kg, will be 250 mg per day.

Thus, the suggested daily dosage of 250 mg in the present clinical trial in a dosing regimen of one 125 mg tablet BID appears to be reasonable and safe for use in children.

The safety profile of the drug in children is not expected to be significantly different from the

[1] Guidelines for conducting preclinical studies of medicinal products. Part One, ed. by A.N. Mironov. 2012, Moscow: Griff & Co. 944

safety profile in the adult population.

However, since Mexidol® in children has not been previously studied in controlled trials, 2 dosing regimens will be used to assess efficacy: 1 tablet 125 mg OD and 1 tablet 125 mg BID.

Group 1 patients receiving Mexidol® 1 tablet of 125 mg OD will additionally take 1 tablet of placebo. The interval between doses should be 12±1 hours. Thus, a single dosing regimen for all three groups - 1 tablet BID to maintain double-blinding of the prescribed therapy - will be followed.

In the approved instruction for medical use of Mexidol® for adults the maximum daily dose is set at 800 mg[1] (6 tablets), the recommended dose is 125-250 mg TID. The duration of treatment is 2-6 weeks.

Thus, the maximum investigational daily dose (250 mg) proposed in this protocol is 3.2 times less than the approved maximum adult dosage.

At the moment, there are no Russian regulatory guidelines for conducting clinical trials of medicines for ADHD, so the recommendations of the European Medicines Agency (EMA) have been used, in which the minimum recommended duration of use of an investigational medicine in a stable dose is 6 weeks[14]. This duration also corresponds to the maximum recommended duration of use of Mexidol® in adults. With this in mind, a duration of 6 weeks of drug administration was chosen for the initial demonstration of efficacy.

In addition, the safety of the drug use in the proposed doses in children is confirmed by the standards of medical care for various diseases in children approved by the Ministry of Health of Russia, starting from the period of newborn, in which the average daily dose is 200 mg, while the minimum weight of boys in the period of newborn averages 3.3 kg, girls - 3.2 kg. Thus, the daily dosage for a boy is 60.6 mg/kg and for a girl 62.5 mg/kg. The daily dosage proposed in this trial is lower than the approved standards and from this point of view seems safe [Order of the Ministry of Health of the Russian Federation from 24 December 2012 №1425n "On approval of the standard of specialised medical care for children with tick-borne viral encephalitis of severe severity"; Order of the Ministry of Health of the Russian Federation from 09.11.2012 №804n "On approval of the standard of specialised medical care for children with generalised meningococcal infection of severe severity"].

In a similar daily dosage, Mexidol® is included for use in children in the clinical recommendations (treatment protocol) "Provision of medical care to children with meningococcal infection" (FSBI NIIDI FMBA of Russia, Public Organisation "Euroasian Society for Infectious Diseases", 2015) and clinical recommendations for the management of children with the consequences of perinatal damage to the central nervous system with diffuse muscular hypotonia (2013). Additionally, the safety of Mexidol® in children, including newborns (at least 763 children), in various nosologies is confirmed by extensive experience in the use of the drug in clinical practice in Russia. In the trial of Askerova J.M.[10] Mexidol® was used in newborn children (both premature and premature) with the syndrome of intrauterine developmental delay in the correction of hypoxic-ischaemic lesions of the central nervous system in a daily dose of 0.1-0.2 ml/kg for 7-10 days, and no side effects were observed. In the trial by Zvonareva E.V.[11] Mexidol® was used in children aged 1-6 months with posthypoxic

[1] When administered intravenously, the maximum daily dose of Mexidol® is 1200 mg

encephalopathy at a daily dose of 5 mg/kg per day for 30 days (tablet form of the drug was used), and good tolerability of the drug and absence of side effects both during its administration and after completion of the course were noted.

In the trial by Tsypina L.G.[12] Mexidol® was used in children aged 2 months to 15 years in the complex therapy of acute neuroinfections. Depending on the degree of aggressiveness and severity of the infection, Mexidol® was administered in the acute stage of the disease by 100-200 mg 1-2 times a day intravenous drip for 5-7 days, then 50100 mg (depending on the age and weight of the child) intramuscularly in a total dose up to 15 days, followed by oral intake for 4-6 weeks. Dosage of the drug when taken orally in children of the first year of life was 1/4 tablet 2-3 times OD, from 1 to 3 years - 1/2 tablet BID, from 3 to 7 years - 1/2 tablet TID and in 7-10 years - 1 tablet 2-3 times a day. No side effects were reported by the authors.

In the trial by Potapova I.S. et al.[9] Mexidol® was used in children aged 7-9 years in the correction of school adaptation of children with attention deficit hyperactivity disorder in a daily dose of 1/2 tablet 2 times a day (daily dose 125 mg) for 30 days. No side effects were reported by the authors. In a trial by OkunevaM.A.[13] Mexidol® was used in adolescents aged 16-20 years for correction of autonomic dysregulation syndrome as a consequence of perinatal CNS lesions in a daily dose of 375 mg for 28 days, the authors did not report any side effects.

Thus, it is suggested that the use of the drug in a daily dose of up to 250 mg is reasonable in terms of safety.

2.5. Conditions of the trial

This clinical trial will be conducted in accordance with this protocol, the principles of the World Medical Association Declaration of Helsinki, the ICH Good Clinical Practice (ICH GCP) standard, and Russian law:

1. Federal Law dated 12 April 2010 N 61-FZ "On Circulation of Medicines" (in the current version);
2. National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice";
3. Order of the Ministry of Health of the Russian Federation No. 200n dated 01 April 2016 "On Approval of the Rules of Good Clinical Practice";
4. Resolution of the Government of the Russian Federation dated 13 September 2010 N 714 "On Approval of Model Rules for Compulsory Life and Health Insurance of a Patient Participating in Clinical Trials of a Medicinal Product" (current version);
5. Order of the Ministry of Health of the Russian Federation No. 986n of 29 November 2012 "On Approval of the Regulations on the Ethics Council";
6. Decision of the Council of the Eurasian Economic Commission of 03.11.2016 No. 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union".

2.6. Description of the trial population

Outpatients - boys and girls, aged 6 to 12 years (inclusive) with a diagnosis of attention deficit hyperactivity disorder, established in accordance with the criteria of the 10th revision of the International Classification of Diseases (ICD-10) (F90.0) and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) by a psychiatrist or neurologist.

3. TRIAL AIMS AND OBJECTIVES

3.1. Trial aimes

To evaluate the efficacy and safety of two dosing regimes of Mexidol® film-coated tablets, 125 mg (PRC Pharmasoft LLC, Russia) vs. placebo in children aged 6 to 12 years inclusive with attention deficit hyperactivity disorder (ADHD).

3.2. Trial objectives

Primary objective:

1. To evaluate the efficacy of Mexidol® film-coated tablets, 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy in relation to the average change in the total score on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP-IV scale when administered at a dose of 125 mg OD.
2. To evaluate the efficacy of Mexidol® film-coated tablets, 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy in relation to the mean change in the total score on the "inattention", "hyperactivity/impulsivity" subscales of the SNAP-IV scale when administered at a dose of 125 mg BID.

Secondary objectives:

1. To evaluate the efficacy of Mexidol® film-coated tablets 125 mg (PRC PHARMASOFT LLC, Russia) vs. placebo after 6 weeks from the beginning of therapy when administered at a dose of 125 mg OD and 125 mg BID on the basis of the following parameters:
    a. mean change on the SNAP-IV subscale - inattention;
    b. mean change on SNAP-IV subscale - hyperactivity/impulsivity
    c. mean change on the SNAP-IV subscale - oppositional defiant disorder;
    d. mean change on the SNAP-IV subscale - Conners' clinical index;
    e. mean change on the Spence Children's Anxiety Scale (SCAS);
    f. mean change on ADHD Rating Scale-IV value;
    g. Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S);
    h. assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores);
    i. Clinical Global Impressions Scale - Improvement (CGI-I).
2. To evaluate the safety of Mexidol® film-coated tablets, 125 mg (RPC PHARMASOFT LLC, Russia) vs. placebo based on the assessment of frequency, severity and nature of adverse events.

4. TRIAL DESIGN

4.1. Efficacy criteria

Evaluation of the efficacy of therapy will be based on primary and secondary efficacy criteria.

Primary efficacy criterion:

1. Mean change in the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline.

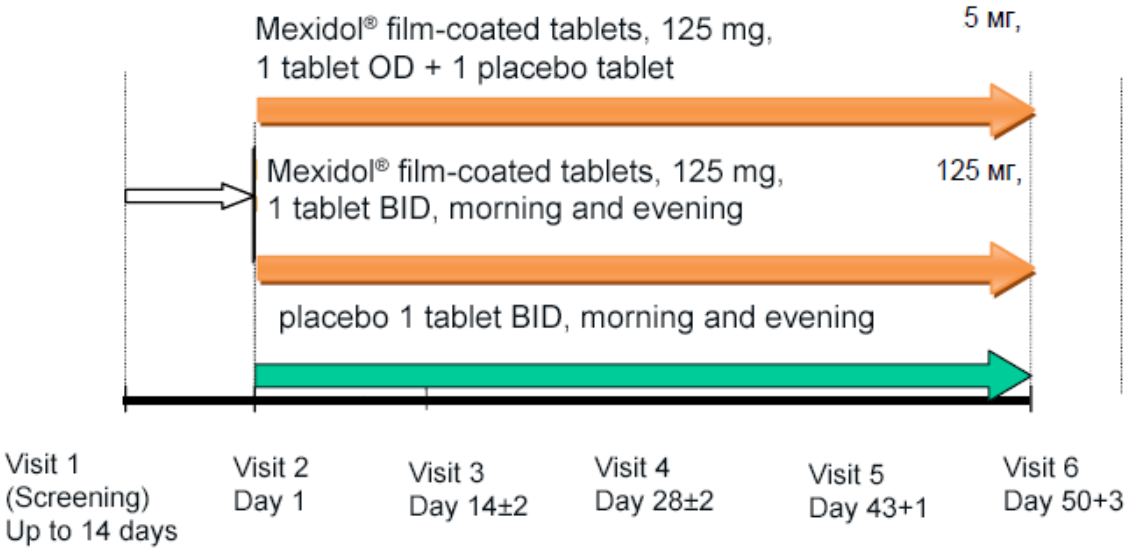
Secondary efficacy criteria:

1. mean change on the SNAP-IV inattention subscale after 6 weeks of therapy vs. baseline;
2. mean change on SNAP-IV subscale hyperactivity/impulsivity after 6 weeks of therapy vs. baseline
3. mean change on the SNAP-IV subscale, oppositional defiant disorder, after 6 weeks of therapy vs. baseline;
4. mean change in SNAP-IV subscale - Conners index after 6 weeks of therapy vs. baseline;
5. mean change on the Spence children's anxiety scale (SCAS) after 6 weeks of therapy vs. baseline;
6. mean change on ADHD Rating Scale-IV scores after 6 weeks of therapy vs. baseline;
7. clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale score after 6 weeks of therapy vs. baseline;
8. assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores);
9. Clinical Global Impressions Scale - Improvement (CGI-I) score after 6 weeks of therapy vs. baseline.

4.2. Trial design

This trial is a multicentre, prospective, double-blind, randomised 1:1:1 clinical trial of the safety and efficacy of Mexidol® film-coated tablets 125 mg in three parallel groups using placebo control (Figure 1).

Figure 1. Graphical design of the trial



4.3. Description of measures aimed at minimising/eliminating subjectivity

4.3.1. Randomisation

Patient randomisation will be performed at Visit 2 with a 1:1:1:1 patient allocation using the online IWRS (Interactive Web Response System). A patient randomisation number will be assigned to the trial subject in the order in which they access the IWRS system.

The corresponding randomisation list will be generated in the statistical software using a random number generator by the responsible biostatistician of the Sponsor/Sponsor's representative company. The randomisation list is not intended to be shared with research centres and will be held by the Sponsor. Due to the use of a centralised randomisation system, envelopes or other means of conducting randomisation will not be provided to centres.

Investigators will be given online training on how to use the IWRS system.

The randomisation list will be included in the Trial Master File and the final clinical trial report.

A register of screened and randomised patients will be maintained for all sites. The register form is contained in the Investigator Site File. The form should be completed by the investigator on a regular basis with all necessary data entered.

The randomisation number is the unique code of the patient in the clinical trial. The investigator records the patient's randomisation number in the source documentation and electronic Case Report Form (eCRF) and enters the randomised patient's information in the list of included patients. The randomisation number cannot be changed during the course of the trial.

The prescribed therapy cannot be changed during the trial.

Patients who early terminate the trial will not be replaced.

Each patient will be assigned an individual identification number of the following form of three digits: _ _ _ - __ __ __ __ - _ _ _ _ _, where the first two digits of the number correspond to the centre number, the next two digits denote the screening number within each clinical centre, the

last three digits of the number correspond to the randomisation number generated by the IWRS randomisation system.

4.3.2. Blinding

The trial is double-blind, so neither the patient nor the investigator will be aware of the therapy group to which the patient will be randomised. To ensure a double-blind trial design, randomisation using the online IWRS system and appropriate labelling of the investigational products is provided.

