BRILLIA FOR CHILDREN

Clinical Summary

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List of abbreviations
ADHD – Attention Deficit Hyperactivity Disorder
ADHDRS-IV-Home Version – ADHD Rating Scale-IV: Home Version
AE – Adverse Event
ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
AURI – acute upper respiratory infections
b.i.d. – twice a day (bis in die, Latin)
bpm – beats per minute
CGI – Clinical Global Impressions Scale
CGI-ADHD-Severity – Clinical Global Impressions-ADHD-Severity
CNS – Central nervous system
DBP – Diastolic blood pressure
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, fourth edition
GABA – Gamma-aminobutyric acid
HR – Heart rate
ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10th Revision
mmHg – millimeters of mercury
MTA – Multimodal therapy of ADHD
SBP – Systolic blood pressure
SCAS – Spence Children's Anxiety Scale
t.i.d. – three times a day (ter in die, Latin)

1. Summary of Clinical Efficacy (Brillia for Children, tablets)

Introduction:

Health "is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (Constitution of the World Health Organization). At the present time the population of children suffering from various anxiety disorders is rising.

Anxiety disorder is characterized by constant, excessive and unwarranted anxiety and excitement that are not associated with a specific object or situation (Keeton et al., 2009). According to the classification of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) anxiety disorder is a heterogeneous group of clinical conditions: from specific phobias to obsessive-compulsive disorder and post-traumatic stress disorder (Wenar, Kerig, 2001; Mash, Wolfe, 2003; Shear et al., 2007). Under the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) anxiety disorders are discussed in the section "Emotional and behavioral disorders with onset usually occurring in childhood and adolescence", under "Emotional disorders with onset specific to childhood" (F93) (http://apps.who.int/classifications/icd10/browse/2010/en#/F93).

The incidence of generalized anxiety disorder reaches 2.9-4.6% among children in the United States, while the prevalence of this condition in the world is unknown. The incidence of anxiety disorders in children of different sex is comparable, none the less F:M sex ratio reaches 6:1 in adolescents.

Anxiety affects all aspects of a child's life, markedly deteriorating their health, complicating learning and relationships with others (Mash, Wolfe, 2003; Shmakova, 2004; Liberman et al., 2006; Sawyer et al., 2009). Moreover, anxiety disorders can cause serious long-term effects. Many children and adolescents with any form of anxiety disorders continue to occasionally experience this state in adulthood. Without early and effective treatment childhood anxiety disorders can cause other serious psychiatric diseases, such as clinical depression and substance abuse.

Anxiety disorders usually develop gradually. The age of onset of anxiety disorders is variable, but they are more common among adolescents and older children. In addition, adolescents and older children

have more symptoms and they are more pronounced than in younger children (Wenar, Kerig, 2004; Venger, 2001, 2002; Mash, Wolfe, 2003; Edwards et al., 2010).

Drug therapy of anxiety disorders should be combined with effective psychotherapy. The first-line drugs for the treatment of childhood anxiety disorders are selective serotonin reuptake inhibitors with broad spectrum activity. Benzodiazepines are usually not used as a first-line therapy in children and adolescents, as they were shown to cause behavioral disinhibition in younger children.

However, despite the variety of drugs for the treatment of anxiety disorders, their administration is limited by frequent and severe adverse events (Arena, Rozenbaum, 2004; Khodarev, 2002).

Disorders in behavior and attention are quite common among pediatric population (Zavadenko, 2006). The symptoms include inattention, hyperactivity and impulsivity. The incidence of attention deficit/hyperactivity disorder (ADHD) children is up to 3-7%. Approximately 30-80% of children with ADHD have it as adults. Most experts believe that the rate is well above 50%.

The ICD-10 referred to this syndrome in the section "Behavioral and emotional disorders with onset usually occurring in childhood and adolescence" of the "Disturbance of activity and attention" (F90.0) and "Hyperkinetic conduct disorder" (F90.1) (http://apps.who.int/classifications/icd10/browse/2010/en#/F90).

According to DSM-IV ADHD can be divided into three subtypes:

1. Predominantly inattentive type;
2. Predominantly hyperactive-impulsive type;
3. Combined type.

Symptoms of ADHD always begin by the age of 7, in most children at the age of 4. The average age of seeing a doctor is 8-10 years.

The treatment program for attention deficit includes psychostimulants, tricyclic antidepressants, tranquilizers, and neuroprotective drugs, but it needs improvement. For example, psychostimulants have adverse effects, such as appetite loss, abdominal pain, headaches, and sleep disturbance (Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents, 2011). The Multimodal Therapy of ADHD (MTA) study showed that psychostimulants decreased growth velocity, particularly in children on higher and more consistently administered doses. However, the effect diminished by the third year of treatment, and reduction in height was only 1-2 cm (Swanson et al., 2007). Some children experience hallucinations and other psychotic symptoms, but these adverse effects are uncommon (Mosholder et al., 2009).

Brillia for Children is a new drug based on ultra-low doses of antibodies to endogenous regulators. Molecular target of Brillia for Children is S-100 protein that couples synaptic and metabolic processes in the brain. Brillia for Children has GABA-mimetic and neurotrophic effects, increases the activity of stress-limiting systems, and improves neuronal plasticity. The drug has a broad spectrum of pharmacological activity due to involvement of the main regulatory systems of CNS.

Thus, the clinical study of the efficacy of Brillia for Children for the treatment of anxiety disorders, disturbances of behavior and attention, accompanied by increased excitability, irritability and hyperactivity is very important and promising.

2. Background and Overview of Clinical Efficacy (Brillia for Children,tablets)

Overview:

The active component of Brillia for Children is affinity purified antibodies to brain-specific S-100 protein/lapine S-100 immune globulin, which are used for saturation of lactose monohydrate in the form of water-ethanol mixture of active substance dilutions with concentration 12C, 30C, 50C.

The drug belongs to the pharmacotherapeutic group of anxiolytics and is intended to help reduce the symptoms of anxiety disorders, disturbances of behavior and attention, accompanied by increased excitability, irritability and hyperactivity in children.

Numerous experimental studies showed that Brillia for Children exerts anxiolytic action and exhibits no adverse hypnogenous and myorelaxant activities. It improves tolerance to psychoemotional

stress and possesses stress-protective, nootropic, antiamnesic, antihypoxic, neuroprotective, antiasthenic and antidepressive effects.

In case of intoxication, hypoxia and stroke, Brillia for Children exhibits neuroprotective effect, restricts the area of damage, and improves cognitive function (learning achievement and memory). Also, the drug modifies the activity of S-100 protein that integrates synaptic and metabolic process in brain.

Brain-specific S-100 protein is expressed in different cell types, including astrocytes and certain neuronal populations. It stimulates cell proliferation and migration and inhibits apoptosis and differentiation in nanomolar concentrations, which might have important implications during brain development and regeneration/repair, activation of astrocytes in the course of brain damage and neurodegenerative processes (Donato et al., 2013). Extracellular brain-specific S-100 protein regulates synaptic plasticity, although the molecular mechanism of this activity is unknown.

Brain-specific S-100 protein is found in pM amounts in human serum, saliva, urine, amniotic fluid and milk. Increased level of S-100 is considered a marker of Blood Brain Barrier failure. Serum levels are elevated after stroke, subarachnoid hemorrhage and brain trauma, and correlate positively with patient outcome. However, brain-specific S-100 protein may be released from non-nervous cells and elevated serum levels are also found in heart diseases and infections. High serum levels of brain-specific S-100 protein is also found in patients with schizophrenia, depressive/bipolar disorders and obesity, but which cells are the sources of S-100 protein in these conditions is unknown.

Providing GABA-mimetic and neurotrophic action, Brillia for Children increases the activity of stress-limiting systems and helps to restore the processes of neuronal plasticity.

3. Clinical Studies Introduction:

To determine the efficacy of Brillia for Children for the treatment of anxiety disorders, disturbances of behavior and attention, accompanied by increased excitability, irritability and hyperactivity in children two clinical studies were carried out (Table 1). The two studies involved 198 subjects in which 98 of them were administered Brillia for Children.

Table 1. Clinical studies of Brillia for Children in treatment of anxiety disorders and disturbances of behavior and attention

Code	Title
MMH-TD-001	Multicenter double-blind placebo-controlled randomized study of Brillia for Children efficacy and safety in 12-week treatment of children with anxiety disorders (phase IV)
TD1061511-01.18.P	A multicenter, double-blind, placebo-controlled, randomized trial of the efficacy and safety of Brillia for Children (2 tablets 2 times daily for 12 weeks) in children with attention deficit hyperactivity disorder (Phase IV)

Consent:

Prior to inclusion in the study the patients or their legal guardians were provided with information about the study and signed an informed consent form. Patient information collected during the study is strictly confidential.

3.1 Study 1 (MMH-TD-001) Summary:

Analysis of the dynamics of anxiety test (R. Temple, M. Dorky, V. Amen) conducted in a phase IV, 12-week, multicenter, double-blind, placebo-controlled, randomized study (MMH-TD-001), proved a significant anxiolytic effect of Brillia for Children compared to placebo. According to patient self-assessment anxiolytic efficacy of Brillia for Children was mostly manifested in young children, which was confirmed by decrease of average anxiety index after 12-week treatment (11.9 points versus 8.3 points in placebo group). After 4 weeks of treatment the percentage of children with severe anxiety disorders significantly declined: from 59% to 33%. The average total score of the Spence Children's

Anxiety Scale (SCAS) according to self-assessment of patients of 8-15 years of age and the reports of parents of children of 5-7 and 8-15 years during the treatment confirmed that Brillia for Children improved the severity of anxiety disorders.

Thus, the clinical studies showed anxiolytic effects of Brillia for Children in treatment of anxiety disorders.