As the trial will investigate 2 dosing regimens - taking 1 tablet OD (group 1) and 1 tablet BID (group 2), to maintain double-blinding of the prescribed therapy, patients in group 1 will take 1 tablet of placebo, 12±1 hours after taking the investigational product. Thus, for all groups, a 2-fold dosing regimen will be followed.

4.4. Investigational products, dosages, routes of administration, packaging, labelling

4.4.1. Information on Investigational Products

Investigational Product

Name	Mexidol®
Group name:	Ethylmethylhydroxypyridine succinate
Dosage form	film-coated tablets
Composition:	**Composition:** Active substance: ethylmethylhydroxypyridine succinate (2-ethyl-6-methyl-3-hydroxypyridine succinate) - 125.0 mg Excipients: lactose monohydrate - 97.5 mg, povidone 25.0 mg, magnesium stearate - 2.50 mg. Film coating: opadray II white 33G28435 - 7.5 mg (hypromellose - 3.0 mg, titanium dioxide - 1.875 mg, lactose monohydrate - 1.575 mg, polyethylene glycol (macrogol) - 0.6 mg, triacetin - 0.45 mg)
Description:	round, biconvex, film-coated tablets, from white to white with creamy colour
Pharmacotherapeutic group	antioxidant agent
ATC Code:	N07XX

Placebo

Name of the drug	not applicable
INN:	not applicable
Dosage form	film-coated tablets
Composition:	**Composition:** lactose monohydrate - 222.5 mg, povidone 25.0 mg, magnesium stearate - 2.50 mg Film coating: opadray II white 33G28435 - 7.5 mg (hypromellose - 3.0 mg, titanium dioxide - 1.875 mg, lactose

	monohydrate - 1.575 mg, polyethylene glycol (macrogol) - 0.6 mg, triacetin - 0.45 mg)
Description:	round, biconvex, film-coated tablets, from white to white with a creamy tinge colour
Pharmacotherapeutic group	not applicable
ATC Code:	not applicable

4.4.2. Production, packaging and labelling

In accordance with the requirements of the Good Manufacturing Practice Rules (approved by Order of the Ministry of Industry and Trade of the Russian Federation No. 916 dated 14 June 2013; current version), the following information will be applied to the primary packaging of medicinal products for clinical trials:

- name of the medicinal product Mexidol® / placebo;
- Sponsor;
- pharmaceutical form, dosage and number of tablets in the package;
- number (code) of the trial;
- "For clinical trials";
- batch number;
- expiry date
- "Morning" or "Evening."

The following information will be labelled on the secondary packaging of the medicinal product for the clinical trial:

- sponsor's name and contact information;
- name and contact details of the manufacturer;
- name of the medicinal product Mexidol® / placebo;
- pharmaceutical form, dosage and number of tablets in the package;
- "If you experience any side effects, consult a doctor!";
- protocol number (code);
- directions for use;
- method of application;
- storage conditions;
- "Keep out of reach of children."
- "For clinical trials";
- "Morning" or "Evening";
- date of prescription;
- return date;
- patient identification information;
- patient's randomisation code;
- visit number;
- Full name of the investigator;
- batch number;
- date of manufacture;
- shelf life.

The following information will be labelled on the tertiary packaging of the medicinal product

for the clinical trial:

- sponsor's name and contact information;
- name and contact details of the manufacturer;
- name of the medicinal product Mexidol® / placebo;
- dosage form, dosage, number of packs and tablets in the pack;
- patient identification information;
- Full name of the investigator;
- protocol number (code);
- Full name of the investigator;
- patient's randomisation code;
- method of application;
- batch number;
- date of manufacture;
- shelf life;
- "If you experience any side effects, consult a doctor!";
- directions for use;
- storage conditions;
- "Keep out of reach of children."
- "For clinical trials".

The primary package will be a blister with 10 tablets. Five blisters will be enclosed in secondary packaging - 2 carton packs, each labelled "Morning" or "Evening" for the morning or evening dose respectively. Patients in all groups will therefore be given a set of two secondary packs contained in a single tertiary pack (carton pack).

4.4.3. Dosing in patients

Investigational product

Mexidol® (ethylmethylhydroxypyridine succinate) film-coated tablets, 125 mg (RPC PHARMASOFT LLC, Russia).

Method of administration:

In **Group 1** , the drug will be administered orally 1 tablet OD. Patients additionally take 1 placebo tablet. The interval between drug and placebo administration was 12±1 hours.

Duration of therapy: 42 days.

In **Group 2** , the drug will be administered orally 1 tablet BID. The interval between doses is 12±1 hours.

Duration of therapy: 42 days.

Placebo film-coated tablets (RPC PHARMASOFT LLC, Russia).

Method of administration:

In group 3, placebo will be administered orally 1 tablet BID. The interval between doses is 12±1 hours.

Duration of therapy: 42 days.

4.5. Expected duration of patient participation in the trial, description of trial periods and procedures

4.5.1. Trial duration

The duration of treatment is 42 days. The duration of the follow-up period is 7 days.

Screening and randomisation can be carried out on the same day provided all screening procedures are performed, and results are available.

The total minimum duration of patient participation in the trial will be 49 full days: a screening and therapy period of 42 days plus a follow-up period of 7 days.

The total maximum duration of patient participation in the trial will be 67 days: a screening period of 14 days plus a therapy period of 42 days plus a follow-up period of 7 days, plus a window for the end-of-therapy visit (Visit 5) of 1 day and the follow-up visit (Visit 6) of 3 days.

4.5.2. Beginning of the Trial. Visit 1 (Day -14 -1) Screening.

The start of the trial will be the inclusion (screening) of the first patient in the trial. In the Russian Federation, in accordance with the Federal Law "On Circulation of Medicines", the head of a medical organisation (research centre) shall, within a period not exceeding three working days from the date of commencement of a clinical trial of a medicinal product for human use, notify the authorised federal executive body that issued the permit to conduct such a trial, in the form established by it.

Each potential research participant should be adequately informed about the aims, methods, expected benefits of the research and the risks and inconveniences associated with participation in the research.

Patients must be provided with comprehensive and accurate information regarding all aspects of the trial prior to any procedures and activities related to the trial. Prior to any procedures, the Patient Information Sheet with the Informed Consent Form (hereinafter referred to as Informed Consent) must be personally signed and dated by one of the patient's parents in 2 copies, thus confirming consent to the patient's participation in the trial, one of which is handed over to the patient's parent. Immediately after signing the Informed Consent, the patient/patient's parent will be issued an Insurance Policy for the patient participating in the clinical trial.

Next, an electronic Case Report Form (eCRF) is created for each patient, where all the necessary data is entered.

The patient's parents are cautioned about restrictions on the use of concomitant therapy during the trial. A list of prohibited medications is listed in the Patient Information Sheet.

In addition, parents will be given a handout with information on how to comply with the rules of patient participation in the trial, restrictions and how to complete the Patient Diary.

Once the Informed Consent is signed by one of the patient's parents, screening procedures are performed.

Screening confirms that the patient fulfils the trial eligibility criteria: fulfilment of all inclusion criteria and absence of all non-inclusion criteria.

The duration of screening can be up to 14 days before randomisation.

At the visit, the investigator records the diagnosis and the following procedures are performed:

- collection of demographic data and history;
- measurement of height, body weight, calculation of body mass index (BMI);
- assessment of inclusion/non-inclusion criteria;
- registration of concomitant and pre-existing pathology;
- registration of concomitant and prior therapy;
- physical examination with recording of BP, HR, and RR;
- Complete Blood Count;
- blood chemistry;
- urinalysis;
- neurological status;
- completion of the SNAP-IV scale by the investigator from the parents' words;
- CGI-ADHD-S scale score by the investigator.

The sum of the total score on the inattention, hyperactivity/impulsivity subscales of the SNAP-IV scale obtained at screening will be considered as the baseline against which the efficacy assessment planned in this protocol will be performed.

A date is set for the next visit (if necessary) or a randomisation visit (Visit 2) is conducted, provided all screening procedures have been completed and results of all tests have been obtained.

4.5.3. Visit 2 (Day 1). Randomization. Initiation of therapy.

The following procedures are performed on Visit 2:

- registration of concomitant therapy;
- assessment of inclusion/non-inclusion criteria;
- evaluation of exclusion criteria;
- AEs registration;
- sNAP-IV and CGI-ADHD-S score if the interval between Visit 1 and Visit 2 is 7 or more days.

In this case, the value obtained at Visit 2 is taken as the initial value of the sum of scores on the "inattention" and "hyperactivity/impulsivity" subscales of the SNAP-IV scale, and this value is used in further calculations of performance indicators.

If the patient continues to meet all the criteria for trial participation, the randomization procedure and the following procedures are performed:

- SCAS score: to be completed by the investigator from the patient's parents
- ADHD Rating Scale IV: to be completed by the investigator from the patient's parents;
- completion of an examination card for a child/adolescent with headache (if the patient has complaints of headache, at Visit 2 it is completed for the previous 3 months);
- completion of the PedMIDAS questionnaire (if the patient has complaints of headache, at Visit 2 it is completed for the previous 3 months).

The drug is dispensed in a quantity sufficient to provide therapy until the date of the next visit. The scheme of administration of the drug is explained. A handout for parents, the Patient Diary and instructions on how to complete it are given. A date is set for the next visit. The patient is

warned to bring all unused medication in its original packaging and a completed Patient Diary to the next visit.

4.5.4. Visit 3 (Day 14±2), telephone contact

Visit 3 takes the form of a telephone contact by the investigator 14 days from the start of treatment with the patient's parents. It is necessary to obtain information from parents about the general tolerability of therapy, adverse events that have occurred since the last assessment, prescribed drugs of concomitant therapy, remind about compliance with the therapy regime. If necessary, an unscheduled visit to the clinical centre by the patient may be scheduled based on the information received, or a follow-up telephone contact may be scheduled at the discretion of the investigator to monitor adherence to recommendations.

4.5.5. Visit 4 (Day 28±2), telephone contact

Visit 4 takes the form of a telephone contact by the investigator 28 days from the start of treatment with the patient's parents. It is necessary to obtain information from parents about the general tolerability of therapy, adverse events that have occurred since the last evaluation, symptom scores according to the ADHD Rating Scale IV, concomitant medications prescribed, and remind them of compliance with therapy. If necessary, an unscheduled visit to the clinical site by the patient may be scheduled based on the information received, or a follow-up telephone contact may be scheduled at the discretion of the investigator to monitor adherence to recommendations.

4.5.6. Visit 5 (Day 43+1). End of therapy.

Visit 5 is conducted after a full 42 days (on day 43+1) from the start of therapy to monitor the patient's condition, assess the efficacy and safety of treatment. Therefore, this visit should be scheduled for the day after the last evening dose of Investigational product/placebo, with a maximum of one follow-up visit allowed. Deviations to the lesser side (i.e. 41st, 40th, etc.) are unacceptable. The following procedures are performed on Visit 5:

- registration of concomitant therapy;
- evaluation of exclusion criteria;
- physical examination with measurement of BP, HR, and RR;
- Complete Blood Count;
- blood chemistry;
- urinalysis;
- AEs registration;
- neurological status;
- SNAP-IV score;
- SCAS score;
- ADHD Rating Scale IV score;
- CGI-ADHD-S score;
- CGI-I score;
- completion of a child/adolescent headache assessment card (if the patient has headache complaints identified at Visit 2, completed at Visit 5 for the past 1.5 months (6 weeks));
- completion of the PedMIDAS questionnaire (if the patient has headache complaints identified at Visit 2, to be completed at Visit 5 for the past 1.5 months (6 weeks).

All scales are completed by the investigator: directly for the CGI-ADHD-S and CGI-I scales, and by the parents for the SNAP-IV, SCAS, ADHD Rating Scale IV, Child/Adolescent Headache Assessment Card and PedMIDAS questionnaire at Visit 5 when visiting the clinical site.

- accounting for the Investigational product;
- assessment of adherence to therapy;
- collecting and supervising the completion of the Patient Diary.

A date is set for the next visit.

4.5.7. Visit 6 (Day 50+3). Follow-up

- registration of concomitant therapy;
- physical examination with measurement of BP, HR, and RR;
- AEs registration;
- neurological status.

Once the procedures of visit 6 have been completed, the trial will be considered complete for the patient.

After completion of all the procedures of the follow-up visit, if necessary, the investigator will prescribe treatment to the patient according to his/her judgement in accordance with current clinical practice.

4.5.8. Unscheduled visits

Additional unscheduled visits may be made if necessary (e.g., in the case of AEs/SAEs). In this case, detailed information about the visit (reason for visit, examination results) is entered on the relevant pages of the eCRF "Unscheduled visit".

4.5.9. Examination in case of early termination

If a patient is early withdrawn from the trial or parents withdraw consent for the patient to participate in the trial after the start of investigational product administration, the patient will be asked to return to the site for a final safety assessment to ensure the patient's well-being. The procedure for this examination is identical to the procedures at Visit 5.

4.5.10. Completion of the trial

The investigational site must fully complete the trial and complete all required documentation in full compliance with the protocol. The trial may be suspended by either the Sponsor or the investigational site until completion of the trial if objective reasons arise. Notices of suspension should be sent to all parties involved in the trial as soon as possible. Any increase in the trial timeline must be agreed between the Sponsor and the investigational site and documented.

Notification of the completion of the trial must be sent to the authorised federal authorities within 5 working days.

4.6. Description of the trial procedures

4.6.1. Collection of demographic data and anamnesis, anthropometry

At the Screening Visit, after signing the informed consent form, the following data will be

collected from all patients:

- Gender, age (date of birth).
- Detailed medical history *(anamnesis vitae et anamnesis morbi*), including: o previous injuries and surgeries (dates, indications, extent of surgical intervention);
  - past illnesses;
  - allergological history;
  - medicines used in the previous 30 days or 5 half-lives (whichever is longer) prior to the screening visit and currently used medicines, as well as herbal medicines and nutritional supplements.

4.6.2. Physical examination

Physical examination will be performed at the screening visit (Visit 1), Visits 5 and 6 to ascertain normal and altered patient physical findings prior to administration of investigational products and to identify possible changes after administration. Acceptable examination turnaround times are shown in Table 1.2.

The physical examination includes assessment of:

- general condition;
- skin conditions;
- musculoskeletal system;
- lymph nodes;
- thyroid gland;
- upper respiratory tract and lungs;
- heart, the blood vessels;
- abdominal organs, kidneys;
- neuropsychiatric status.

4.6.3. Vital signs

Measurement of vital signs of body activity will be performed at each visit (except for the randomization visit). Allowable time periods are shown in Table 1.2.

The assessment includes:

- systolic and diastolic blood pressure (BP);
- pulse rate per 1 minute;
- respiratory movements per 1 minute

BP and pulse rate measurements are taken on the same arm in a seated or semi-recumbent position, after 5 minutes of rest and, if possible, by the same investigational site team member during a particular patient's participation in the trial.

4.6.4. Neurological status

Neurological status will be assessed at the screening visit to see if there are changes in

neuropsychiatric status prior to administration of Investigational products, and at visits 5 and 6 to see if there are possible changes after administration. Acceptable examination turnaround times are shown in Table 1.2. Neurological status includes assessment of general symptomatology and history, general cerebral and focal symptoms, assessment of motor functions, assessment of sensory sphere, reflexes, assessment of other systems and organs (including memory functions, intellectual level, emotional state).

4.6.5. Anthropometry

Anthropometry involves measuring:

- height (without shoes), the value obtained is recorded by rounding to the nearest integer value in centimetres.
- body weight (without street clothes and shoes), the value obtained is recorded by rounding to the nearest tenth of a kilogram.

Body mass index is calculated using the formula weight / (height, m)^2 (kg/m^2).

4.6.6. Patient diary

The patient diary is issued at Visit 2 after randomization. In the Diary, the patient/patient's parents should record the dates and times of drug administration, any adverse events that occurred during treatment, if any, and all concomitant medications (both those first prescribed during the trial and dosage changes to previously prescribed medications, including withdrawals). The patient diary is returned at Visit 5. The investigator should check the quality and completeness of the completion of the Patient Diary.

4.6.7. Completion of questionnaires

The SNAP-IV, SCAS, ADHD Rating Scale IV questionnaires, child/adolescent headache examination charts, and PedMIDAS questionnaires are completed by the investigator from the patient's parents at the trial visits (Table 1.2). The questionnaires should be assessed by the same parent throughout the trial. The Child/Adolescent Headache Assessment Card and PedMIDAS questionnaire are completed only if the patient has headache complaints identified at Visit 2; scale data are completed at Visit 2 for the past 3 months, at Visit 5 for the past 1.5 months (6 weeks).

The CGI-ADHD-S, CGI-I scales are assessed by the investiator. These scales are scored and completed by the same researcher who made the original measurements.

4.6.8. Laboratory tests

Clinical laboratory tests (including collection of biological samples) will be performed by the local laboratory of the research centre according to the standards of the respective centre. The physician researcher will receive the results of the tests, review, assess the clinical significance of each parameter deviating from normal values (used in the local laboratory), date and sign and store as source documentation. Blood samples for laboratory tests are taken on an empty stomach, i.e. the patient should not eat or drink anything other than water for 10 hours before the sample is taken.

Complete blood count

The examination of blood samples will be carried out in the laboratory of the Investigational

site, according to the methodology adopted by the laboratory of the site. Blood tests should be taken in fasting condition. The following parameters are investigated:

- haemoglobin;
- haematocrit;
- red blood cell count;
- platelet count;
- white blood cell count and complete white blood cell count;
- ESR.

Biochemical blood test

- total protein;
- albumin;
- glucose;
- ALT;
- AST;
- total bilirubin;
- alkaline phosphatase (ALP);
- amylase;
- creatinine.

Clinical urinalysis with sediment microscopy:

- colour;
- transparency;
- pH;
- specific gravity;
- protein;
- glucose;
- white blood cells;
- red blood cells;
- bacteria;
- cylinders;
- salt.

4.7. Termination of the trial

Exclusion criteria for individual patients are described in section 5.3.

If a patient is excluded from the trial, or the parents decide to terminate the patient's participation in the trial, or if the trial is early terminated, patients must participate in a final physical examination in accordance with Visit 5 procedures. The final examination is performed to ensure patient safety: this examination may reveal any patient health conditions that require treatment and are related to the patient's participation in the trial.

In accordance with the rules of good clinical practice, a clinical trial may be suspended or terminated if a danger to the life, health of patients is detected in the process of conducting the trial. In case of danger to the life, health of a patient participating in a clinical trial, the investigators are obliged to inform the head of the medical organisation and the organisation that has received permission from the authorized federal executive body to organise a clinical trial of a medicinal product. The decision to suspend a clinical trial of a medicinal product is made by the head of the medical organisation and (or) the Sponsor of the trial, the decision to terminate such a trial is made by the authorized federal executive authority based on a written report from the head of the medical organisation or the Sponsor of the trial.

Within a period not exceeding five working days from the date of completion, suspension or termination of a clinical trial of a medicinal product, a notification thereof shall be sent to the authorised federal executive body in the form established by it.

The investigator is obliged to immediately inform the trial subjects about the suspension or termination of the trial, provide them with appropriate medical care and supervision. In terminating the trial, the investigator must ensure that the interests of the trial subjects are adequately protected.

The investigator and/or medical organisation must promptly inform the Sponsor of the termination or suspension of the trial with a detailed explanation of the reasons in writing.

If the Sponsor terminates or suspends the trial, the investigator must immediately notify the health care provider administration.

The investigator and/or health care institution must immediately inform the Ethics Council of the termination or suspension of the trial with a detailed explanation of the reasons in writing.

If the Ethics Council definitively or temporarily withdraws the decision to conduct the trial, the investigator must inform the administration of the medical institution.

The investigator and/or health care institution must immediately inform the development organisation of the final or temporary withdrawal of the decision to conduct a clinical trial, with a detailed written explanation of the reasons.

A clinical trial may be suspended or terminated upon submission by the relevant authorized federal executive body of a conclusion on the conduct of a clinical trial with violations of the rules of Good Clinical Practice, based on the results of an audit of the activities of one or more medical organisations that conduct clinical studies of a medicinal product.

An individual centre-based trial may be discontinued if the Sponsor or its representatives, the investigator, regulatory authorities or the clinical centre's local ethics committee (LEC) deems it necessary for any reason.

4.8. Accounting for Investigational products

The Investigational product and placebo for the trial will be handed over by the Sponsor to the trial organizer with an acceptance certificate and quality assurance document. Supplies of the investigational products from the Sponsor must be received and administered by a responsible person (investigator or his/her authorized person). The investigational products will be stored in a specially equipped room suitable for storage of medicinal products, in conditions of limited access with regular monitoring of the temperature regime, at a temperature not exceeding 25°C (for the Investigational product and placebo) in a place protected from exposure to intense light.

The trial organizer sends the investigational product and placebo to the investigational site in sufficient quantities for the trial.

The control, record keeping and storage of the medicinal products at the investigational site is carried out by a responsible person authorized by the Principal Investigator in accordance with the internal regulations of the investigational site and instructions provided by the Sponsor. Investigational products must be stored in accordance with the instructions provided by the Sponsor (instructions for the medical use of the drug) and applicable regulatory requirements.

Records of the investigational product and placebo are kept by the investigator in a logbook for recording, storing and dispensing the investigational products. Dispensing of the investigational products to patients will be documented in the Investigator Site File. The investigator is responsible for using the investigational product and placebo in strict accordance with the approved protocol. Any discrepancies should be explained and documented.

The record of dispensed investigational products is kept for each patient, and the number and initials of the patient to whom the investigational product was dispensed, the date of dispensing the investigational product to the patient, the quantity of the investigational product dispensed, the date of return of the unused investigational product, and the quantity of the returned unused investigational product are recorded. The person responsible for recording and storing the investigational product and the Principal Investigator shall prepare and sign the report.

Upon completion of the trial, all unused or partially used investigational product must be returned to the Sponsor with the appropriate report.

4.9. Storage of randomization codes and procedure for their disclosure

The patient's randomisation code is provided in documents for use outside the Investigational site (eCRFs, SAEs reports, etc.). The assigned patient code is entered into the eCRF and associated forms. The patient code does not change during the course of the trial.

The randomization plan is kept on file with the Sponsor or its representative. Members of the trial staff are responsible for following the centralized randomization procedure.

In the event of unintentional unblinding of a patient or members of the trial staff, the Sponsor must be notified as soon as possible.

In cases where unblinding of the treatment group and the investigational product used is necessary to ensure the safety of the trial participant (e.g., if a SAEs develops), unblinding must be done after approval and with the knowledge of the Sponsor's medical expert. The fact of disclosure of the randomization code should be reflected in the source documentation and the eCRF.

Disclosure of the randomization code as a whole will be made after the trial is completed and

the database is closed.

4.10. Data recorded directly in the eCRF

In this trial, the eCRF will not act as source documentation, all data entered into the eCRF will be corroborated by other source documents.

Source data are all information contained in the original medical records and certified copies thereof, describing the results of clinical observations, examinations, and other activities that allow for the reconstruction and evaluation of the clinical trial. Source data are contained in source documentation (originals or certified copies).

The investigator authorises trial monitoring, audit(s), LEC review and regulatory inspection, and the submission of direct access to source data/records.

Source records should be retained for 25 years. For each included patient, the investigator will indicate in the soutce records the fact that the patient is participating in this trial and complete trial information.

The Investigator Site File should contain complete information about the trial, with all the events and the times in which they occurred.

5. PATIENT SELECTION AND EXCLUSION

The patient is considered to be enrolled in the trial from the moment the informed consent is signed.

5.1. Inclusion criteria

To participate in the trial, the patient must meet all of the following criteria:

1. Signed written informed consent for participation in the trial from the patient's parents[1].
2. Patients are boys and girls, aged 6 to 12 years, inclusive, at the time of signing the informed consent.
3. Child is being raised by the father and/or mother.
4. Child's attendance at a mainstream pre-school or school.
5. Diagnosis of attention deficit hyperactivity disorder established according to ICD-10 and DSM-5 criteria by a psychiatrist or neurologist, namely:
   According to the DSM-5
   a. 6 or more symptoms of inattention persisting for at least 6 months and/or
   b. 6 or more symptoms of hyperactivity and impulsivity persisting for at least 6 months
   c. symptoms are present in at least two areas of activity (preschool or school and home).
      and/or
   According to the ICD-10
   d. at least 6 symptoms of attention deficit disorder
   e. at least 3 symptoms of hyperactivity
   f. at least 1 symptom of impulsivity

[1] Hereinafter in the protocol: the term "parents" refers to both, either the mother or the father or one of them

g. stable for at least 6 months.

6. Moderate severity of ADHD according to the General Clinical Impression of ADHD Severity Scale (CGI-ADHD- S), not requiring hospitalization for treatment.
7. Not more than two comorbid disorders not requiring, in the opinion of the investigator, additional pharmacotherapy at the time of the trial

5.2. Non-Inclusion criteria

Patients with at least one of the following criteria should not be included in the trial:

1. Hypersensitivity to the active substance of the investigational product (ethylmethylhydroxypyridine succinate) and/or other components of the product.
2. Liver dysfunction: ALT and/or AST ≥2.5 upper limit of normal (ULN) by screening tests.
3. Renal function disorders: blood creatinine ≥1.5 ULN by screening tests.
4. Intracranial pathology (including but not limited to: intracranial haemorrhage, tumour, infection, history of head injury, excluding concussion).
5. Associated autism spectrum disorders, Asperger's syndrome
6. Mental retardation of any degree
7. Other mental illnesses, except behavioural disorders (ICD-10 code F91).
8. Failure to withdraw psychotropic medications used to treat ADHD.
9. Other somatic and/or neurological diseases, the treatment of which requires the use of drugs that may affect the efficacy of the Investigational product (including but not limited to: epilepsy, depression).
10. Administration of nootropics, vasoactive drugs, neuroprotectants, antioxidants, metabolic drugs for 7 days or 5 half-lives (whichever is longer) before randomization
11. Presence of any history of cancer within 5 years prior to the screening visit.
12. Participation in any other clinical trial of drugs and/or medical devices within 3 months prior to the screening visit and/or 5 half-lives, whichever is longer.
13. Inability or impossibility to follow the requirements of the protocol, including for physical, mental or social reasons, in the opinion of the investigator.
14. Lactose intolerance, lactase deficiency, glucose-galactose malabsorption.