3.2 Study 2 (TD1061511-01.18.P) Summary:

A phase IV, multicenter, randomized, double-blind, placebo-controlled study (TD1061511-01.18.P) showed that Brillia for Children significantly reduced symptoms of ADHD. Brillia for Children for 12 weeks (2 tablets b.i.d.) significantly reduced clinical signs of ADHD by 39.5% (ADHD Rating Scale-IV Home Version) and 26.9% (Conners scale), severity of state by 10% (CGI-ADHD-S).

Thus, monotherapy with Brillia for Children diminished all clinical manifestations of disturbances of behavior and attention (hyperactivity, behavioral disorders, cognitive deficit), improved school performance, reduced severity of accompanying asthenic and neurotic disorders in patients.

4. Study 1 (MMH-TD-001):

4.1 Materials and Methods:

Study design: multi-center, double-blind, placebo-controlled, randomized study.

Study objective: to assess clinical efficacy and safety of Brillia for Children in children with anxiety disorders.

Inclusion criteria:

1. Males and females 5-15 years old;
2. At least one of the diagnoses according to ICD-10:
   a. Separation anxiety disorder of childhood – F93.0;
   b. Phobic anxiety disorder of childhood – F93.1;
   c. Social anxiety disorder of childhood – F93.2;
   d. Other childhood emotional disorders – F93.8;
3. Mild or moderate severity of the disease under anxiety scale of G.P. Lavrentieva and T.M. Titarenko (see Appendix) and according to anxiety test of R. Temple, M. Dorky, V. Amen;
4. Absence of significant impairment of general intelligence;
5. Absence of pharmacotherapy of anxiety disorders in the last two weeks;
6. Signed informed consent form.

The study involved 98 patients 5-15 years of old with emotional disorders with onset specific to childhood (F93 under ICD-10). The patients were randomized into 2 groups:

1. Treatment group (n=48) was administered Brillia for Children (1 tablet t.i.d.);
2. Control group (n=50) was administered placebo (1 tablet t.i.d.).

The duration of treatment was 12 weeks.

Efficacy criteria:

1. Comparison of the therapy with Brillia for Children and placebo therapy in terms of anxiety severity assessed by the test of R. Temple, M. Dorky, V. Amen and SCAS;
2. Comparison of the therapy with Brillia for Children and placebo therapy in terms of proportion of patients with improvement of anxiety disorder;
3. Dynamics of anxiety disorders depending on their types under the subscales of SCAS;
4. Therapeutic dynamics and dynamics of adverse events by the end of the treatment under the Clinical Global Impression Scale (CGI) compared to placebo.

4.2 Results:

Table 2. Dynamics of anxiety severity by the of test R. Temple, M. Dorky, V. Amen (points, M±SD)

Drug	Baseline	4 weeks	8 weeks	12 weeks

Brillia for Children	54.3±16.3	48.0±13.2	46.3±11.9	42.9±12.5 ***
Placebo	57.3±12.5	54.9±11.9	50.3±12.2	47.6±12.0 **

Note: ** - p<0.01; *** - p<0.001, significance of differences in comparison to baseline

12-week treatment resulted in significant reduction of severity of anxiety disorders compared to baseline parameters in both groups (Table 2). The average index of anxiety in treatment group decreased from 54.3±16.3 to 42.9±12.5 points after completion of therapy (p<0.001).

Table 3. Anxiety index according to self-assessment of children of 5-7 and 8-15 years old (points, M±SD)

Drug	Baseline	4 weeks	8 weeks	12 weeks
Younger children (5-7 years old)				
Brillia for Children, n=13	54.4±12.0	49.0±13.0	44.6±11.0	42.5±10.0
Placebo, n=24	58.6±11.0	57.4±12.0	53.8±14.0	50.3±13.0
Older children (8-15 years old)				
Brillia for Children, n=33	54.3±14.0	47.6±13.0	47.0±12.0	43.1±13.0
Placebo, n=24	56.0±13.0	52.3±11.0	46.7±9.5	45.0±13.0

Analysis of parameters of self-assessment of anxiety severity depending on the age of the patients showed more pronounced positive effect of Brillia for Children in younger children (Table 3).

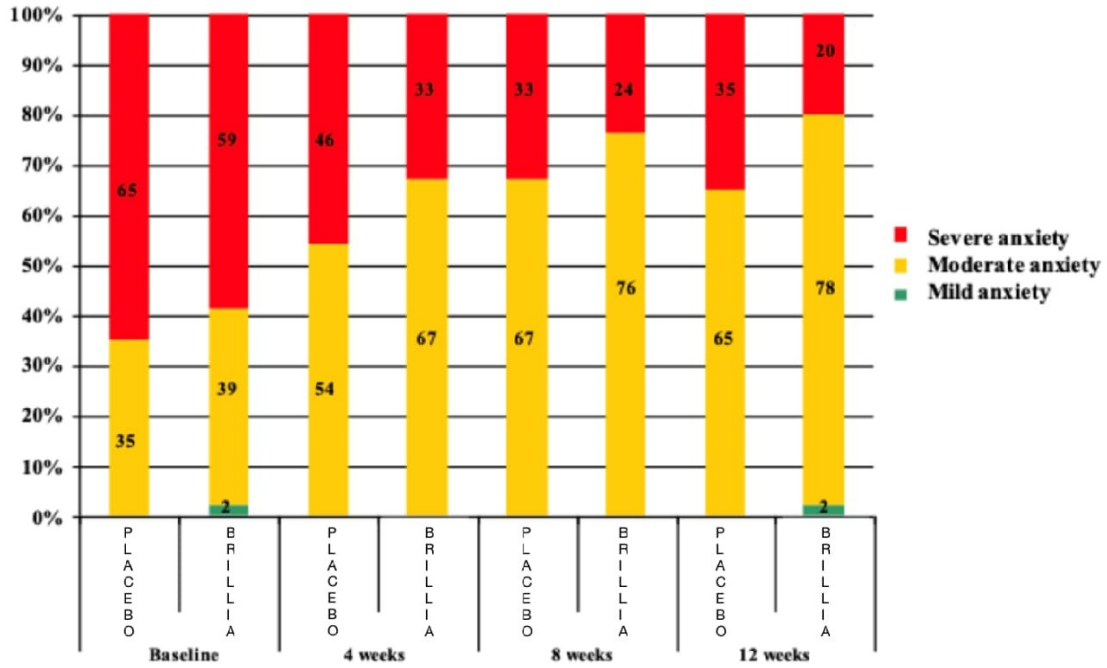

Figure 1. Dynamics of proportion of patients with various severity of anxiety

Initial incidence of anxiety disorders of different severity was comparable in both groups. By the end of the treatment with Brillia for Children the proportion of children with severe anxiety was only 20% (vs. 35% in the control group), and the proportion of patients with moderate anxiety increased to 78% (vs. 65% for placebo) (Figure 1).

Frequency analysis of the proportion of patients with different severity of anxiety disorders using the χ^2 test in the modification of Cochran-Mantel-Haenszel revealed significant differences between study and control groups ($\chi^2_{(1)}$=6.0; p=0.014) in the dynamics of four consecutive visits. The average total scores of the severity of anxiety disorders (SCAS) according to self-assessment of patients and the results of the reports of their parents at various stages of study are presented in Table 4.

Table 4. Total score of SCAS (points, M±SD)

Drug	Baseline	4 weeks	8 weeks	12 weeks
Self-assessment of children 8-15 years old				
Brillia for Children, n=33	39.2±14.47	32.5±17.63	30.3±17.29	26.9±15.69
Placebo, n=24	33.6±12.70	27.8±12.49	25.7±12.93	21.4±12.12
Assessment of parents of children 8-15 years old				
Brillia for Children, n=33	36.9±14.38	32.5±11.22	29.0±12.10	25.7±10.14
Placebo, n=24	34.1±16.08	30.2±12.41	25.3±13.14	23.1±14.06
Assessment of parents of children 5-7 years old				
Brillia for Children, n=13	36.1±13.99	32.4±12.95	26.6±13.10	24.6±12.13
Placebo, n=24	44.7±13.13	37.9±13.07	35.7±17.36	31.0±15.78

Table 5. ANCOVA of the dynamics of the average SCAS score

Groups	Factors			Interactions		
	Drug (1)	Domain (2)	Visit (3)	(1)*(2)	(1)*(3)	(1)*(2)*(3)
Parents of children 5-7 years old	$F_{1/28}$=0.1; p=0.8	$F_{4/112}$=0.9; p=0.4	$F_{2/56}$=0.3; p=0.7	$F_{4/112}$=1.5; p=0.2	$F_{2/56}$=0.2; p=0.7	$F_{8/224}$=0.9; p=0.5
Parents of children 8-15 years old	$F_{1/49}$=0.8; p=0.4	$F_{5/245}$=1.7; p=0.15	$F_{2/98}$=0.9; p=0.4	$F_{5/245}$=1.4; p=0.2	$F_{2/98}$=0.2; p=0.8	$F_{10/490}$=0.8; p=0.6
Children 8-15 years old	$F_{1/50}$=0.1; p=0.8	$F_{5/250}$=1.3; p=0.3	$F_{2/100}$=0.1; p=1.0	$F_{5/250}$=1.3; p=0.3	$F_{2/100}$=0.2; p=0.8	$F_{10/500}$=0.8; p=0.6

In addition, four-way analysis of variance (ANOVA) (drug, visit, group, domain) showed a significant improvement of anxiety in all subgroups (both for Brillia for Children and placebo) after four weeks of therapy (Table 6).