5.3. Patient exclusion criteria

The investigator must inform patients that their participation in the clinical trial is purely voluntary and they have the right to terminate their participation in the trial at any time without giving reasons. Information about the voluntary participation in the trial will be included in the text of the Patient Information Sheet with the Informed Consent Form.

A patient's parent may withdraw consent to participate in the trial at any time without giving a reason. In this case, the patient's parent should immediately contact the investigator and inform them of the decision to withdraw the patient from the trial.

Possible reasons for early termination of participation in the clinical trial include:

1. Withdrawal of informed consent by the patient's parent.
2. Adverse events requiring cancellation of the investigational product
3. Need for drugs that are prohibited under the terms of the protocol.
4. Continued participation in the trial is contrary to the patient's best interests.

5. Discontinuation of the trial by the Sponsor.
6. Discontinuation of the trial by regulatory authorities.
7. Loss of communication with the patient.

If a patient early terminates the trial, all procedures of the follow-up visit should be performed, if possible (see procedure schedule - Visit 5), within 24 hours of the decision to exclude the patient from the trial.

The investigator must indicate the reason for early termination in the source documentation and eCRF. If the patient/patient's parents wish to terminate (the patient's) participation in the trial of their own decision, the investigator should try to find out the reason. If the early withdrawal is due to an adverse event, the investigator should make every effort to collect information about the outcome and record it in the eCRF in the adverse event section. If the withdrawal from the trial was due to a SAE, the procedure for immediately notifying the Sponsor on the SAE must be followed.

To establish loss of contact with the patient, the investigator must make three attempts to contact the patient's parents on the telephone numbers provided by the patient at 2-day intervals. If the patient's parents remain unavailable for contact for the specified period of time, the investigator records this data in the eCRF and the patient is excluded from the trial.

Follow-up of early withdrawn patients is not specifically planned. If a patient drops out of the trial due to AE/SAE, the patient will be followed until the AE/SAE resolves or becomes chronic.

5.4. Rules for participation in the trial

The patient/patient's parents must agree with the following restrictions and requirements, which are described in the Patient Information Sheet:

- adherence to the trial visit schedule;
- consent not to use any prohibited concomitant therapy and, if it is necessary, to inform the investigator immediately.

5.5. Collection of data from trial subjects who has early discontinued their participation in the trial

All participant withdrawals from the trial will be documented. The investigator must indicate the date and reason for early trial discontinuation in the source documentation and eCRF in the section on trial completion.

If a patient wishes to stop participating in a trial, the investigator should try to find out the reason. If early patient discontinuation is due to an AE or serious adverse event (SAE), the investigator should make every effort to collect information about the patient's outcome and record it in the eCRF in the section on AEs/SAEs. If exclusion/withdrawal from the trial was due to a SAE, the procedure for notifying the Sponsor of the SAE must be followed (see section 8.4).

All AEs that occurred during the trial in patients who dropped out of the trial, including AEs at the time of discontinuation of the patient's participation in the trial, will be analysed and included in the final clinical trial report.

If dropout/exclusion from the trial occurs after the investigational product has been

administered, patient data collected up to the time of dropout/exclusion from the trial will be considered in the safety analysis and, if possible, in the efficacy analysis.

5.6. Substitution procedure

Patients who drop out before randomisation will not be replaced by new patients but will be treated as not screened. Patients who drop out of the trial after randomisation and administration of the investigational product will not be replaced by new patients and their data will be included in the final analysis.

5.7. Follow-up of patients who early terminated their participation in the trial

Follow-up of early withdrawn patients is not specifically planned.

If a patient dropped out of the trial due to an AE/SAE, the patient will be followed until the AE/SAE resolves or is deemed "chronic" or "stable" by the investigator. Follow-up of patients who early terminated their participation in the trial and still experience AE is also described in section 8.3.

5.8. Documentation of data from patients who failed screened

The investigator is responsible for all patients whose parent has signed informed consent.

Patients whose parent has signed informed consent and yet do not fulfil the inclusion/non-inclusion criteria as a result of the screening performed are considered as screening failure.

The reason why a patient cannot be randomised into the trial should be stated in the source documentation.

Identification numbers assigned to patients who failed screening cannot be reused.

For patients who have failed screening, the investigator will need to complete the source documentation and screening visit in the eCRF.

6. TREATMENT

6.1. Use of Investigational products

Patients who meet the trial eligibility criteria will be randomised to one of the three therapy groups in a 1:1:1:1 ratio:

1. therapy group 1 - Investigational product Mexidol® film-coated tablets, 125 mg, 1 tablet OD + 1 placebo tablet;
2. therapy group 2 - Investigational product Mexidol® film-coated tablets, 125 mg, 1 tablet BID, morning and evening;
3. therapy group 3 - placebo 1 tablet BID, morning and evening.

Method of administration: the Investigational product or placebo will be administered orally, with an interval between doses of 12±1 hours.

Duration of therapy: 42 days.

6.2. Allowed and prohibited concomitant therapies

6.2.1. Psycho-correctional therapy

Since psychocorrectional therapies are multimodal and individualized for each patient, it is not possible within the scope of this protocol to standardize these approaches and generalize them to the whole patient sample.

Nevertheless, in order to maintain uniformity in the nature of psychotherapeutic care applied to all patients, this protocol provides for consultations by a psychologist or psychotherapist for children with ADHD and their parents (one of the parents) during treatment with Mexidol®/placebo, i.e. family and parental therapy with parental competence skills. The purpose of these consultations is to inform parents about general principles of parenting children with ADHD and to teach techniques to modify the child's behaviour and to plan and structure time in daily interactions with the child.

6.2.2. Allowed concomitant therapy

At the screening visit the investigator shall record all medications (including herbal medicines) being taken at the time of the initial assessment in the source documentation and eCRF. Information on prior therapy should be evaluated to determine if it is consistent with the list of prohibited drugs. If such drugs are strictly indicated and their withdrawal is not safe, the patient cannot participate in the trial.

Concomitant therapy and all changes (cancellations, changes in dosage and dosing regimen, new prescriptions) should be recorded in the source documentation and eCRF by the investigator at each visit.

If concomitant somatic or psychiatric pathology is not a criterion for non-inclusion or does not prevent the patient's participation in the trial, its treatment during the trial should be carried out in accordance with the approved standards of medical care and clinical recommendations. However, concomitant preparations must not be in the group prohibited by this Protocol (see Section 6.2.2.).

Taking into account the proposed restrictions on the selection criteria and on the medicinal products that are prohibited to be taken concomitantly with the Investigational product Mexidol® / placebo, the randomized nature of the trial will maintain the equality of the groups on this factor and will not lead to systematic error or distortion of the results of the trial.

Information on concomitant medications (INN, dosage, indication, frequency of administration, route of administration, start date, discontinuation date) that the patient was taking before and during the trial should be recorded in the appropriate section of the eCRF, including the screening visit. All subsequent changes in concomitant therapy during the trial should also be reflected in the eCRF.

6.2.3. Prohibited concomitant therapy

The following medications are prohibited in this trial for the duration of the trial:

1. neuroprotectants, antioxidants, metabolic drugs, vasoactive and nootropic agents, including but not limited to: actovegin, Aminalon, Biotredine, Vasobral, Gliatilin, Glycine, Dimefosfon, Instenon, Cogitum, Cortexin, Cudesan, Minisem, Noben, Pantogam, Picamilon, Piracetam, Tenoten Children's, Phenibut, Cerebrolysin, Cinnarizine, Encephabol;
2. other agents affecting the central nervous system: ginkgo biloba leaf extract,

atomoxetine, tranquillisers and antidepressants.

6.3. Methods for monitoring compliance with trial procedures

It is the responsibility of the investigator to ensure that the trial procedures are followed.

Adherence to therapy will be monitored at visit 5 by counting the Investigational product given and returned.

The investigator is responsible for monitoring compliance with the visit schedule. To ensure that the patient's visit schedule is adhered to, the investigator should remind the patient of the date and time of the visit well in advance of the scheduled outpatient visit (phone call, fax, email, etc.). Attempts to contact the patient and reschedule the visit are recorded three times. If the patient cannot perform the next visit at the scheduled time, the possibility of rescheduling the visit is discussed, taking into account tolerances.

7. EFFICACY EVALUATION

7.1. Efficacy criteria

Evaluation of the efficacy of therapy will be based on primary and secondary efficacy criteria.

Primary efficacy criterion:

1. Mean change in the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline.

Secondary efficacy criteria:

1. Mean change on the SNAP-IV inattention subscale after 6 weeks of therapy vs. baseline;
2. Mean change on SNAP-IV subscale hyperactivity/impulsivity after 6 weeks of therapy vs. baseline.
3. Mean change on the SNAP-IV subscale, oppositional defiant disorder, after 6 weeks of therapy vs. baseline.
4. Mean change in SNAP-IV subscale - Conners index after 6 weeks of therapy vs. baseline.
5. Mean change on the Spence children's anxiety scale (SCAS) after 6 weeks of therapy vs. baseline.
6. Mean change on ADHD Rating Scale-IV scores after 6 weeks of therapy vs. baseline.
7. Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S).
8. assessment of the dynamics of PedMIDAS questionnaire scores (number of days with restriction of daily activity due to headache, number of days with headache, average headache severity and maximum headache severity in scores).
9. The Clinical Global Impressions Scale - Improvement (CGI-I) score.

At the moment there are no Russian regulatory recommendations for conducting clinical studies of medicinal products for ADHD, so the recommendations of the European Medicines Agency (EMA)[14] are used as the main ones, according to which it is recommended to use rating scales as the main criterion for assessing efficacy.

7.2. Methods and timing for estimating efficacy parameters

Primary and secondary efficacy criteria will be assessed using appropriate scales (scales are provided in Section 17).

8. SAFETY ASSESSMENT

Safety analyses will be based on an assessment of adverse events based on patient complaints and interview, physical examination (including assessment of vital signs) and laboratory results.

All laboratory analyses will be carried out in the sites' local laboratories. Reference ranges of local laboratory normal values will be applied. Prior to the start of therapy (at visit 2), medical events will be recorded to correctly assess the patient's baseline condition.

During screening, information about medical adverse events will be attributed to the patient's medical history

(pre-existing/concomitant illnesses). Clinically significant abnormalities detected by objective examination and laboratory and instrumental examination at screening should not be reported as AEs, but should be recorded as associated pathology. A worsening of the original disease/condition, if it occurred during the trial, should be recorded as an AE.

8.1. Safety parameters

1. Number of adverse events (AEs)/serious AEs (SAEs).
2. Frequency and severity of AE/SAE associated with Investigational product/placebo.

Patients/patient's parents will be interviewed for adverse events by members of the trial staff at each visit. Spontaneous and identified adverse events will be entered on the Clinical Trial Adverse Event Reporting Form, source documentation and reported in the eCRF. In case of adverse events, the investigator may decide to repeat the clinical examination and/or laboratory tests.

Measurement of vital signs (systolic and diastolic blood pressure, HR, RR) will be performed at all visits (except the randomisation visit).

Physical examination will be performed at visits 1, 5, and 6.

Complete blood count will be performed at visits 1 and 5.

Biochemical blood tests will be performed at visits 1 and 5.

Clinical urinalysis will be performed at visits 1 and 5.

8.2. Adverse events

8.2.1. Definition of adverse events

An adverse event (AE) is any adverse change in the health status of a patient or subject of a clinical trial to whom a medicinal (investigational) product has been administered, regardless of the causal relationship with its use. An adverse event may be any unfavourable and unintended change (including a deviation of a laboratory indicator from the norm), symptom or disease, the time of occurrence of which does not exclude a causal relationship with the use of the medicinal product, regardless of the presence or absence of a relationship with the use of the medicinal product.

8.2.2. Reporting adverse events

The investigator and members of the trial staff at the Investigational site are responsible for

identifying, providing appropriate medical care, documenting and reporting cases that fall within the definition of adverse events and serious adverse events.

The protocol provides for the recording of all AEs that occur to the patient after the first administration of the trial therapy and until the end of the patient's participation in the trial.

During screening, information about medical adverse events will be attributed to the patient's medical history

(pre-existing/concomitant illnesses).

The planned trial will record all deviations in the health status of patients (based on the results of physical examination, laboratory and instrumental methods of investigation) from the data obtained at the Screening and from the accepted reference values.

After obtaining the necessary information, the investigating physician will categorise the patient's condition as 'normal', 'clinically insignificant abnormalities' or 'clinically significant abnormalities'. In case the abnormalities detected during the trial have not been previously reported, or there is an aggravation of the patient's condition vs. the data obtained at Screening, the detected abnormalities will be classified as AEs.

The patient will be informed by the investigator to report all adverse events that occur during the trial.