Table 6. Average data of SCAS in both groups (points, M±SD)

Drug	Baseline	4 weeks	8 weeks	12 weeks
Brillia for Children, n=46	6.6±3.61	5.8±3.53	5.2±3.50 ***	4.7±3.19 ***
Placebo, n=48	6.9±4.17	5.9±3.71 **	5.4±4.00 ***	4.7±3.77 ***

Note: ** - p<0.01; *** - p<0.001, significance of differences vs baseline

Table 7 contains data on the distribution of patients by types of anxiety disorders, age and groups. The study aimed to evaluate the dynamics of anxiety disorders, depending on their types under the subscales of SCAS (Table 8).

Table 7. Distribution of patients by type of anxiety disorder, age and groups

Group	Age	Type of anxiety disorder (ICD-10)				Total
		F 93.0	F 93.1	F 93.2	F 93.8	
Brillia for Children	5-7 years	1 (8%)	1 (8%)	6 (46%)	5 (38%)	13 (100%)
	8-15 years	0 (0%)	8 (24%)	12 (36%)	13 (39%)	33 (100%)
	Total	1 (2%)	9 (20%)	18 (39%)	18 (39%)	46 (100%)
Placebo	5-7 years	2 (8%)	10 (42%)	5 (21%)	7 (29%)	24 (100%)
	8-15 years	1 (4%)	4 (17%)	8 (33%)	11 (46%)	24 (100%)

	Total	3 (6%)	14 (29%)	13 (27%)	18 (38%)	48 (100%)

Table 8. Values of SCAS subscales according to the assessment of children and their parents (points, M±SD)

Drug	Baseline	4 weeks	8 weeks	12 weeks
Panic attacks and agoraphobia, self-assessment of children 8-15 years old				
Brillia for Children, n=33	5.4±4.2	4.4±3.5	3.8±3.5	3.5±3.6
Placebo, n=24	4.4±3.1	3.1±2.8	2.3±2.9	2.0±2.5
Panic attacks and agoraphobia, assessment of parents of children 8-15 years old				
Brillia for Children, n=33	4.7±3.9	3.8±2.6	3.3±2.9	2.6±2.7
Placebo, n=24	4.2±4.0	4.0±3.3	2.7±3.0	2.5±3.2
Separation anxiety, self-assessment of children 8-15 years of old				
Brillia for Children, n=33	6.9±3.8	5.4±3.9	5.0±3.8	4.6±3.6
Placebo, n=24	5.6±3.5	4.5±3.4	4.5±3.4	3.6±3.5
Separation anxiety, assessment of parents of children 8-15 years old				
Brillia for Children, n=33	6.3±3.4	5.9±3.3	5.2±3.0	4.6±2.7
Placebo, n=24	5.7±3.9	4.7±2.8	4.3±3.1	3.6±3.1
Fear of injury, self-assessment of children 5-7 years old				
Brillia for Children, n=13	8.0±3.9	6.1±3.8	5.0±3.6	5.1±3.6
Placebo, n=24	11.9±4.5	10.1±4.6	10.1±6.4	9.1±6.1
Fear of injury, assessment of parents of children 5-7 years old				
Brillia for Children, n=33	8.6±4.0	7.1±4.2	6.2±3.8	5.7±3.4
Placebo, n=24	6.6±3.4	5.7±3.2	5.8±3.7	5.0±3.5
Social phobia, self-assessment of children 5-7 years old				
Brillia for Children, n=33	8.9±3.3	7.3±3.3	6.5±3.6	5.7±3.2
Placebo, n=24	7.0±4.1	6.3±3.6	5.8±3.422	5.4±3.432
Social phobia, assessment of parents of children 5-7 years old				
Brillia for Children, n=13	9.6±5.5	8.1±4.5	6.6±3.4	5.5±3.9
Placebo, n=24	9.8±4.6	8.2±4.1	6.9±4.2	6.4±3.9

4.3 Conclusions:

Efficacy results:

Over the observation period 4 patients were withdrawn. The analysis of study drug efficacy was based on the data of 94 patients.

Two-way analysis of covariance (ANCOVA) showed that anxiety severity under the test of R. Temple, M. Dorky, V. Amen in the study and control groups differed by a drug factor (Brillia for Children and placebo, $F_{1/91}=4.31$; $p=0.04$). The results confirmed that Brillia for Children was superior to placebo. Furthermore, ANCOVA revealed that anxiety severity significantly decreased in treatment group after 8 weeks of treatment.

The results of testing of children and their parents during the study indicated that the use of the active drug or placebo had a significant positive impact on the severity of anxiety disorders compared to baseline state. Three-way ANCOVA (drug, visit, domain) with repeated measures revealed no significant differences between study and control groups in terms of the dynamics of anxiety disorder severity (Table 5).

According to patients and their parents, Brillia for Children had marked anxiolytic effect in children 8-15 years old with panic attacks and agoraphobia. The treatment improved separation anxiety also mostly in older children. In addition, parents of younger children believed that Brillia for Children significantly reduced the fear of injury in their children. Finally, treatment with Brillia for Children had a positive impact on the degree of social phobia in children, regardless of age (Table 8).

However, in the absence of randomization criteria depending on age, treatment and placebo groups were not equal in regard to age. Analysis of SCAS in whole or at the level of subscales (domains) revealed no significant differences between two groups. Comparison of average scores of the CGI Scale between the groups using the Student's t-test for independent samples revealed no significant differences.

Thus, Brillia for Children (1 tablet t.i.d. for 12 weeks) is effective in children with anxiety disorders.

5. Study 2 (TD1061511-01.18.P):

5.1 Materials and Methods:

Study design: multicenter, double-blind, placebo-controlled, randomized study.

Study objective: to assess the efficacy and safety of Brillia for Children in children with ADHD.

Inclusion criteria:

1. Children aged 6-12 years;
2. Diagnosis of ADHD according to DSM-IV;
3. Mild to severe ADHD (CGI-ADHD-S);
4. Clinical signs of ADHD of at least 22 points (ADHDRS-IV Home Version);
5. Absence of thyroid gland pathology;
6. Absence of significant impairment of general intelligence;
7. Absence of pharmacotherapy for ADHD within 2 weeks prior to the study;
8. Informed consent form signed by child's legal representative.

The study included 100 children, who were randomized into two groups:

1. Treatment group (n=50) was administered Brillia for Children (2 tablets b.i.d.) for 12 weeks;
2. Control group (n=50) was administered placebo (2 tablets b.i.d.) for 12 weeks.

Efficacy criteria:

1. The proportion of responders;
2. The average reduction of clinical signs of ADHD (ADHDRS-IV Home Version);
3. The average reduction of ADHD severity (CGI-ADHD-S);
4. The average reduction of clinical signs of ADHD (Conners scale);
5. The average dynamics of clinical manifestations of ADHD according to daily assessment of parents.

5.2 Results:

Table 9. The results of the ADHD Rating Scale-IV Home Version (points, M±m)

Treatment phase	**Brillia for Children**	**Placebo**
Total score		
Baseline	32.5±1.14	33.6±0.96
2 weeks	25.1±1.03 *** °	28.8±1.26 ***
4 weeks	22.7±1.23 *** °°	29.9±1.06 ***
6 weeks	20.8±1.06 *** °°	29.0±1.25 ***
8 weeks	20.9±1.30 *** °°°	27.6±1.35 ***
12 weeks	20.1±1.84 *** °°	27.3±1.48 ***
Inattention		
Baseline	17.4±0.57	18.4±0.43
2 weeks	13.7±0.68 *** °	16.1±0.66 ***
4 weeks	12.9±0.79 *** °°°	16.4±0.57 ***
6 weeks	11.9±0.64 *** °°°	16.0±0.70 ***
8 weeks	11.5±0.70 *** °°°	15.1±0.76 ***
12 weeks	11.4±0.68 *** °°	14.9±0.78 ***
Hyperactivity/impulsiveness		

Baseline	15.1±0.77	15.2±0.62
2 weeks	11.4±0.61 ***	12.7±0.74 ***
4 weeks	9.8±0.64 *** °°°	13.5±0.67 **
6 weeks	8.9±0.64 *** °°°	12.9±0.73 **
8 weeks	9.5±0.76 *** °°	12.5±0.81 ***
12 weeks	8.7±0.70 *** °°°	12.5±0.82 ***

Note: * - p<0.05; ** - p<0.01; *** - p<0.001, significance of differences vs. baseline; ° - p<0.05; °° - p<0.01; °°° - p<0.001, significance of differences vs. baseline

Brillia for Children reduced inattention and hyperactivity/impulsivity. Total score of ADHDRS-IV Home Version decreased by 38.2% and 18.8% in treatment and control group, respectively (Table 9).

Table 10. ADHD severity according to CGI-ADHD-S (abs(%))

Treatment phase	Brillia for Children	Placebo
Minor ADHD		
Baseline	0 (0%)	0 (0%)
4 weeks	0 (0%)	0 (0%)
12 weeks	1 (2%)	0 (0%)
Mild ADHD		
Baseline	2 (4.0%)	0 (0.0%)
4 weeks	12 (24.0%)	6 (12.0%)
12 weeks	19 (38.0%)	11 (22.0%)
Moderate ADHD		
Baseline	48 (96.0%)	50 (100.0%)
4 weeks	38 (76.0%)	44 (88.0%)
12 weeks	30 (60.0%) *	39 (78.0%)

Note: * - p<0.05, significance of differences vs. placebo

In treatment group ADHD severity improved from moderate to mild (Table 10).

Table 11. Total score of CGI-ADHD-S (points, M±m)

Treatment phase	Brillia for Children	Placebo
Baseline	4.0±0.03	4.0±0.00
4 weeks	3.8±0.06 **	3.9±0.05
12 weeks	3.6±0.08 ***	3.8±0.06 ***

Note: ** - p<0.01; *** - p<0.001, significance of differences vs. baseline

By the end of therapy Brillia for Children reduced ADHD severity by 10%, placebo – by 5% (Table 11).