Investigators should document all adverse events that were observed in the patient during the trial in medical histories and Case Report Forms. The patient is warned to report any new symptoms they develop to the investigator between visits.

Each individual AE should be described in detail. Regardless of the presumed causal relationship, all adverse events spontaneously reported by the patient, or identified by the investigator and/or members of the trial staff, should be reported on the adverse event form of the eCRF. For serious AEs (SAEs), a SAE form must also be completed.

The registration of an AE is completed according to the results of the examination at the 6th visit.

Records of adverse events should include the following:

- date of the Investigational product therapy start (if applicable);
- date of an AE onset;
- patient identification (initials, age, randomization number in the trial;
- description of the event (symptoms, diagnosis) and its outcome;
- classification (severity, foreseeability, severity, outcome, relationship to drug use);
- measures taken (therapeutic or diagnostic measures prescribed, if applicable);
- description of the results of therapeutic and diagnostic measures (if applicable);
- date the AE resolved.

An additional procedure must be followed for serious AEs (SAEs) (see section 8.4).

8.2.3. Determination of adverse event parameters

According to current guidelines, the parameters of AEa in relation to the variables of severity, foreseeability, severity, outcome and causality will be assessed as follows:

Severity:

"Serious" adverse event is defined as any adverse medical event that, regardless of the dose of the medicinal product:

- resulted in death;
- was life-threatening;
- has caused severe or permanent disability or incapacity for work;
- required an inpatient admission (other than a previously planned admission) or causes an extension of the current hospitalization;
- resulted in a congenital anomaly/developmental defect;
- required medical intervention to prevent the above conditions;
- there has been transmission of an infectious agent through a medicinal product.

In addition, a serious adverse event includes any event that does not formally fit the above criteria but is a significant medical event from the investigator's point of view.

"Serious" adverse reaction is a serious adverse event with a causal relationship (possible, probable, or credible) to the use of the Investigational product;

All other AEs that do not meet these criteria will be considered as “non-serious".

Listedness: Unlisted adverse reaction - an adverse reaction whose nature, severity or outcome is not consistent with the information contained in the investigator's brochure.

Severity:

The severity of AEs is assessed as follows:

The investigator assesses the severity of an adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE) current version at the time of the trial. If an adverse event cannot be classified according to the CTCAE criteria, the Investigator will select the closest description of the severity of the adverse event from those given in the classification based on personal clinical experience:

Degree of severity	Category	Definition/Description
1	Mild	No symptoms or mild symptoms, only clinical or diagnostic follow-up is required; no intervention is indicated
2	Moderate	Only minimal, localised or non-invasive interventions are indicated; limitation of daily living activities
3	Severe	Severe or clinically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disability; limitation of self-care in activities of daily living
4	Life-threatening/ Disability to work	Life-threatening consequences, urgent intervention required
5	Fatal	Death associated with an adverse event

"Severe" adverse event will not necessarily be “serious" in nature, “serious" adverse event will not necessarily be "severe" by definition.

Outcome:

The outcome of an AE is assessed as follows:

Transition to the SAE:	AE resulted in a condition that meets the criteria of seriousness (resulted in death, was life-threatening, required hospitalization of the patient or its prolongation, resulted in permanent or pronounced disability or incapacity, congenital anomalies or malformations, required medical intervention to prevent the development of these conditions. In case of any unexpected suspected transmission of an infectious agent through a medicinal product has occurred)
Recovery without consequences	The AE has completely resolved without observed residual events
Improved condition	AE in the process of resolution
No change in condition	AE has not resolved
Recovery with consequences	The resolution of the AE has occurred, but the patient still has some residual effects
Death	Patient died due to an AE (death is an outcome, not an AE)
Unknown	The outcome of an AE is unknown because the patient did not show up for the follow-up examination and attempts to obtain follow-up information were unsuccessful (lost for follow-up)

Relationship to the use of the Investigational product:

Determination of the relationship of an AE with the use of the Investigational product

The association of an AE with the use of investigational products will be assessed using World Health Organisation (WHO) criteria:

- *Definite.* Clinical manifestations of an AE, including abnormalities of laboratory parameters occurring during the period of drug administration, which cannot be explained by the presence of existing diseases and the influence of other factors and chemical compounds. Manifestations of adverse reaction regress after drug withdrawal and occur with repeated administration.
- *Probable.* Clinical manifestations of an AE that include changes in laboratory values that are temporally related to the use of the Investigational product, that are unlikely to be related to comorbidities or other factors, and that regress with drug withdrawal. The response to rechallenge is unknown.
- *Possible.* Clinical manifestations of an AE that include changes in laboratory values that are temporally related to drug administration but can be explained by the presence of comorbidities or the administration of other drugs and chemical compounds. Information on response to drug withdrawal is unclear.

- *Doubtful*. Clinical manifestations of an AE that include changes in laboratory values that occur in the absence of a clear temporal relationship to drug administration; other factors (drugs, diseases, chemicals) are present that may be responsible for their occurrence.
- *Conditional*. Clinical manifestations of an AE involving abnormalities of laboratory indications categorised as 'adverse reactions' that need further data (for accurate assessment) or these obtained data are currently being analysed.
- *Unclassifiable.* Reports of a suspected adverse reaction cannot be evaluated because there is insufficient or conflicting information.

The occurrence of an adverse event will be related to the Investigational product if the relationship is considered by the investigator as definite, probable, possible.

Physician's actions in relation to the AE:

1. No action required (continuation of the trial according to the protocol).
2. Reducing the dose, which could mean:
   - reducing the dose of the Investigational product;
   - maintaining a certain dose despite the protocol's request to increase it;
   - reducing the frequency of administration/intake.
3. Cancellation of Investigational product followed by resumption.
4. Complete withdrawal of the Investigational product (complete discontinuation of the Investigational product).
5. Prescribing other treatments, such as:
   - for the treatment of the AE;
   - changing the dosage of the concomitant therapy drug;
   - prescribing non-pharmacological therapy.

8.3. Continued follow-up period for the AE

All AEs should be traced to their resolution or until they are deemed by the physician to be "recovered with consequences".

If a serious adverse event occurs, the patient will be monitored until the SAE is resolved by telephone calls to discuss complaints and history, as well as during visits that are not part of the trial schedule but are necessary for patient safety.

If, in the opinion of the attending physician, an adverse event that is not serious requires follow-up of the patient, such follow-up may also be conducted by telephone calls and visits, with questioning of complaints and history.

The Sponsor will report all serious unexpected adverse reactions (hereinafter referred to as SUAR) for the Investigational product identified during the clinical trial to the regulatory authorities:

- no later than 7 calendar days from the date of receipt of information on the identification of SUARs, if they have resulted in death or were life-threatening;
- no later than 15 calendar days from the date of receipt of information on the identification of SUARs for other serious unexpected adverse reactions.

8.4. SAE reporting

When a SAE occurs, the development of the SAE should be recorded in the source documentation and an SAE reporting form should be completed.

The SAE Reporting Form must be submitted to the CRO/Sponsor representative within 24 hours of the investigators' receipt of the SAE information.

Representative of a contract research organisation (CRO):

Maria Igorevna Shunikova

Tel./fax: + 7 (4852) 594779

E-mail: mi_shunikova@cphd.ru

Sponsor's Representative:

Qualified Person Responsible for Pharmacovigilance (QPPV) of RPC PHARMASOFT LLC:

Irina Vladimirovna Medvedeva

Tel: +7 (495) 626 47 55 ext. 162

E-mail: pv@pharmasoft.ru

The SAE Reporting Form should be sent even if the investigator has incomplete information on the SAE. Each initial report should contain at least the following information:

- Trial number (identifier or protocol number).
- Patient number.
- Investigator's full name and contact details.
- Description of the adverse event (date of onset, outcome as of the date of the report).
- The result of the investigator's assessment of the seriousness and severity.
- The result of the investigator's assessment of relationship with the Investigational product.

The investigator must receive confirmation that the information has been delivered. An initial report containing incomplete information about a SAE should be immediately followed up with a subsequent detailed written report when new information becomes available to the investigator.

If significant new information is received on an identified SAE, this information should be provided in the form of a follow-up communication. The investigator must comply with the following timelines for sending reports on SAEs to the Qualified Person Responsible for Pharmacovigilance:

- Within 24 hours of being informed of the SAE onset.
- After 30 days, if the SAE is still in progress.
- After the end of the SAE.

Notification to the LEC of all SAE cases at the clinical site is carried out by the investigator within the timeframes specified in the LEC's SOPs.

Where applicable requirements apply, Sponsor will provide appropriate notifications of SAEs to authorized health authorities.

9. STATISTICS

9.1. Description of statistical methods

Demographic and other baseline patient characteristics (age, gender, disease duration, prior and concomitant disease, prior and concomitant therapy) will be compared between therapy groups to demonstrate comparability between groups at baseline using appropriate statistical tests.

Descriptive statistics for data whose distribution follows the law of normal distribution will be presented using the arithmetic mean and standard deviation. For otherwise distributed data descriptive statistics will be presented using non-parametric measures (median/mod, quartiles).

Two-sided confidence intervals will be used to assess treatment efficacy (primary and secondary efficacy criteria).

For primary and secondary efficacy criteria, differences will be considered statistically significant at the p-value level of <0.05.

In accordance with the purpose of the trial, statistical analysis of the results is planned to compare the efficacy of the therapy regimen including Mexidol® in the treatment of attention deficit hyperactivity disorder (ADHD) in children 6-12 years old at different dosing regimens with the efficacy of the regimen including placebo and a combination of the Investigational product and placebo.

The main efficacy criterion is the mean change in the total score on the inattention and hyperactivity/impulsivity subscales of the SNAP-IV scale after 6 weeks of therapy vs. baseline. Descriptive statistics for this indicator will be given and the following statistical hypotheses will be tested:

$$H^0 : \mu_p=\mu_T;$$
$$H^1: \mu_T <\mu_P$$

μ_T - mean change in SNAP score in the trial group (group 1 Mexidol®, 125 mg OD, or group 2 (Mexidol®, 125 mg BID);

μ_P - mean change in SNAP score in control group 3 (placebo). The sign "<" is associated with the fact that the change has a negative value.

Comparison of the values of the two groups of patients will be performed by calculating the two-sided 95% confidence interval for the difference of μ1 (μ2) and μ0 values. A conclusion on superiority can be made if the upper bound of the two-sided 95% confidence interval for the difference in mean changes in SNAP scores of Mexidol® vs. placebo is negative.

Testing of the null statistical hypothesis can be done using one-factor analysis of variance with Dunnett's posterior criterion and evaluation of contrasts or similar applicable statistical analysis method.

The χ-square test or Fisher's exact test will be used to assess differences in event rates.

The χ-square test or Fisher's exact test will also be used to assess differences in patient adherence.

Safety parameters will be tabulated for all patients receiving Investigational product/placebo. Comparisons of safety outcomes between trial groups will be made using the χ-square or Fisher's exact test (for qualitative data) and the t-test for data whose distribution follows the law

of normal distribution or its non-parametric analogue (for data whose distribution does not follow the law of normal distribution).

A detailed plan for the statistical analysis of the data will be presented in a separate document to be included in the clinical trial report submitted to the regulatory authority.

Deviations from the statistical analysis plan that occur will be described in the clinical trial report.

9.2. Planned number of patients

To justify the sample size, a search was conducted for publications on the efficacy of treatments for children and adolescents with ADHD that evaluated efficacy using the SNAP scale.

Among studies conducted on a similar population with similar endpoints, Dell'Agnello G, Maschietto D, Bravaccio C, Calamoneri F, Masi G, Curatolo P, Besana D, Mancini F, Rossi A, Poole L, Escobar R, Zuddas A was detected; LYCY Trial Group. Atomoxetine hydrochloride in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: A placebo-controlled Italian trial. Eur Neuropsychopharmacol. 2009 Nov;19(11):822-34, in which the change in the sum of scores on the "inattention" + "hyperactivity/impulsivity" domains of the SNAP-IV scale was evaluated as the primary endpoint - this trial was used to estimate the magnitude of effect in the placebo group. According to the data published in the above trial, the change in score in the placebo group was -2.0 (4.7).

Since no studies of Mexidol® for the indication under study have been conducted previously, the data of the above-mentioned trial and the trial by Shang CY et al[15] were used for approximate estimation of the effect size.

Based on the data from the two studies cited, a similar SNAP rate would be expected at an average level across the two studies:

- Change -8.1 (9.2), n=105; 95% CI: -9.88 to -6.32 (minimum value -6.32).
- Change, 3.33 (5.58), n=75; 95% CI: -4.64 to -2.02 (minimum value, 2.02.

95% confidence intervals were calculated based on the following formulae:

$$SEM = \frac{SD}{\sqrt{n}}$$

$$DI = M \pm t_{\alpha,n-1} \times SEM$$

where: SEM - standard error of the mean;

SD - standard deviation;

n - number of observations;

CI - confidence interval;

M - mean.

Using the minimum values (lower limits of the confidence interval), the weighted average was calculated using the following formula:

$$m = \frac{-6.32 \times 105 - 2.02 \times 75}{105 + 75} = -4.5283$$

For further calculations, -4.5 scoresrounded to tenths were used.

Although this estimate is based on experience with another ADHD medication, it suggests minimal clinically significant differences and can be used to justify the sample size for Mexidol®.

To assess the variability of the effect, the coefficient of variation (CV) value was calculated for all the above change values in the active treatment group:

$$CV = \frac{SD}{M}$$

The following values are obtained:

- 114%
- 167%

of which the maximum of 167% was used to estimate the standard deviation, which for the selected value of change corresponds to the value of 4.5*1.67 = 7.515.

For the placebo group, the actual data above were used (-2.0 and -4.7 for mean and standard deviation, respectively).

In order to calculate the sample size, the following assumptions were made:

1. One-sided hypothesis of superior efficacy of Mexidol® over placebo.
2. The mean change in SNAP score in the placebo group is -2.0 points, and the standard deviation for the change is 4.70 points.
3. The mean change in SNAP score in the Mexidol® group is -4.5 points, and the standard deviation for the change is 7.515 points.
4. The modulus of the difference in mean SNAP scores between the Mexidol and placebo groups is 2.5 points
5. The pooled variance estimate (pooled variance) is:

$$SE = \sqrt{\frac{CO^2_1 + CO^2_2}{2}} = \sqrt{\frac{0.12, 0.46}{2}} = 6.27$$

6. The minimum adequate strength is 80% (consequently, the II error is 0.20).
7. The ratio of group volumes is 1:1:1:1.
8. The significance level is 95% (respectively, the I error is 0.05). Since the boundaries of the 95% confidence interval must be two-sided and testing of the superiority hypothesis is one-sided, a one-sided error I of 0.025 will be applied to test the hypothesis, which is equivalent to an error of 0.05 for a two-sided test.
9. 20% drop-out rate during screening.
10. 10% drop out rate during follow-up (based on the above studies).

All calculations were based on the formulae from the book[16] (page 228), where the approximating function for power is given by the following equation

$$1 - \beta = 1 - F(t_{K,\alpha} - \quad \Delta \quad)$$

$\overline{\sigma\sqrt{2/n}}$

Where Δ - clinically acceptable minimal difference (difference) from placebo and Fz = $\int z_{\infty}$ *Normal(0.1),* which can also be written by the following expression for n:

$$n = \frac{2\sigma^2 [t_{\kappa.\alpha}{}^{+} z_{\beta}]^2}{\Delta^2}$$

Calculations were performed using the statistical package PASS 11 (NCSS Inc., USA), which is a validated package that uses formulae directly from the book by Chow et al. cited above.

The results of the calculations are as follows:

- number of patients to complete the trial according to the protocol = at least 100 in each group or a total of at least 300;
- number of randomized patients = 111 in each group or a total of 333;
- number of patients screened, taking into account expected drop-out rate at screening of ≈20% = 417.

9.3. Applied significance level

The plan is to apply a significance level of 0.05 and calculate a two-sided 95% confidence interval.

9.4. Criteria for trial termination

The trial does not include interim data analyses and statistical criteria for trial termination.

9.5. Procedures for recording missing, unanalysable and questionable data

Missing, unanalysable and questionable data will not be replaced and taken into account in the statistical analysis of results.

9.6. Procedures for reporting any deviations from the original statistical plan

The details of the statistical analysis will be presented in the statistical analysis plan. The statistical analysis plan will be approved before the database cut off. All deviations from the approved version of the statistical analysis plan will be justified in the clinical trial report.

9.7. Selection of data for statistical analysis

Analyses will be conducted in the following populations:

1) safety population - will include all randomized patients who have taken at least one dose of the Investigational product;
2) the full analysis set (FAS) population will include all randomised patients who have taken at least one dose of Investigational product and who have an assessment of response to therapy after 6 weeks of therapy. This will be the main population for efficacy analyses;
3) PP (per protocol population) is a subgroup of the FAS population that will include patients in the absence of significant protocol deviations with respect to inclusion/exclusion criteria, adherence to therapy, and use of concomitant therapy. This will be an additional population used for efficacy analyses.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

It is the responsibility of the investigator to provide direct access to the source data/documentation to the employees of RPC PHARMASOFT LLC and its representatives, employees of authorized bodies for the purposes of monitoring, audit, expertise, and inspection. The Sponsor / Sponsor's representative must ensure that one of the patient's parents has given written consent for direct access to the patient's original medical records for the purposes of monitoring, auditing, ethical review, and inspection by authorized bodies.

10.1. Protocol compliance

The investigator conducts the clinical trial in accordance with a protocol developed by the Sponsor and approved by the appropriate regulatory authorities/independent ethical committee. Changes to the protocol are not permitted unless there is an immediate threat to trial subjects and if the changes relate to organizational and financial matters. The Sponsor must submit all protocol changes to the regulatory authorities/independent ethics committee as required. Any deviation from the protocol during its execution must be recorded and reflected in the trial documentation.

10.2. Deviations from protocol

In general, any deviation from the protocol may be accepted only in an urgent case or after obtaining written agreement from the Sponsor and subject to approval by the Ethics Committee. Any deviation from the protocol should be clearly explained in the source documentation and in the eCRF. Classification of protocol deviations will be made before the database cutt off by the Sponsor's medical expert. Deviations from the protocol will be considered significant in the following cases (the list may be expanded in a subsequent evaluation of protocol deviations):

- skip of visit 5;
- violation of inclusion / non-inclusion criteria;
- violation of the exclusion criteria;
- taking the Investigational product/placebo <80% or >120% of the total number of tablets prescribed;
- administration of prohibited drugs.

If significant deviations from the protocol are identified, the CRA must immediately inform the Sponsor.

In the absence of data at Visit 5 when data are available at Visit 6, these patients will not be included in the FAS and PP populations, but will be analysed in the safety population.

In the presence of data at Visit 5 and the presence of the other listed significant protocol deviations, these patients will be included in the full analysis population, safety population, but excluded from the protocol population.

10.3. Confidentiality of patient data

The investigator will ensure that the confidentiality of patient data is maintained. In the eCRF and any other documents submitted to the Sponsor, patients will be referred to by assigned numbers (codes) rather than by their names. Initials will not be used in this process. Documents not intended to be sent to the Sponsor, such as a list of personal data and associated patient identification numbers, must be kept strictly confidential by the investigator.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Selection of Investigational sites

The selection of investigational sites will be approved by the Sponsor prior to start of the trial to ensure that the personnel required in the trial are available and to assess the ability of these personnel to perform the trial in accordance with Good Clinical Practice requirements.

11.2. Trial conduction

All aspects of the clinical trial protocol must be adhered to during the clinical trial. If changes are necessary, they should be discussed without delay by the Investigator, CRA and Sponsor. Amendments to the clinical trial protocol must be made in writing and include a detailed justification for the changes. Amendments must be submitted to the Ministry of Health (MOH) and, once authorised by the MOH, to the LEC.

Each deviation from the trial protocol must be documented and justified by the investigator (or person designated by the investigator) in the appropriate place in the eCRFs and Investigator Site Files.

All other persons involved in the clinical trial process will be instructed by the investigator or CRA as to their tasks. This is the responsibility of the investigator.

11.3. Monitoring

Monitoring is the process of progress of a clinical trial control to ensure that it is conducted, documented and reported to the appropriate authorities in accordance with the Protocol and Good Clinical Practice guidelines. The person conducting the monitoring is approved by the Sponsor. The CRA is the primary link between the Sponsor and the Investigator. The CRA, as required by the Sponsor, shall ensure that the trial is properly conducted and documented.

Quality control of trial execution is provided by the Principal Investigator and quality assurance is achieved by monitoring visits, the timing of which is determined by the Sponsor.

The Sponsor's representative or designated individual will monitor the trial to ensure that:

- data is correct, accurate and complete;
- patient safety and rights are protected;
- the trial is conducted in accordance with the currently approved version of the protocol and any other trial agreements, the rules of Good Clinical Practice, and all applicable regulations.

The CRA will periodically contact the investigator and perform visits to review all source data/records relevant to the trial, verify adherence to the protocol and the completeness, correctness and accuracy of all entries in the eCRF compared to the source data. The investigator will work with the CRA to resolve any discrepancies identified.

In this trial, the monitoring visits to the investigational sites are planned to take place throughout the trial in accordance with the approved monitoring plan.

11.4. Data identification

All data contained in the eCRF should be supported by data in the patients' source

documentation. Source documentation represents source documents and records (laboratory records, techniques, case histories, outpatient charts, automated device records, documents completed during examinations) and includes source patient data. For identification purposes, all source documentation and data will be labelled with a patient number.

11.5. Audit and inspection

Audit - a comprehensive and independent examination of trial-related activities and documentation conducted to confirm compliance of those activities and procedures for collecting, analysing and reporting data with the protocol, the Sponsor's Standard Operating Procedures, Good Clinical Practice and regulatory requirements.

Audit observations and findings should be documented.

Inspection is the action of the Authorised Body to formally inspect documentation, equipment and other materials deemed by the Authorised Body to be relevant to the clinical trial that are located at the investigational site, the premises of the Sponsor and/or Contract Research Organisation, and other organisations deemed by the Authorised Body to be relevant to the trial.

Upon completion of the review, a report shall be prepared and shall be made available to the Sponsor subject to confidentiality.

To ensure compliance with the Good Clinical Practice Guidelines and all applicable regulatory requirements, at any time during or after completion of the trial, the Sponsor or regulatory authority may audit or inspect the Investigational site. In the case of an audit or inspection, the investigator (as well as the institution) must agree to allow the auditor(s) and inspector(s) direct access to all documents relevant to the trial and to schedule time for them and members of the trial team to discuss the relevant results or issues.

The investigator will ensure that all source data and records pertaining to the trial are available to a qualified quality assurance auditor authorised by the Sponsor or to regulatory inspectors upon proper notification. The primary objectives of audits and inspections are to confirm that the rights and welfare of patients taking part in the trial are protected and that all the data relevant to the assessment of investigational products have been processed and reported in accordance with the Good Clinical Practice Guidelines and applicable regulatory requirements.

12. ETHICAL AND LEGAL REQUIREMENTS

12.1. General requirements

Patient participation in the clinical trial is voluntary. The patient (patient's parents) has the right to refuse to participate (patient) in an ongoing trial at any stage of the trial. The trial is conducted in accordance with the principles set out in the WMA Declaration of Helsinki (adopted at the 18th WMA Assembly in Helsinki in June 1964, revised 2013).

Investigators recruited to participate in a clinical trial will provide the Sponsor with signed and dated summaries describing their clinical research experience, professional and scientific background prior to the commencement of the clinical trial.

12.2. Ethical review

Ethical review of clinical trials of medicinal products is conducted by the Ethics Council under

the Ministry of Health of the Russian Federation and the LEC of each investigational site. The Ethics Council and LECs are dedicated to protecting the rights, safety, and well-being of all patients participating in a clinical trial. The Ethics Council of the Ministry of Health of the Russian Federation and the LEC of each investigational site must assess the relevance of the investigator's qualifications to the proposed trial on the basis of the investigator's curriculum vitae. A list of all local ethics committees (for each participating Investigational site) as well as the committee chairperson(s) will be included in the clinical trial report.

Investigators must ensure that the clinical trial is initiated and conducted under the supervision and approval of a LEC that complies with current Good Clinical Practice and applicable regulatory requirements. Before starting the trial, investigators must send copies of the protocol, informed consent forms, investigator brochures, investigator CV, Patient Diary and other documents that are reflected in the LEC requirements of each investigational site for approval to conduct the clinical trial. Prior to initiation of the trial at the site, the investigator must receive from the LEC full confirmation of approval of the protocol and other submitted documents in writing and dated.

Investigators must not make any changes to the trial or the conduct of the trial without LEC approval unless these changes are necessary to address obvious immediate threats to the welfare of volunteers. Corrections of minor inaccuracies or minor changes to the protocol that do not carry ethical significance will be sent to the LEC for notification purposes.

The investigator must immediately report to the LEC any changes in the trial, unexpected problems, including risks to volunteers or others, and any deviations from the protocol to address immediate risks to patients.

As part of the LEC's requirements for continued review of approved studies, the investigator must provide the LEC with a final clinical trial report upon completion of the trial.

12.3. Regulatory permission

Permission to conduct a clinical trial is issued by the authorized body based on the results of expert examination of the documents required for obtaining permission to conduct the trial. Permission must be obtained before patients perform any trial procedures, including examination during screening to assess eligibility for the trial.

12.4. Informed consent

The patient's informed consent must be obtained and executed in accordance with local requirements, Good Clinical Practice and the ethical principles set out in the Declaration of Helsinki.

Prior to obtaining informed consent, the investigator or the investigator's authorized person must provide the patient and the patient's parents with information in a language and with a level of sophistication that the patient and parents can understand, either verbally or in writing. Each patient (patient's parents) should have the opportunity to discuss the trial and its alternatives with the investigator.

Prior to participation in the trial, the informed consent form must be personally signed and dated in duplicate by one of the patient's parents and the person who conducted the informed consent procedure (the investigator or a person authorized by the investigator). A dated copy of the

informed consent must be given to the patient's parent and a second copy must be attached to the clinical trial documents at the investigational site. When providing informed consent, the patient's parent must consent to direct access to the patient's medical records for monitoring and auditing in the trial and checks by the LEC and authorized bodies.