Table 12. Assessment of ADHD symptoms under Conners scale (points, M±m)

Treatment phase	Brillia for Children	Placebo
Total score		
Baseline	45.8±1.61	50.8±1.61
4 weeks	35.6±1.52 *** °°°	48.0±1.68 *
12 weeks	32.6±1.84 *** °°°	43.8±2.17 ***
Oppositional behavior		
Initially	8.4±0.46	9.7±0.51
4 weeks	6.6±0.44 *** °°°	9.9±0.52
12 weeks	6.3±0.51 *** °°	8.4±0.55
Cognitive impairment		

Baseline	11.4±0.50	12.1±0.50
4 weeks	9.7±0.56 *** °°	12.1±0.51
12 weeks	8.6±0.63 *** °°	10.9±0.53 *
Hyperactivity		
Baseline	9.1±0.49	11.0±0.52
4 weeks	6.2±0.44 *** °°°	9.2±0.50 ***
12 weeks	5.6±0.39 *** °°°	9.0±0.59 ***
ADHD index		
Baseline	22.4±0.78	24.1±0.71
4 weeks	18.3±0.81 *** °°°	23.1±0.77
12 weeks	16.5±0.88 *** °°°	21.4±0.98 **

Note: * - p<0.05; ** - p<0.01; *** - p<0.001, significance of differences vs. baseline; ° - p<0.05; °° - p<0.01; °°° - p<0.001, significance of differences vs. placebo

By the end of the study total score of Conners scale decreased by 28.8% and 13.8% in treatment and control group, respectively (Table 12).

Table 13. Dynamics of ADHD symptoms according to parents' assessment (points, M±m)

Treatment phase	**Brillia for Children**	**Placebo**
Total score		
Baseline	12.7±0.90	13.0±0.97
2 weeks	9.5±0.70 *** °	12.1±1.05
4 weeks	9.4±0.66 ***	10.9±0.72 *
8 weeks	7.3±0.85 *** °°°	12.5±0.89
12 weeks	6.8±0.74 *** °	10.0±0.99 *
Morning subscale score		
Baseline	3.1±0.35	3.0±0.38
2 weeks	1.8±0.24 *** °	2.7±0.31
4 weeks	1.6±0.24 ***	2.4±0.33
8 weeks	1.4±0.24 *** °°°	3.0±0.31
12 weeks	1.2±0.20 *** °°	2.1±0.23
Night subscale score		
Baseline	9.5±0.66	10.0±0.72
2 weeks	7.7±0.56 **	9.6±0.79
4 weeks	7.8±0.54 *	8.7±0.52 *
8 weeks	5.9±0.64 *** °°°	9.4±0.65
12 weeks	5.5±0.63 *** °	7.8±0.80 **

Note: * - p<0.05; ** - p<0.01; *** - p<0.001, significance of differences vs. baseline; ° - p<0.05; °° - p<0.01; °°° - p<0.001, significance of differences vs. placebo

The results of the analysis of primary and secondary efficacy criteria were proved with the analysis of daily parents' reports about clinical symptoms of ADHD in children. Brillia for Children significantly decreased total and subscale scores and exceeded placebo (Table 13).

5.3 Conclusions:

Brillia for Children had pronounced therapeutic effect in patients with mild to moderate ADHD. Brillia for Children in a dose of 2 tablets b.i.d. for 12 weeks reduced clinical symptoms of ADHD according to ADHDRS-IV Home Version and Conners scale, and ADHD severity under CGI-ADHD-S.

Thus, Brillia for Children can be recommended for children with disturbances of behavior and attention.

6. Discussion of Both Study 1 (MMH-TD-001) and Study 2 (TD1061511-01.18.P):

6.1 Study Populations (Brillia for Children, tablets)

The studies for the efficacy of Brillia for Children included 198 patients, 98 children were administered Brillia for Children.

194 patients completed the studies. Four patients discontinued from the study of Brillia for Children efficacy in treatment of anxiety disorder (2 patients from treatment group and 2 patients from placebo group) because of decision of their parents. The final analysis of the efficacy of Brillia for Children in children with anxiety disorders included 94 patients (MMH-TD-001). All of 100 patients completed the study of Brillia for Children efficacy in treatment of disturbances of behavior and attention (TD1061511-01.18.P).

Brillia for Children experimental groups were compared with placebo groups.

Table 14. Demographic characteristics of patients (abs(%))

Parameter		Brillia for Children	Placebo	Total
MMH-TD-001				
Sex	M	29 (60.4%)	34 (68.0%)	63 (64.3%)
	F	19 (39.6%)	16 (32.0%)	35 (35.7%)
Comorbidities: Hypoxia in perinatal period/ during childbirth		27 (56.3%)	27 (54%)	98 (55.1%)
Comorbidities: Nervous system diseases		2 (4.2%)	1 (2%)	3 (3.1%)
Comorbidities: Mental and behavioral disorders		4 (8.3%)	2 (4%)	6 (6.1%)
Comorbidities: Respiratory system diseases		4 (8.3%)	2 (4%)	6 (6.1%)
Comorbidities: Digestive system diseases		2 (4.2%)	2 (4%)	4 (4.1%)
Comorbidities: Diseases of the musculoskeletal system		1 (2.1%)	3 (6%)	4 (4.1%)
Comorbidities: Diseases of eye adnexa		-	1 (2%)	1 (1%)
Comorbidities: Congenital anomalies		1 (2.1%)	1 (2%)	2 (2%)
Age, years (M±m)		8.1±2.89 (5-15)	9.0±2.82 (5-15)	8.6±2.88 (5-15)
Connection with definite event		14 (29.2%)	18 (36.0%)	32 (32.7%)
Initial level of anxiety under anxiety scale of Lavrentieva and Titarenko, points (M±m)		10.9±3.06	10.7±3.00	-
TD1061511-01.18.P				
Age, years (M±m)		9.3±0.25	9.3±0.24	6-12
Sex (abs (%))	M	38 (76.0%)	39 (78.0%)	77 (77.0%)
	F	12 (24.0%)	11 (22.0%)	23 (23.0%)
Weight, kg (M±m)		33.2±1.51	30.9±0.86	-
Height, sm (M±m)		138.7±1.71	137.4±1.38	-
Age of diagnosis, years (M±m)		5.1±0.28	5.5±0.24	-
ADHD type according to DSM-IV (abs (%))	Combined	45 (90.0%)	50 (100%)	95 (95.0%)
	Predominantly inattentive	5 (10.0%)	0	5 (5.0%)
	Predominantly hyperactive-	0	0	0

Parameter		Brillia for Children	Placebo	Total
	impulsive			

Demographic characteristics of patients are presented in Table 14. In all cases, treatment and control groups were comparable by sex, age, severity of the initial state, comorbidities. Sample size was sufficient for statistical analysis and assessment of clinical efficacy.

MMH-TD-001 study did not include age randomization criteria. Thus, the assessment of the efficacy of Brillia for Children in children aged 5-7 years with SCAS was carried out in unbalanced groups (13 patients in treatment group, 23 patients in control group).

Sample volume was still sufficient for statistical analysis and assessment of clinical efficacy.

6.2 Comparison of Efficacy Results of Both Studies (Brillia for Children, tablets)

6.2.1 Anxiety disorders

The efficacy of treatment of anxiety disorder was assessed by standard scales, questionnaires and tests designed to assess the severity of anxiety and depression.

In general, Brillia for Children demonstrated high efficacy in the treatment of emotional disorders with the onset specific for childhood (under ICD-10, separation anxiety disorder of childhood – F93.0; phobic anxiety disorder of childhood – F93.1; social anxiety disorder of childhood – F93.2; other childhood emotional disorders – F93.8), exceeding the efficacy of placebo (MMH-TD-001).

ANCOVA showed that anxiety severity under the test of R. Temple, M. Dorky, V. Amen in treatment and control groups significantly differed during the study by drug factor ($F_{1/91}$=4.31; p=0.04). The results confirmed superiority of Brillia for Children over placebo. According to ANCOVA anxiety severity in children treated with Brillia for Children significantly decreased after 8 weeks of treatment. This effect was steadily growing to week 12 of the therapy.

In addition, frequency analysis of patients with various anxiety severity showed significant differences between treatment and control groups ($\chi^2_{(1)}$=6.0; p=0.014). By week 12 of the treatment with Brillia for Children the proportion of children with severe anxiety was 20% (vs. 35% in control group), and the proportion of patients with moderate anxiety increased to 78% (vs. 65% in control group).

The average total score of severity of anxiety disorders according to self-assessment of patients aged 8-15 years and the results of reports of parents of children aged 5-7 years and 8-15 years under SCAS confirmed that treatment with Brillia for Children had positive influence on severity of anxiety disorders compared to the initial state. Thus, the total score in treatment group (children aged 8-15 years) decreased from 39.2±14.5 to 26.9±15.7 points (standard: 27.38±16.50 points). Similar results were obtained when analyzing the reports of parents of children aged 5-7 years and 8-15 years.

Analysis of results on the efficacy of Brillia for Children showed that the drug had sedative and anxiolytic effects, improved tolerance of psychoemotional stress. The efficacy of Brillia for Children is superior to placebo.

6.2.2 Disturbances of behavior and attention

The treatment efficacy of disturbances of behavior and attention was analyzed according to standard scales and questionnaires designed to assess the ADHD severity: ADHDRS-IV Home Version, CGI-ADHD-S and Conners scale.

Monotherapy with Brillia for Children neutralized all clinical manifestations of disturbances of behavior and attention (hyperactivity, behavioral disorders, cognitive deficit), improved school performance, reduced severity of accompanying asthenic and neurotic disorders in patients.

By the end of 12-week treatment with Brillia for Children inattention and hyperactivity/impulsivity decreased by 34.5% and 42.4%, respectively, according to ADHDRS-IV Home Version. Monotherapy with Brillia for Children also increased the number of patients with mild ADHD and reduced the number of patients with a moderate ADHD. According to CGI-ADHD-S total score

decreased by 10% in treatment group. Conners scale showed positive dynamics of opposition in child's behavior, cognitive impairment, hyperactivity, ADHD index. Under all questionnaires and scales the efficacy of Brillia for Children was superior to placebo.
Thus, Brillia for Children is a highly effective drug and can be recommended for children 6-12 years old suffering from disturbances of behavior and attention.

6.3 Discussion of Results in Subpopulations (Brillia for Children, tablets)

6.3.1 Efficacy of Brillia For Children in various age groups

Analysis of self-assessment of anxiety severity depending on age showed that the most marked improvement among patients with anxiety disorders (F93) occurred in younger children (5-7 years old) treated with Brillia for Children (MMH-TD-001). After 12 weeks of treatment average anxiety index according to the test of R. Temple, M. Dorky, V. Amen fell by 11.9 points vs. 8.3 points in patients aged 5-7 years treated with placebo. A similar analysis carried out in older children (8-15 years old) also testified the efficacy of Brillia for Children, but positive dynamics of anxiety index was less pronounced (decrease by 11.2 points with Brillia for Children and 11 points with placebo). Thus, the anxiolytic efficacy of Brillia for Children was mainly manifested in young children.

The most significant effect of the treatment regarding anxiety severity level was observed in younger children. By the end of the therapy total SCAS score according to parent's opinion was close to standard indices (24.6±12.1 vs. 31.0±15.8 points in control group). Total SCAS score in older children reached 26.9±15.69 points according to self-assessment and 25.7±10.14 points according to parents' opinion.

However, due to the absence of randomization criteria depending on patient's age, groups of patients were not equal. Analysis of SCAS results revealed no significant differences between treatment and control groups. Nevertheless, the most distinct effect of Brillia for Children was observed in younger children. Pronounced anxiolytic effect of Brillia for Children was revealed in children of 8-15 years old with separation anxiety, panic attacks, agoraphobia.

Thus, the best efficacy of Brillia for Children in the younger group (5-7 years old) confirms the need for early diagnosis and treatment of anxiety disorders in children.

Subpopulations were not identified in clinical study TD1061511-01.18.P and, therefore, the analysis of the efficacy in subpopulations was not performed.

Treatment and control groups were formed uniformly under demographic and anthropometric data. The study mainly included children with combined type of ADHD (95.0% of patients). Patients with predominantly inattentive amounted to only 5% of the total population of patients and no patients with predominantly hyperactive-impulsive types of ADHD were enrolled in the study.

Thus, the analysis of the efficacy of Brillia for Children, depending on the type of ADHD was not possible, due to the insufficient number of enrolled patients with predominantly inattentive and predominantly hyperactive-impulsive types of ADHD.

7. Discussion of Clinical Information Relevant to Dosing Recommendations (Brillia for Children, tablets)

It is recommended to take 1 or 2 tablets per intake. The drug should be taken 2-3 times daily. The overall duration of treatment is 3 months; the treatment can be repeated in 1 month, if necessary.

In study of the efficacy of Brillia for Children for the treatment of anxiety disorders, in children the following dosage regimens were used: 1 tablet t.i.d. The duration of the treatment with Brillia for Children was 12 weeks. The study of the efficacy of Brillia for Children for treatment of disturbances of behavior and attention used following dosage regimen: 2 tablets b.i.d. for 12 weeks.

These schemes of drug administration proved to be effective. However, special analysis of correlation of dosage regimen with efficacy of Brillia for Children was not performed. However, the possibility of flexible dose titration (2-6 tablets a day), its repeated use during the day, depending on the

severity of the disease and current condition of the patient allows choosing the optimum regimen and achieving positive outcomes in each case.

Thus, the recommended dosage regimen of the drug is efficient and can be used for the treatment of children with anxiety disorders and disturbances of behavior and attention, accompanied by increased excitability, irritability and hyperactivity.

8. Persistence of Efficacy and/or Tolerance Effects (Brillia for Children, tablets)

The duration of the treatment in both studies with Brillia for Children was 12 weeks.

Anxiolytic, antidepressant, and antiasthenic effects of Brillia for Children were gradually increasing during the treatment (MMH-TD-001).

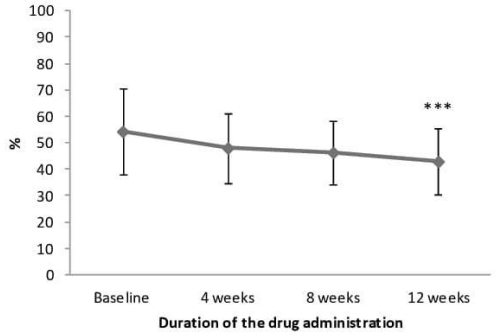

Figure 2. Dynamics of anxiety severity under the test of R. Temple, M. Dorky, V. Amen depending on the duration of the treatment with Brillia for Children

Note: *** - $p<0.001$, significance of differences vs baseline

Thus, administration of Brillia for Children led to a gradual decrease in anxiety severity in children during the treatment (Figure 2). Besides, the marked reduction of anxiety severity was reported after 8 weeks of treatment. The influence of the factor of therapy duration on anxiety severity was obtained using two-way ANOVA. The analysis showed that anxiety severity under the test of R. Temple, M. Dorky, V. Amen significantly decreased by week 8 of the treatment and this effect was steadily growing to week 12.

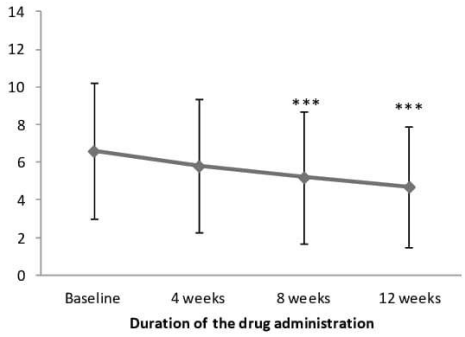

Figure 3. Dynamics of SCAS averaged data depending on the duration of the treatment with Brillia for Children

Note: *** - $p<0.001$, significance of differences vs. baseline

In addition, SCAS averaged data proved positive dynamics of anxiety severity (Figure 3). Post-hoc analysis showed significant reduction of anxiety by week 4 of the treatment with Brillia for Children. The results obtained after the completion of therapy (12 weeks) were significantly better than the initial values and the results of week 4.

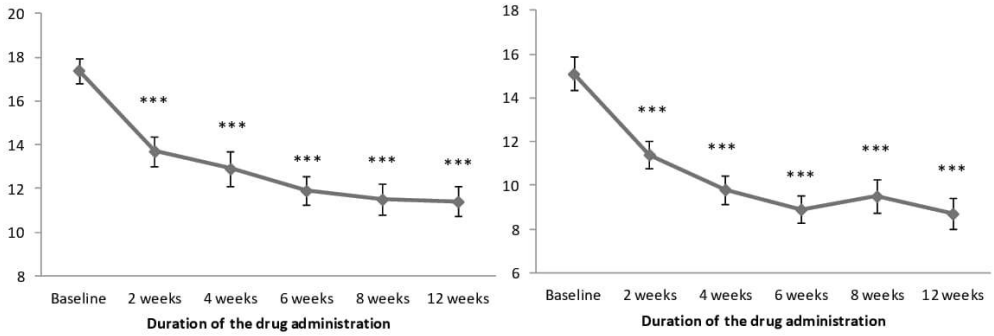

Figure 4. The dynamics of inattention (A) and hyperactivity/impulsiveness (B) according to ADHDRS-IV Home Version depending on duration of Brillia for Children administration

Note: *** - $p<0.001$, significance of differences vs. baseline

A decrease of the efficacy of Brillia for Children with an increase of the duration of therapy was not observed in the study. Thus, long-term use of Brillia for Children does not decrease the efficacy and/or promote tolerance and/or addiction.

Moreover, Brillia for Children gradually reduced inattention and hyperactivity, impulsiveness, cognitive impairment (TD1061511-01.18.P).

Thus, Brillia for Children led to gradual decline in both inattention and hyperactivity/impulsiveness in children (Figure 4). Besides, the marked reduction in anxiety severity was reported after 2 weeks of the drug administration.

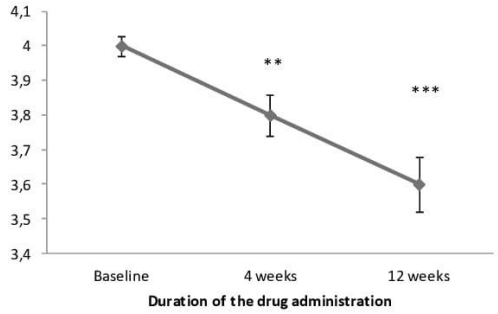

Figure 5. The dynamics of ADHD severity under CGI-ADHD-S depending on duration of Brillia for Children administration

Note: * - $p<0.05$, ** - $p<0.01$, significance of differences vs. baseline

In addition, CGI-ADHD-S proved the reduction of ADHD severity (Figure 5). According to the total score dynamics, a 4-week therapy with Brillia for Children significantly reduced ADHD severity.