The informed consent form is modified and amended when new information becomes available that may be relevant to the patient. An amended informed consent form must then be signed and dated by one of the patient's parents.

The investigator will explain that patients (patient's parents) have every right to refuse (patient's) participation in the trial or withdraw consent at any time, without any consequences for their further treatment and without giving reasons.

13. DATA MANAGEMENT AND RECORD KEEPING

13.1. Data processing

All documentation related to the trial, as well as information regarding patients participating in the trial, is strictly confidential.

The investigator is responsible for providing accurate, complete and reliable data in the Case Report Forms and all required reports.

All patient data obtained during the trial are first entered into the source documentation and then transferred to the Case Report Forms. The data contained in the eCRF must match the data in the source documentation. The eCRF must be completed no later than 5 days after the patient's visit to the Investigational site. The eCRF must be signed by the investigator or an authorized trial staff by marking it electronically. These signatures certify that the information contained in the eCRF is accurate. The Principal Investigator has ultimate personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the eCRF.

Informed consent from the patient's parents and inclusion of the patient in the trial should be reflected in the patient's source documentation. These data should include trial identification and dates of patient participation.

13.2. Data storage

All records and documents of the clinical trial, including Case Report Forms, Patient Information Sheets, Patient Lists, Investigator Site File are retained at the investigational sites where the trial is conducted for at least 15 years after completion of the trial. Archiving will be carried out at each Investigational site in accordance with each Investigational site's current archiving procedures.

The investigator should take all possible steps to prevent accidental or premature destruction of records. If archiving of records at the Investigational site becomes impossible, the investigator must notify the Sponsor.

14. FINANCING AND INSURANCE

Prior to the start of the trial, a procedure is in place to insure the health of patients participating in a clinical trial of a medicinal product. In the event of injury to the patient's health related to

the clinical trial, the insurance company through which the Sponsor has contracted for insurance will reimburse all costs of necessary medical examination and treatment required as a result of direct exposure to the investigational product and/or medical manipulations administered in accordance with the Clinical Trial Protocol.

The clinical trial is sponsored by RPC Pharmasoft LLC. In this trial, the health of all patients will be insured, for which purpose the Sponsor / Sponsor's representative has entered into a contract on life and health insurance of patients participating in a clinical trial of medicinal products with the insurance company IPJSC INGOSSTRAKH.

15. USE OF INFORMATION AND PUBLICATIONS

All previously unpublished information on investigational product studies and procedures used by the Sponsor is considered confidential. All rights to this information are solely owned by the Sponsor. The investigator agrees to use confidential information only within the scope of the trial; otherwise, only after written consent from the Sponsor.

The investigator should be aware that data obtained in the course of the trial may be used by the sponsor company or its agent to provide data to other investigator or government organisations. It must be realised that all data obtained during the trial must be made available at the first request of the Sponsor.

A representative of the Sponsor, as well as representatives of government agencies, should have access to any source documents, but the anonymity of trial subjects should be respected as a professional norm.

16. FINAL REPORT

The clinical trial report is prepared after statistical analysis and statistical report. The clinical trial report includes the clinical part of the trial and summarised results. The report shall be submitted by the contract research organisation responsible for the preparation of the final report to the Sponsor on an electronic medium for approval. The clinical trial report, as well as other clinical trial documents, is confidential information that cannot be disclosed by the investigators without the appropriate authorization of the Sponsor.

17. APPENDICES

17.1. SNAP-IV scale

James M. Swanson, PhD, University of California, Irvine, CA 92715

Child's Name: _____ Gender_____ Age: _____ Class: _____

Ethnic group (circle as appropriate): African American, Asian, Caucasian, Hispanic, Other ____

By whom filled: _____ Class Type: _____ Number of people in the class _____

For each statement, select the answer choice that best describes the child's behaviour	Never	Sometimes	Often	Very often
1. Often unable to concentrate on details, causing ridiculous mistakes on school assignments	-	-	-	-

For each statement, select the answer choice that best describes the child's behaviour	Never	Sometimes	Often	Very often
2. Often has difficulty sustaining attention for long periods of time on tasks or play activities	-	-	-	-
3. Often does not listen when addressed	-	-	-	-
4. Often unable to follow instructionsOR complete school assignments, daily chores, and other responsibilities	-	-	-	-
5. Often finds it difficult to organize and carry out tasks in a rational way	-	-	-	-
6. Often avoids, dislikes or does not agree to perform tasks that require prolonged mental effort	-	-	-	-
7. Often loses things needed for tasks or activities (toys, books, pencils, etc.)	-	-	-	-
8. Often easily distracted by extraneous stimuli	-	-	-	-
9. Often forgetful in daily activities	-	-	-	-
10. Often has difficulty maintaining attention when completing tasks or instructions	-	-	-	-
11. Frequently moves arms or legs restlessly, fidgets in place	-	-	-	-
12. Frequently leaves his/her seat in the classroom or similar behaviour in situations where sitting is required	-	-	-	-
13. Often starts running or climbing somewhere, in situations where this is inappropriate	-	-	-	-
14. Often makes a lot of noise during play and finds it difficult to spend leisure time in some quiet activity	-	-	-	-
15. Often behaves as if he/she has a motor attached to him/her	-	-	-	-
16, Often overly talkative	-	-	-	-
17. Frequently shouts out an answer after not hearing the question all the way through	-	-	-	-
18. Often struggles to wait his/her turn	-	-	-	-
19, Often interrupts others or interferes (e.g. in conversations or games)	-	-	-	-
20. Often unable to remain calm, sit still and restrain his/her impulses in the classroom or at home	-	-	-	-
21. Often loses self-control	-	-	-	-
22. Often argues with adults	-	-	-	-
23. Often disobeys and refuses to comply with adult demands	-	-	-	-
24. Often deliberately commits acts that annoy other people	-	-	-	-
25. Often blames others for his/her mistakes and behavioural problems	-	-	-	-

For each statement, select the answer choice that best describes the child's behaviour	Never	Sometimes	Often	Very often
26. Has hypersensitivity or is easily irritated by contact with others	-	-	-	-
27. Often angry or resentful	-	-	-	-
28. Can often be angry and vindictive	-	-	-	-
29. Often quarrelsome	-	-	-	-
30. Often demonstrates negative, defiant behaviour, disobedience or hostility towards authority figures	-	-	-	-
31. Often makes noise (humming or making unintelligible noises)	-	-	-	-
32. Often excitable, impulsive	-	-	-	-
33. Can often cry easily	-	-	-	-
34. Often unable to work in a group	-	-	-	-
35. Often tries to "smarten up"	-	-	-	-
36. Often restless and hyperactive.	-	-	-	-
37. Often bothers other children	-	-	-	-
38. Frequent and severe mood swings	-	-	-	-
39. Often gets upset if his/her wish is not fulfilled immediately	-	-	-	-
40. Often interferes with other children, teases them	-	-	-	-
41. Often shows aggression towards other children (fighting, bullying)	-	-	-	-
42. Often breaks things belonging to other people (vandalism)	-	-	-	-
43. Lies frequently (e.g. stealing, cheating, forging, copying other people's work or manipulating others)	-	-	-	-
44. Has frequent and serious misbehaviour (e.g. truancy, running away or completely ignoring classroom rules)	-	-	-	-
45. Persistently violates the inherent rights of others or fundamental social norms	-	-	-	-
46. Not always able to restrain aggressive impulses (may attack others or destroy their property)	-	-	-	-
47. Has motor or verbal tics (sudden, rapid, repetitive, non-rhythmic motor or verbal activity)	-	-	-	-
48. Presence of repetitive movements (waving arms, swaying torso or picking at skin)	-	-	-	-
49. Having obsessive-compulsive thoughts - obsessions (e.g. persistent and intrusive inappropriate ideas, thoughts or impulses)	-	-	-	-
50. Presence of compulsive behaviours - compulsions (behavioural or thought actions to reduce anxiety or tension)	-	-	-	-
51. Often experiences a feeling of being "strung out", a state "on the verge of a nervous breakdown" 52. Often gets tired quickly	-	-	-	-
53. Has difficulty concentrating or a "blank mind"	-	-	-	-
54. Often irritable	-	-	-	-

For each statement, select the answer choice that best describes the child's behaviour	Never	Sometimes	Often	Very often
55. Often feels muscle tension	-	-	-	-
56. Often feels tense, anxious (premonition of trouble ahead)	-	-	-	-
57. Frequent daytime sleepiness (unintentional falling asleep in inappropriate situations)	-	-	-	-
58. Often over-emotional and seeking to be the centre of attention	-	-	-	-
59. Frequent sense of grandiosity, need for admiration and lack of empathy	-	-	-	-
60. Frequent instability in relations with others, reactive mood and impulsiveness in actions	-	-	-	-
61. Periods of heightened self-esteem, sense of self-importance lasting at least a week	-	-	-	-
62. Periods of increased talkativeness, eagerness to strike up conversations lasting at least a week	-	-	-	-
63. Periods, lasting at least a week, when there was an influx of thoughts or a spurt of ideas	-	-	-	-
64. Periods of elevated expansive or euphoric mood lasting at least a week	-	-	-	-
65. Periods of engagement in enjoyable but risky activities lasting at least a week	-	-	-	-
66. Periods of depressed mood (sadness, hopelessness, despondency) of at least 2 weeks duration	-	-	-	-
67. Periods of irritable or cranky mood (inadequate to the situation) lasting at least 2 weeks	-	-	-	-
68. Intermittent distinct decline in interest or enjoyment in most activities for 2 weeks	-	-	-	-
69. Periods of psychomotor agitation (more than usual) lasting at least 2 weeks	-	-	-	-
70. Periods of psychomotor retardation (in most activities) of at least 2 weeks duration	-	-	-	-
71. Periods of fatigue or lack of energy lasting at least 2 weeks	-	-	-	-
72. Intermittent feelings of worthlessness or inadequate feelings of excessive guilt lasting less than 2 weeks	-	-	-	-
73. Intermittent decrease in attention and thinking ability for at least 2 weeks	-	-	-	-
74. Consistently low self-esteem most of the time for at least a year	-	-	-	-
75. Persistent decreased concentration or difficulty in making decisions most of the time for at least a year	-	-	-	-
76. A constant feeling of hopelessness most of the time for at least a year	-	-	-	-
77. Presently there is increased arousal (alertness and anxiety only) or increased startle response	-	-	-	-
78, Currently experiencing irritability, outbursts of anger, or difficulty concentrating.	-	-	-	-
79. There is now an emotional response (e.g. feelings of tension, anxiety, hopelessness, tears) to stress	-	-	-	-
80. Behavioural reactions (e.g. fighting, vandalism, truancy) to stress are now observed	-	-	-	-
81. Struggles to complete school assignments	-	-	-	-

For each statement, select the answer choice that best describes the child's behaviour	Never	Sometimes	Often	Very often
82. Has difficulty concentrating on a task throughout the lesson	-	-	-	-
83. Struggles to complete schoolwork	-	-	-	-
84. Struggles to maintain accuracy and neatness when completing written work at school	-	-	-	-
85. Experiencing difficulties in group classesa nd discussions	-	-	-	-
86. Has difficulty moving on to the next topic went to the next class	-	-	-	-
87. Has difficulty in communicating with peers in the classroom	-	-	-	-
88. Has difficulty communicating with school staff (teachers and other staff)	-	-	-	-
89. Struggles to remain calm in the classroom	-	-	-	-
90. Struggles to sit on the chair during the lesson	-	-	-	-

17.2. Child Anxiety Scale (SCAS) - parental assessment

Susan H. Spence, 2000 (translated into Russian by Professor N.N. Zavadenko)

Completion date_____

Your child's first and last name

_____

Your surname and initials, degree of relationship

_____

Please rate your child's condition ***for the past three months***.
For each item, select the most appropriate answer:

"Never," "Sometimes," "Often," or ***"Always."***. Circle the number in the appropriate column.