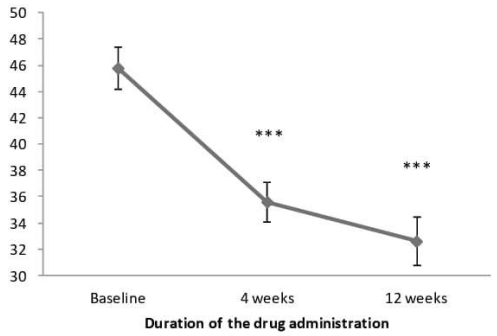

Figure 6. The dynamics of total score of Connors scale depending on duration of Brillia for Children administration

Note: *** - $p<0.001$, significance of differences vs. baseline

Connors scale also showed the reduction of the clinical manifestations of ADHD (opposition in child's behavior, cognitive impairment, hyperactivity) (Figure 6). The positive effect of Brillia for Children was registered after 4 weeks of therapy. By the end of the treatment (12 weeks) total score decreased by 28.8%.

8.1 Conclusions:

The duration of the treatment with Brillia for Children did not impact the efficacy.

Thus, long-term treatment with Brillia for Children does not lead to a decrease in efficacy, the development of tolerance and addiction, but rather to a positive effect, which confirms the need for a long-term course of Brillia for Children.

9. Discussion of Clinical Efficacy (Brillia for Children, tablets)

9.1 Exposure to the drug (Brillia for Children, tablets)

9.1.2 Overall Safety Evaluation Plan and Narratives of Safety Studies (Brillia for Children, tablets)

The study of Brillia for Children safety involved all patients initially randomized in the clinical studies. Total number of participants made up 198 persons, among whom 98 patients administered Brillia for Children.

The assessment of the safety of Brillia for Children in humans was carried out during routine examinations by recording adverse reactions associated with drug administration, as well as by analysis of laboratory (urinalysis, complete blood count) and vital (blood pressure, pulse) parameters.

9.2 Study 1 (MMH-TD-001) Safety Evaluation:

Study design: multicenter, double-blind, placebo-controlled, randomized.

The study involved 98 patients (5-15 years old) with emotional disorders with onset specific for childhood (F93 in ICD-10):

1. Treatment group (n=48) was administered Brillia for Children (1 tablet t.i.d.);
2. Control group (n=50) was administered placebo (1 tablet t.i.d.).

Duration of the treatment was 12 weeks.

Safety criteria:

1. Nature and duration of adverse events (AEs) and their relationship to study drug;
2. Dynamics of vital functions.

Table 15. Dynamics of vital parameters (M±SD)

Drug	Baseline	4 weeks	8 weeks	12 weeks
Systolic blood pressure, mmHg				
Brillia for Children	105.8±9.27	105.3±10.61	105.7±9.25	105.5±10.2
Placebo	102.7±12.36	102.6±12.01	102.3±10.54	102.0±10.53
Diastolic blood pressure, mmHg				
Brillia for Children	67.8±6.54	66.6±7.14	65.4±7.92	66.1±7.43
Placebo	66.8±8.59	65.6±7.93	65.7±7.04	65.6±6.22
Breathing rate, breaths per minute				
Brillia for Children	20.1±4.63	19.9±4.39	19.6±3.78	19.5±3.66
Placebo	21.2±7.89	21.2±7.02	20.6±6.45	20.5±6.38
Heart rate, bpm				
Brillia for Children	75.5±10.03	76.8±10.3	75.8±8.69	76.5±8.53
Placebo	76.2±10.77	77.7±10.6	77.4±8.85	77.9±8.26

During the study the patients did not report any abnormalities during at physical examination. Respiratory rate, blood pressure and heart rate of children were in range of an age norms. Significant differences between two groups were not revealed (Table 15).

Table 16. Adverse events

No.	Description of adverse event	Relation to study drug
Brillia for Children		
01-001-001	Acute bronchitis	Unlikely
02-008-018	Aggravation of chronic maxillitis and chronic tonsillitis	Unlikely
03-004-024	Cephalgia, spotted sore throat	Unlikely
03-005-025	Acute nasopharyngitis	Unlikely
03-007-027	AURI, acute catarrhal otitis, right ear	Unlikely
03-010-030	AURI	Unlikely
03-014-074	Increase in frequency of motor tics, vocalisms, twisting of fingers	Unlikely
03-017-077	AURI	Unlikely
04-003-033	Allergic rhinitis	Unlikely
04-018-058	Ambrosial hay fever	Unlikely
04-019-059	AURI	Unlikely
04-021-061	AURI	Unlikely
04-022-062	AURI	Unlikely
04-026-066	AURI, acute laryngotracheitis and gastroenteritis	Unlikely
04-045-105	Punctate rash of unspecified nature and genesis, pruritus	Possible
Placebo		
03-002-022	AURI	Unlikely
03-006-026	Increase in frequency of motor spasms, vocalisms, AURI	Unlikely
03-008-028	Acute intestinal infection	Unlikely
03-009-029	AURI	Unlikely
04-001-031	AURI	Unlikely
04-011-051	AURI	Unlikely
04-028-068	AURI	Unlikely

No.	Description of adverse event	Relation to study drug
04-029-069	AURI	Unlikely
04-030-070	AURI	Unlikely
04-032-082	AURI	Unlikely
04-033-083	AURI	Unlikely
04-035-085	AURI	Unlikely

Table 17. The number of adverse events (n=98)

AEs	Brillia for Children	Placebo
Cephalgia	4 cases (1 patient)	–
Sore throat, acute nasopharyngitis	2 cases	–
Acute catarrhal otitis	1 case	
AURI	10 cases (7 patients)	13 cases (11 patients)
Increase in frequency of motor spasms	2 cases (1 patient)	2 cases (1 patient)
Increase in frequency of vocalisms	2 cases (1 patient)	2 cases (1 patient)
Increase in frequency of twisting of fingers	1 case	–
Allergic rhinitis	1 case	–
Ambrosial hay fever	1 case	–
Acute bronchitis	1 case	–
Aggravation of chronic tonsillitis and maxillitis	2 cases	–
Acute gastroenteritis	1 case	1 case
Punctate rash of unspecified nature and genesis, pruritus	1 case	–

In the course of study, serious AEs were not reported. AEs were observed in 15 patients in treatment group and 12 patients in control group. A list of AEs and their connection with Brillia for Children or placebo are presented in Table 16; the distribution and nature of adverse AEs in groups – in Table 17.

One patient in treatment group had AEs that were characterized as possibly related – punctate rash and pruritus. Two patients (one in treatment group and one control group, acceleration of motor ticks and vocalisms) had AEs with a relationship to study drug characterized as unlikely related since it had equal frequency in both groups. Other AEs were also characterized as unlikely to study drug.

The majority of patients were administered concomitant therapy for AEs, predominantly for acute upper respiratory infections (AURI).

Thus, Brillia for Children is safe when used in patients with anxiety disorders in a dose of 1 tablet t.i.d. for 12 weeks.

9.3 Study 2 (TD1061511-01.18.P) Safety Evaluation:

Study design: double-blind, placebo-controlled, randomized study.

The study included 100 children:

1. Treatment group (n=50) was administered Brillia for Children (2 tablets b.i.d.) for 12 weeks;
2. Control group (n=50) was administered placebo (2 tablets b.i.d.) for 12 weeks.

Safety criteria:

1. Nature of AEs and their relation to study drug;
2. Dynamics of laboratory parameters (complete blood count, urinalysis, biochemical blood assay).

Safety results. All patients completed the study.
During the study serious AEs were not reported and the drug was well-tolerated by all patients.

Table 18. AEs in placebo and Brillia for Children groups

Adverse event	**Specification**	**Brillia** (n=50)	**Placebo** (n=50)
AURI	Frequency, n (%)	2 (4%)	2 (4%)
	Severity	Mild / Moderate	Mild / Moderate
	Relationship with treatment	Unlikely	Unlikely
Acute bronchitis	Frequency, n (%)	–	1 (2%)
	Severity		Mild
	Relationship with treatment		Unlikely
Sleepwalking	Frequency, n (%)	–	1 (2%)
	Severity		Mild
	Relationship with treatment		Unlikely
Headaches	Frequency, n (%)	1 (2%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Impaired glucose tolerance	Frequency, n (%)	1 (2%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Hay fever (exacerbation)	Frequency, n (%)	1 (2%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Total:		14	12

During the study 9 cases of AEs were registered, 5 cases were registered in Brillia for Children group and 4 cases – in placebo group (Table 18). Safety profile of Brillia for Children was comparable to placebo. No cases of AEs with certain or probable/likely relationship with medicinal product intake were registered in clinical study. Most frequent AE was acute upper respiratory infection. It was mild and investigators and doctors characterized AURI as unlikely related to medicinal product intake. Adverse events were mild and did not require drug discontinuation or administration of other drugs.

Table 19. Dynamics of vital parameters (M±m)

Index	**Brillia for Children**			**Placebo**		
	Baseline	**4 weeks**	**12 weeks**	**Baseline**	**4 weeks**	**12 weeks**
HR, bpm	84.4±1.64	84.0±1.17	81.0±0.74	82.7±1.04	84.4±1.64	84.0±1.17
SBP, mmHg	100.4±1.57	98.3±1.26	98.1±1.41	95.7±1.45	100.4±1.57	98.3±1.26
DBP, mmHg	68.7±1.21	66.9±0.73	65.5±0.81	63.9±0.76	68.7±1.21	66.9±0.73
Body temperature, °C	36.6±0.02	36.5±0.02	36.6±0.02	36.5±0.02	36.6±0.02	36.5±0.02

Note: HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure

Analysis of vital parameters revealed no pathological changes during the therapy (Table 19). The differences at visits and between groups were not significant.

Table 20. Dynamics of complete blood count (M±m)

Parameter	**Standard**	**Brillia for Children**	**Placebo**

		Baseline	12 weeks	Baseline	12 weeks
ESR (mm/h)	0.0-15.0	6.4±0.97	8.5±1.05	6.6±1.11	6.9±0.71
Leucocytes (10^3/μl)	4.5-13.5	6.1±0.19	7.3±0.34	6.2±0.22	6.3±0.24
Hemoglobin (g/l)	115.0-145.0	129.8±1.17	132.0±1.23	131.4±0.89	129.4±1.06
Erythrocytes (10^6/μl)	3.8-4.9	4.6±0.03	4.7±0,04	4.7±0.,04	4.7±0.04
Hematocrit (%)	33.0-41.0	37.7±0.25	38.7±0.29	37.5±0.58	37.6±0.36
Thrombocytes (10^3/μl)	150.0-400.0	301.4±7.86	303.9±7.02	313.9±8.18	305.6±8.07
Neutrophils (%)	42.0-66.0	41.6±1.63	49.6±1.72	44.9±1.17	43.4±1.44
Basophils (%)	<1.0	0.5±0.09	0.3±0.05	0.3±0.05	0.5±0.08
Eosinophiles (%)	1.0-5.0	5.1±0.70	4.2±0.49	4.4±0.37	4.5±0.46
Monocytes (%)	3.0-9.0	10.7±0.96	9.6±0.44	10.6±1.22	9.4±0.33
Lymphocytes (%)	30.0-50.0	42.1±1.42	36.1±1.82	41.0±1.17	42.1±1.34

Table 21. Dynamics of urinalysis

Parameter	Standard	Brillia for Children		Placebo	
		Baseline	12 weeks	Baseline	12 weeks
Specific gravity (M±m)	1012.0-1025.0	1024.2±1.02	1021.7±1.35	1022.6±1.07	1023.2±0.96
Protein, g/l (abs (%))	≤0.140	37 (74.0%)	39 (78.0%)	40 (80.0%)	40 (80.0%)
Glucose (abs (%))	absent	50 (100.0%)	50 (100.0%)	50 (100.0%)	50 (100.0%)

Table 22. Dynamics of biochemical blood assay (M±m)

Parameter	Standard	Brillia for Children		Placebo	
		Baseline	12 weeks	Baseline	12 weeks
Glucose (μmol/l)	3.3-5.6	5.2±0.07	5.1±0.06	5.3±0.05	5.2±0.05
Total bilirubin (μmol/l)	3.4-17.1	10.4±0.88	9.2±1.07	8.9±0.68	9.9±0.89
ALT (U/l)	<39	13.9±0.60	14.9±1.05	14.1±0.47	13.6±0.52
AST (U/l)	<47	25.5±1.05	25.8±1.47	23.9±1.00	24.9±1.24
Total protein (g/l)	60.0-80.0	71.4±0.473	70.5±1.76	71.5±0.57	70.7±0.56
Albumin (g/l)	38.0-54.0	49.7±0.38	49.4±0.36	50.2±0.39	49.0±0.38
Creatinine (μmol/l)	27.0-62.0	54.5±0.93	55.9±1.01	53.1±1.11	54.9±1.42
Urea (μmol/l)	1.8-6.4	4.8±0.17	4.2±0.16	5.5±0.92	4.5±0.16
Alkaline phosphatase (U/l)	≤500.0	220.4±7.44	226.4±9.23	227.8±8.08	218.1±9.71

The safety of study drug was confirmed by absence of pathological changes in blood and urine tests (Table 20, 21, 22). Differences between laboratory tests at visits and in groups were not significant and were in physiological range.

Thus, Brillia for Children (4 tablets a day) for 12 weeks is safe for children with ADHD.

9.4 Demographic and Other Characteristics of Study Population (Brillia for Children, tablets)

The studies of the safety of Brillia for Children included 198 females and males under 16. 98 patients were administered Brillia for Children.

The studies compared the safety of Brillia for Children with safety of placebo (n=100).

Demographic characteristics of patients participating in clinical studies of the efficacy and safety of Brillia for Children are presented in Table 14. In all cases treatment and control groups were comparable by sex, age, severity of the initial state, and comorbidities.

10. Adverse Events (Brillia for Children, tablets)

10.1 Analysis of Adverse Events (Brillia for Children, tablets)

AEs in case of administration of Brillia for Children were studied in all clinical studies. 2 clinical studies (MMH-TD-001, TD1061511-01.18.P) included 198 subjects. 98 patients were administered Brillia for Children.

Patients withdrew from the studies if they wished so; if they needed drugs that were not valid for use in the study; if further participation in the study would damage their health; if serious AEs developed.

194 of 198 patients completed the study. Two patients withdrew from treatment group and 2 children withdrew from control group (MMH-TD-001). The patients prematurely completed the study due to the reluctance of parents to continue.

The following convention has been used for the classification of undesirable effects in terms of frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000), not known (cannot be estimated from the available data).

Only single cases of transient, mostly mild and non-serious adverse reactions were registered in controlled clinical studies. The frequency categories associated with the adverse events are estimates. For most events, suitable data for estimating incidence were not available.

Table 24. AEs in placebo and Brillia for Children groups

Adverse event	**Specification**	**Brillia** (n=98)	**Placebo** (n=100)
AURI	Frequency, n (%)	9 (9.2%)	13 (13%)
	Severity	Mild / Moderate	Mild / Moderate
	Relationship with treatment	Unlikely	Unlikely
Acute bronchitis	Frequency, n (%)	1 (1.02%)	1 (1%)
	Severity	Mild	Mild
	Relationship with treatment	Unlikely	Unlikely
Sleepwalking	Frequency, n (%)	–	1 (1%)
	Severity		Mild
	Relationship with treatment		Unlikely
Headaches	Frequency, n (%)	2 (2.04%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Impaired glucose tolerance	Frequency, n (%)	1 (2%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Hay fever (exacerbation)	Frequency, n (%)	2 (2.04%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Acute catarrhal otitis	Frequency, n (%)	1 (1.02%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Acute nasopharyngitis	Frequency, n (%)	2 (2.04%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Increase in frequency of motor spasms	Frequency, n (%)	1 (1.02%)	1 (1%)
	Severity	Mild	Mild
	Relationship with treatment	Unlikely	Unlikely

Adverse event	Specification	**Brillia** (n=98)	**Placebo** (n=100)
Increase in frequency of vocalisms	Frequency, n (%)	1 (1.02%)	1 (1%)
	Severity	Mild	Mild
	Relationship with treatment	Unlikely	Unlikely
Increase in frequency of twisting of fingers	Frequency, n (%)	1 (1.02%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Aggravation of chronic tonsillitis and maxillitis	Frequency, n (%)	2 (2.04%)	–
	Severity	Mild	
	Relationship with treatment	Unlikely	
Acute gastroenteritis	Frequency, n (%)	1 (1.02%)	1 (1.02%)
	Severity	Mild	Mild
	Relationship with treatment	Unlikely	Unlikely
Punctate rash of unspecified nature and genesis, pruritus	Frequency, n (%)	1 (1.02%)	
	Severity	Mild	
	Relationship with treatment	Possible	

Adverse reactions in the list below had mostly unlikely causal relationship with medicinal product intake (Table 24). Only skin allergies reactions (rash and pruritus) had a possible causal relationship to Brillia for Children intake. The AEs listed may also be associated with the underlying disease and/or concomitant medicinal products. No AEs with certain causal relationship with medicinal product intake were registered in controlled clinical studies.

No cases of AEs with certain causal relationship to Ergoferon intake were registered in controlled clinical studies. Decision on inclusion of undesirable effects in patient's information leaflet and summary of product characteristic should be made on the basis of information from post-marketing safety studies, spontaneous reporting and safety monitoring.

10.2 Common Adverse Events (Brillia for Children, tablets)

Common adverse events with a p causal relationship with Brillia for Children were not registered.

10.3 Deaths (Brillia for Children, tablets)

Fatal cases during the treatment with Brillia for Children (12 weeks) were not registered (MMH-TD-001, TD1061511-01.18.P).

10.4 Other Serious Adverse Events (Brillia for Children, tablets)

In these studies, no serious AEs requiring therapy withdrawal, treatment with other medications or hospitalization were reported.

10.5 Other Significant Adverse Events (Brillia for Children, tablets)

No other significant AEs caused by Brillia for Children were observed.

10.6 Analysis of Adverse Events by Organ System or Syndrome (Brillia for Children, tablets)

Table 25. AEs according to MedDRA system organ class

LLT term/ code	**PT term/ code**	**HLT term/ code**	**HLGT term/ code**	**SOC term/ code**

Skin hyperemia/ 10040864	Erythema/ 10015150	Erythemas/ 10015151	Epidermal and dermal conditions/ 1001498	Skin and subcutaneous tissue disorders/ 10040785
Itching/ 10023084	Pruritus/ 10037087	Pruritus NEC/ 10049293		

AEs according to MedDRA system organ class are presented in Table 25. Since this is only a single case of reaction decision on inclusion undesirable effects in patient's information leaflet and summary of product characteristic should be made on the basis of information from post-marketing safety studies, spontaneous reporting and safety monitoring.

10.7 Narratives (Brillia for Children, tablets)

Serious AEs or deaths in patients who were administered Brillia for Children were not registered. Two (0.67%) patients were withdrawn from treatment group at the request of the parents.

11. Clinical Laboratory Evaluations (Brillia for Children, tablets)

The parameters of complete and biochemical blood counts and urinalysis were analyzed in patients before and after the treatment with Brillia for Children.

Changes in complete blood count (ESR, leucocytes, hemoglobin, erythrocytes) were not significant and/or did not exceed physiological ranges (Table 20).