	Never	***Sometimes***	***Often***	***Always***	
1.	0	1	2	3	My child worries about everything
2.	0	1	2	3	My child is afraid of the dark
3.	0	1	2	3	When my child faces challenges, he/she complains of unusual sensations in the abdomen
4.	0	1	2	3	My child complains of feeling scared, frightened
5.	0	1	2	3	My child is afraid to stay home alone
6.	0	1	2	3	My child is afraid of tests and exams
7.	0	1	2	3	My child is afraid to use public toilets and baths
8.	0	1	2	3	It is painful for my child to be without me/parents
9.	0	1	2	3	My child is afraid of doing something stupid in public
10.	0	1	2	3	My child is worried that he/she won't do well at school
11.	0	1	2	3	My child is worried that something terrible will happen to someone in our family
12.	0	1	2	3	My child complains of suddenly feeling like he/she can't breathe, even though there is no reason for it
13.	0	1	2	3	My child is constantly checking that he/she has done

	Never	***Sometimes***	***Often***	***Always***	
					everything right (like turning off lights, appliances, or locking the door)
14.	0	1	2	3	My child gets anxious if he/she has to sleep alone at night
15.	0	1	2	3	My child has a hard time going to school in the morning because he/she feels anxious or afraid
16.	0	1	2	3	My child is afraid of dogs
17.	0	1	2	3	My child cannot get bad or stupid thoughts out of his/her head
18.	0	1	2	3	When my child faces challenges, he/she complains that his/her heart starts beating too fast (often)
19.	0	1	2	3	My child suddenly starts shaking or trembling when there is no reason to do so
20.	0	1	2	3	My child is afraid something bad will happen to him/her
21.	0	1	2	3	My child is afraid of going to doctors and dentists
22.	0	1	2	3	When faced with a problem, my child experiences doubt and hesitation
23.	0	1	2	3	My child is afraid of being at heights (like at the top of a steep mountain) or in lifts
24.	0	1	2	3	My child has special thoughts (techniques) to keep something bad from happening (like numbers or words)
25.	0	1	2	3	My child is scared when he/she has to ride in the car, bus or train
26.	0	1	2	3	My child worries about what other people think of him/her
27.	0	1	2	3	My child is afraid of being in crowds (e.g. shopping centres, cinemas, buses, sports grounds)
28.	0	1	2	3	In all unexpected situations, my child feels frightened even though there is no reason for it
29.	0	1	2	3	My child is afraid of insects and spiders
30.	0	1	2	3	My child complains of sudden dizziness or fainting spells for which there is no cause whatsoever
31.	0	1	2	3	My child experiences fear when he/she has to speak in front of the whole class
32.	0	1	2	3	My child complains that his/her heart starts beating too fast all of a sudden for no reason at all
33.	0	1	2	3	My child fears that he/she will suddenly panic, even though he/she really has nothing to fear
34.	0	1	2	3	My child is afraid of being in confined enclosed spaces such as a small room or tunnel
35.	0	1	2	3	My child does certain things over and over again (e.g., repeatedly washing hands, cleaning/wiping objects, arranging/laying things out in a certain order)
36.	0	1	2	3	My child is plagued by bad and silly intrusive thoughts or pictures that pop into his/her head
37.	0	1	2	3	My child needs to do certain things in a certain right way to prevent something bad from happening
38.	0	1	2	3	My child gets anxious when he/she has to stay out of the house all night
39.	0	1	2	3	Is there anything else your child fears/is afraid of? Please specify below exactly what it is and howit often happens 1.

	Never	*Sometimes*	*Often*	*Always*	
	0	1	2	3	2. _____
	0	1	2	3	3. _____

17.3. ADHD Rating Scale-IV

Circle the answer number that best describes the child's behaviour in the last 6 months	Never rarely	Sometimes	Often	Very often
1. Cannot focus on details, which makes him/her make ridiculous mistakes when doing homework.	0	1	2	3
2. Restless movement of arms or legs, fidgeting in place.	0	1	2	3
3. Has difficulty holding attention for long periods of time while performing tasks or play activities.	0	1	2	3
4. Leaves his/her seat in the classroom or similar behaviour in a situation where sitting is required.	0	1	2	3
5. Does not listen when addressed.	0	1		3
6. Starts running or climbing somewhere, in situations where this is inappropriate.	0	1	2	3
7. Does not follow the instructions received or does not follow through with what has been started.	0	1	2	3
8. Experiences difficulty in spending leisure time in some quiet activity.	0	1	2	3
9. Has difficulty in organising tasks and activities.	0	1	2	3
10. Behaves as if he/she has a motor attached to it.	0	1	2	3
11. Avoids tasks (e.g., classwork or homework) that require prolonged mental effort.	0	1		3
12. Overly talkative.	0	1	2	3
13. Loses things needed to complete tasks or some activity.	0	1	2	3
14. Shouts out the answer after not hearing the question all the way through.	0	1	2	3
15. Easily distracted.	0	1	2	3
16. Barely waiting his/her turn.	0	1	2	3
17. Forgetful in day-to-day activities.	0	1		3
18. Interferes with other people's conversations, gets in the way.	0	1	2	3

From ADHD Rating Scale IV: Checklists. Norms, and Clinical Interpretation, ©George J. Duaul, Thmas J. Power, Arthur D. Anastopoulos and Robert Reid. Reprinted by permission of the Guilford Press New York.

17.4. Clinical Global Impressions-ADHD-Severity - CGI-ADHD-S

"1" Normal, healthy
- The child is adequate in any environment
- No external structure is required
- No different from other children

"2" Minimal disease severity
- Minor difficulties in any one setting
- If an external structure is required, it is only slightly
- Borderline deterioration

"3" Mild disease severity
- Some deterioration in any one environment

"4" Moderate severity of the disease
- Some deterioration in at least two types of environments
- Significant difficulties at school and/or controlling one's behaviour

"5" Extreme severity of the disease
- Deterioration in all kinds of environments
- Significant stress for others
- Social ties are disrupted

"6" Severely ill
- Significant deterioration at all times in all types of environments
- Failure in academic/social environment
- Requires daily supervision for all or most of the day

"7" One of the most difficult patients
- The most severe form of the disease
- Total insolvency even with constant supervision

17.5. Clinical Global Impressions Scale - Improvement (CGI-I)

Patient: Date:

Doctor:

Clinical global impression- global improvement

Assess global improvement, even if, based on your clinical experience, you think it is related to medicinal drug only.

How great are the changes compared to the patient's condition at the time of the first assessment?

□ 0 = No evaluation was carried out.
□ 1 = very significant improvement - improvement on virtually all measures; good level of functioning; minimal symptom severity; demonstrates very significant change

□ 2 = significant improvement - marked improvement with significant reduction in symptom severity; increased level of functioning, but some symptoms persisted

□ 3 = slight improvement - slight improvement with a slight or clinically insignificant reduction in symptoms. Relatively small changes in clinical status, self-care and functional capacity relative to baseline level

□ 4 = no change in symptomatology with little or no change in symptomatology

□ 5 = slight deterioration, possibly clinically insignificant; may reflect a very slight change in clinical status of functional capacity relative to the BASELINE level

□ 6 = significant deterioration - clinically significant increase in symptom severity and decline in functioning

□ 7= very significant deterioration - marked exacerbation of symptoms and loss of function

Adapted from Spearing M.K., Post R.M., Leverich G.S., et al. Modification of the Clinical Global Impressions (CSI) Scale tor use in bipolar illness (BP): the CGI BP Psychiatry Res 1997; 73(3): 159-71.

17.6. Patient diary

(only the pages to be filled in are given)

DAY 1 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 2 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 3 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 4 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 5 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 6 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 7 OF MEXIDOL®/PLACEBO	**DATE _ _ _ / _ _ _ / _ _ _ _ _ _**

ADMINISTRATION _ _ _ _ _		
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 8 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 9 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 10 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 11 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 12 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 13 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 14 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE** _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _	
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 15 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 16 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 17 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 18 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 19 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 20 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

D1 DAYS OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 22 OF MEXIDOL®/PLACEBO ADMINISTRATION	**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 23 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 24 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 25 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 26 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 27 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 28 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 29 OF MEXIDOL®/PLACEBO ADMINISTRATION	DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _

Drug administration	Morning	Evening
	Yes ☐ No ☐	Yes ☐ No ☐

DAY 30 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 31 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 32 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 33 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 34 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 35 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 36 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐ No ☐**	**Evening** **Yes ☐ No ☐**

DAY 37 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning**	**Evening**

	Yes ☐	**No ☐**	**Yes ☐**	**No ☐**

DAY 38 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐** **No ☐**	**Evening** **Yes ☐** **No ☐**

DAY 39 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐** **No ☐**	**Evening** **Yes ☐** **No ☐**

DAY 40 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐** **No ☐**	**Evening** **Yes ☐** **No ☐**

DAY 41 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐** **No ☐**	**Evening** **Yes ☐** **No ☐**

DAY 42 OF MEXIDOL®/PLACEBO ADMINISTRATION		**DATE _ _ _ / _ _ _ / _ _ _ _ _ _ _ _ _ _**
Drug administration	**Morning** **Yes ☐** **No ☐**	**Evening** **Yes ☐** **No ☐**

17.7. Assessment card for a child/adolescent with headache.

(Visit 2 is filled out for the last 3 months, Visit 5 is filled out for the last 1.5 months (6 weeks))

Examination card for a child/adolescent with headache

Date of examination _____

Patient's full name _____

Date of birth _____ **Age** _____ years _____ months

At what age did the headache first occur _____

At what age did the headaches become frequent/severe _____

FOR THE LAST 3 (1.5) MONTHS

How often (how many times per month or week) there were the headaches (underline and write in the appropriate):

1) every day or almost every day

2) several times a week; specify:_____ times a week
3) about once a week
4) 1 to 4 times a month; specify:_____ times a month
4) once a month
5) at least once a month

How long the headache usually lasts (underline and insert as appropriate)

1) 0-1 hour: _____ minutes
2) 1-6 hours: _____ hours
3) 6-12 hours: _____hours
4) 12-24 hours: _____hours
5) 24-48 hours: _____hours
6) 2-3 days: _____ twenty-four hours
7) more than 3 days: _____ twenty-four hours
8) pain is constant
9) duration varies greatly (specify: from_____ to_____)

What is the most common intensity of headache (underline the appropriate)
Mild, moderate, tolerable, severe, intolerable

Time of onset of headache (underline as appropriate)
Morning, afternoon, evening, night, at different times

Whether there are provoking factors for the headache:
fatigue, emotional stress, odours (which:_____), sleep deprivation/ nighttime sleep disturbances, weather changes, habitual daily physical activity (which: climbing stairs, _____), other physical activity/exertion (which: _____), coughing, skipping meals, alcohol consumption, menstruation, sudden head turns, other
_____

The nature of the headache (underline as appropriate)
Aching, pressing, squeezing, tightening, cramping, throbbing, shooting
Mixed character - specify_____

Headache localization
Whole head, half of the head (_____ side)
Temporal, frontal- temporal, parieto-occipital, occipital clarification and comments
_____

Whether there are accompanying symptoms during the headache
Nausea, vomiting, dizziness (systemic/nonsystemic), photophobia, phonophobia, lacrimation, eyelid swelling, sclera injection on the side of pain, pain or stiffness in the neck
Other _____

17.8. PedMIDAS questionnaire (to be completed only if the child has a headache)

(Visit 2 is filled out for the last 3 months, Visit 5 is filled out for the last 1.5 months (6 weeks))

Completion date _____

Surname and first name _____

Please answer each question about how your life has been affected by the headaches you have had in the past three (1.5) months

The number of days on which there was some difficulty due to headache should be entered in the box.

If there were no difficulties, 0 days are indicated.

If the number of days is difficult to be exact, count them roughly but most reliably.

1	How many school days have been completely missed at school (institution) due to headaches in the last 3 (1.5) months?	☐ days
2	How many school days were partially missed at school (institution) due to headaches in the last 3 (1.5) months? (not including completely missed days in the answer to question 1)	☐ days
3	How many days in the last three (1.5) months have you done less than half-heartedly at school because of a headache? (not including the days listed in the answers to questions 1 and 2)	☐ days
4	How many days in the last three (1.5) months have you been unable to do things at home (e.g., daily chores, homework, etc.) because of a headache?	☐ days
5	How many days in the last three (1.5) months have you been unable to participate in other activities (e.g., participate in games, walks, sports) because of a headache?	☐ days
6	How many days in the last three (1.5) months were you able to participate in these activities but did less than half-heartedly? (not including the days listed in the answer to question 5)	☐ days
TOTAL		☐ days

A	How many days in the last three (1.5) months have you had a headache? (If the headache lasted more than one day, all days are counted)	☐ days
B	On a scale of 0 to 10 (put a vertical line), rate how much ***on average*** the headaches have been severe over the past 3 (1.5) months. 0 1 2 3 4 5 6 7 8 9 10 0 = no pain 10 = pain unbearable	
C	Rate on a scale of 0 to 10 points (put a vertical line) ***worst*** headaches you have had in the last three (1.5) months. How many times have it happened? _____ How long did it last? _____ 0 1 2 3 4 5 6 7 8 9 10 0 = no pain 10 = pain	

		unbearable	

ADVERSE EVENTS AND MEDICAL DRUGS TAKEN

Please indicate any significant changes in your child's medical condition and any new medications that have needed to be administered during the trial for any reason.

If there are any problems, seek advice from a doctor at the investigational site.

No.	Symptom	Date (dd/mm/yyyyy) and time (hh:min) of onset	Date (dd/mm/yyyyy) and time (hh:min) of completion	Has the medication been taken?	Name of the medicinal product, dosage form, pharmaceutical form and dosage frequency
example	***headache***	***01.01.2016 (10.00)***	***01.01.2016 (13.00)***	***Yes √ No ☐***	***Paracetamol 1 tablet, 100 mg***
1.				Yes ☐ No ☐	
2.				Yes ☐ No ☐	
3.				Yes ☐ No ☐	
4.				Yes ☐ No ☐	
5.				Yes ☐ No ☐	
6.				Yes ☐ No ☐	

18. REFERENCE LIST

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