Significant changes of biochemical blood assays after the course of therapy with Brillia for Children compared to baseline levels or normal physiological values were not recorded (Table 22). Thus, no pathological changes in liver, kidneys, pancreas were revealed in patients after the treatment with Brillia for Children.

Pathological changes in urinalysis after the course of treatment were not observed (Table 21).

Thus, changes of clinical and laboratory parameters were not significant and did not go beyond physiological deviations. By the nature of the influence on clinical and laboratory indices Brillia for Children is not inferior to placebo, indicating a high degree of safety of the drug.

12. Vital signs, Physical Findings, and Other Observations Related to Safety (Brillia for Children, tablets)

Experimental studies showed that Brillia for Children did not impact vital signs, structure, and functions of various organs and systems.

Brillia for Children did not impact HR, respiratory rate, arterial blood pressure (Table 15, 19). The differences in these parameters at visits and between groups were not significant and did not go beyond physiological ranges.

Clinical studies did not reveal adverse effect of Brillia for Children on vital signs. Physical and laboratory examinations indicate high safety of Brillia for Children.

13. Safety in Special Groups and Situations (Brillia for Children, tablets)

13.1 Intrinsic Factors (Brillia for Children, tablets)

In controlled clinical studies, no relationship between safety of Brillia for Children and age, sex, severity and duration of a disease, comorbidities were revealed.

Brillia for Children contains lactose monohydrate and is not recommended for treatment of patients with congenital galactosemia, glucose or galactose malabsorption syndrome, or congenital lactase deficiency.

13.2 Extrinsic Factors (Brillia for Children, tablets)

Influence of Brillia for Children on the body depending on external factors was not studied.

13.3 Drug Interactions (Brillia for Children, tablets)

Incompatibility or undesirable drug interactions of Brillia for Children were not observed.

13.4 Pregnancy and Lactation (Brillia for Children, tablets)

The safety of Brillia for Children in pregnancy and lactation was not studied. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It is unknown whether active substance of Brillia for Children and/or metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. As a precautionary measure, it is preferable to avoid the use of Brillia during pregnancy. Brillia should not be used during breast-feeding.

13.5 Overdose (Brillia for Children, tablets)

Up to the present day, no overdoses were registered. In case of accidental overdose dyspeptic reactions are possible due to the fillers.

13.6 Drug Abuse (Brillia for Children, tablets)

Long-term administration of Brillia for Children for 12 weeks did not cause tolerance and drug abuse. Due to the properties of Brillia for Children (ultra-low doses of antibodies to brain-specific protein S-100) drug abuse is not possible.

13.7 Withdrawal and Rebound (Brillia for Children, tablets)

After the completion of Brillia for Children treatment, withdrawal syndrome was not reported.

13.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability (Brillia for Children, tablets)

Since Brillia for Children exhibits no hypnogenous and myorelaxant effects, it does not impair ability to drive or operate potentially dangerous machinery or perform activities requiring increased attention and prompt reactions.

Brillia for Children reduces manifestations of anxiety and improves psycho-emotional state of patients.

14. Post-marketing Data (Brillia for Children, tablets)

Over the past period, serious AEs associated with drug administration were not reported. Single cases of non-serious adverse reactions included allergic reactions, erythema, headache, weakness, lack of efficacy, increased hyperactivity and other. Causal relationship to Brillia for Children intake was defined as unlikely, conditional, possible or probable/likely. These reactions were mild, self-limiting and resolved with no sequelae. At the present time there were no reports on adverse reactions with certain causal relationships to the administration of Brillia for Children.

The adverse reactions detected during the reporting period represent isolated single cases, not reliably attributable to the product and having no impact on the benefit-risk profile. Most of these reactions are hypersensitivity manifestations (erythema or other allergic reactions) or are attributed to the primary disease (epilepsy, birth trauma, hyperactivity disorder). No safety risks were identified.

15. Summary of Biopharmaceutical Studies and Associated Analytical Methods (Brillia for Children, tablets)

Biopharmaceutical studies (bioavailability, bioequivalence) of Brillia for Children and its active components (affinity purified antibodies to brain-specific protein S-100/lapine S-100 immune globulin) were not conducted. The sensitivity of modern physico-chemical methods of analysis (gas-liquid chromatography, high performance liquid chromatography, gas chromatography-mass spectrometry) does

not allow quantitative evaluation of active substances in body fluids, tissues and organs, which makes bioavailability and bioequivalence studies of Brillia for Children technically unfeasible.

According to Part II of the Directive 2003/63/EC of the European Parliament and of the Council dated 25.06.2003 (with amendments to the Directive 2001/83/EC of the European Parliament and the Council on the Community code concerning medicinal products for human use) the absence of some data on the studied drug is acceptable, if the current state of scientific knowledge does not allow performance of appropriate studies.

16. Summary of Clinical Pharmacology Studies (Brillia for Children, tablets)

Clinical pharmacology studies (study of pharmacokinetics, pharmacodynamics) of Brillia for Children and its active components (affinity purified antibodies to brain-specific protein S-100/lapine S-100 immune globulin) were not carried out. The sensitivity of modern physico-chemical methods of analysis (gas-liquid chromatography, high performance liquid chromatography, gas chromatography-mass spectrometry) does not allow quantitative evaluation of active components of the drug in body fluids, tissues and organs, which make it impossible to conduct technical studies of pharmacokinetics and pharmacodynamics of Brillia for Children.

According to Part II of the Directive 2003/63/EC of the European Parliament and of the Council dated 25.06.2003 (with amendments to the Directive 2001/83/EC of the European Parliament and the Council on the Community code concerning medicinal products for human use) the lack of some data on the drug is allowed if the current state of science does not allow performance of appropriate studies.

17. Appendix

Lavrentieva G.P. and Titarenko T.M. Questionnaire
Helps to identify an anxious child in a group of peers.
Questions for parent:
1. Child can't work for a long time without getting tired.
2. It is difficult for him to concentrate on something.
3. Any task causes unnecessary concern.
4. During the execution of tasks he/she is very tense, constrained.
5. More embarrassed than others.
6. Often speaks of tense situations.
7. Generally blushes in an unfamiliar setting.
8. Complains that he has terrible dreams.
9. His hands are usually cold and wet.
10. He often has stool disturbances.
11. Sweats heavily when worried
12. Does not have a good appetite.
13.He sleeps restlessly, falls asleep with difficulty.
14. Shy, a lot of things frighten him.
15. Usually restless, easily upset.
16. Often cannot hold back tears.
17. Poorly endures waiting.
18. He does not like to take up a new business.
19. Not confident in himself, in his abilities.
20. Afraid to face difficulties.

Summarize the number of "pluses" to get a total anxiety score.
High anxiety - 15 - 20 points;
Average anxiety —7 - 14 points;
Low anxiety - 1-6 points.

18. References (Brillia for Children, tablets)

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition, Text Revision. 4th ed. Washington, DC: APA Press; 2000.
2. Arena J, Rozenbaum J. Pharmacotherapy of mental disorders: Tr. from English. M.: Binom, 2004. 416 p.
3. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents, American Academy of Pediatrics, 2011.
4. Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use.
5. Constitution of the World Health Organization. Geneva, Official records of WHO, No. 2:100.
6. Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
7. Donato R., Cannon B.R., Sorci G., Riuzzi F., Hsu K., Weber D.J., and Geczy C.L. Functions of S100 Proteins. Curr Mol Med. 2013 January;13(1):24–57.
8. Edwards SL, Rapee RM, Kennedy SJ, Spence SH. The assessment of anxiety symptoms in preschool-aged children: the revised Preschool Anxiety Scale. J Clin Child Adolesc Psychol. 2010;39(3):400-9.
9. Guidelines for experimental (preclinical) studies of new pharmacological agents. Ed. Habriev RU. M.: OJSC "Publishing House "Medicine", 2005. 832 p.
10. Keeton CP, Kolos AC, Walkup JT. Pediatric generalized anxiety disorder: epidemiology, diagnosis, and management. Paediatr Drugs. 2009;11(3):171-83.
11. Khodarev SV. Approaches to the diagnosis and correction of anxiety disorders in children / Khodarev SV, Poddubnaya TM, Simaeva AR. Curr Pediat Iss. 2002;1(4):92-4.
12. Liberman LC, Lipp OV, Spence SH, March S. Evidence for retarded extinction of aversive learning in anxious children. Behav Res Ther. 2006;44(10):1491-502.
13. Mash E, Wolf D. Children's psychopathology: Violations of the child's mind: Trans. from English. St. Petersburg: Prime-Evroznak, 2003. 384 p.
14. Mosholder AD, Gelperin K, Hammad TA, Phelan K, Johann-Liang R. Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. Pediatrics. 2009;123(2):611–6.
15. Sawyer MG, Pfeiffer S, Spence SH. Life events, coping and depressive symptoms among young adolescents: a one-year prospective study. J Affect Disord. 2009 Sep;117(1-2):48-54.
16. Shear MK, Bjelland I, Beesdo K, Gloster AT, Wittchen HU. Supplementary dimensional assessment in anxiety disorders. Int J Methods Psychiatr Res. 2007;16(Suppl 1):S52-64.
17. Shmakova OP. School adaptation of children and adolescents with psychiatric disorders: Abs. Ph.D. M., 2004. 24 p.
18. Swanson J, Elliott GR, Greenhill LL, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry. 2007;46(8):1015–27.
19. Wenar Ch, Kering P. Psychopathology of childhood and adolescence. Developmental psychopathology: Tr. from English. St. Petersburg.: Prime-Evroznak, 2004. 384 p.
20. Zavadenko NN. Attention deficit hyperactivity disorder in children: diagnosis and treatment. Russian medical J. 2006;14(1):51-6.