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EDMS-PSDB-1718058 **Date:** 11-Jul-2002

Identification of original report

CLINICAL RESEARCH REPORT			
R - number:	R064766	**Non-proprietary name:**	Risperidone
EDMS-BEBE-3202516		**Report date:**	25 October 2001
Title:	The long-term safety and efficacy of Risperdal® in conduct disorder in mild, moderate and borderline mentally retarded children aged 5 to 14 years. Final report.		
Authors:	G. De Smedt, Y. Xie, B. Lyons, L. Goscinsky, A. Glass, L. Masukawa, M. Eerdekens		
Department:	Global Biometric Sciences and Reporting Global Clinical Pharmacokinetics and Clinical Pharmacology Global Clinical Research and Development and Regulatory Affairs/ Pharmacovigilance, Worldwide		
Trial number:	RIS-INT-41	**Clinical phase:**	III
Trial dates:	Start: 18 March 1997— end: 10 July 2001		
Investigator:	Multicenter		

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Amendment 1: 15 May 2002 (Amendment at the end of the document)

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PLAINTIFF'S EXHIBIT 12

EXHIBIT P-12
Date:
M.L. GRAY, CSR, RPR

JANSSEN RESEARCH FOUNDATION
a division of Janssen Pharmaceutica N.V.

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SYNOPSIS

Trial identification

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Risperdal® **Active ingredient**: risperidone (R064766)		
Title: The long-term safety and efficacy of Risperdal® in conduct disorder in mild, moderate and borderline mentally retarded children aged 5 to 14 years. Final report.	**Trial No.**: RIS-INT-41 **Clinical phase**: III	
Investigator: Multicenter	**Country**: International	
Reference: JRF, Clinical Research Report RIS-INT-41, October 2001 (EDMS-BEBE-3202516)		
Trial period: Start: 18 March 1997 End: 10 July 2001	**No. of investigators**: 89 **No. of patients entered**: 504	

Protocol summary

Indication / objectives: Conduct and other disruptive behavior disorders in children and adolescents 5 to 14 years of age inclusive with borderline intellectual functioning or mild to moderate mental retardation/ to assess the safety of 0.02 to 0.06 mg/kg/day of oral risperidone. Long-term efficacy was also explored.

Trial design: Multinational, multicenter, open-label, single-group, long-term follow-on trial with a 1-week placebo run-in phase.

Main selection criteria:

- Inclusion criteria:
  - Patients with a DSM-IV, Axis I diagnosis of Conduct Disorder (312.8); or Oppositional Defiant Disorder (313.81); or Disruptive Behavior Disorder not otherwise specified (312.9); and a total rating of ≥ 24 in the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (parent version), as assessed at Visits 1 and 3. Patients who fulfilled this criterion, and, in addition, had Attention Deficit/Hyperactivity Disorder (314.xx; 314.9), were eligible for entry. The Conduct Problem subscale score for those patients who had participated in RIS-CAN-19 was to be waived for inclusion into this trial.
  - Patients with a DSM-IV, Axis II diagnosis of Mild Mental Retardation (317), Moderate Mental Retardation (318.0) or Borderline Intellectual Functioning (V62.89). These 3 diagnoses represent IQs ranging from 84 to 35 inclusive.
  - Patients with a Vineland Adaptive Behavior Scale score of ≤84, except those patients who had participated in RIS-CAN-19.
  - Between 5 and 14 years of age (extremes included).
  - Informed consent form had been signed.
  - Patient was healthy based on a pre-trial physical examination, medical history and electrocardiogram (ECG).
  - A responsible person was available to accompany the patient to the investigator site on each assessment day as scheduled in the flow chart, was able to provide reliable information for the rating scales and was able to reliably and accurately dispense the trial medications as directed.
  - Patients who had participated in RIS-CAN-19 should have completed at least 2 weeks (14 days) of double blind medication.
  - Current symptoms requiring antipsychotic treatment in the opinion of an independent investigator (Germany only).
    Note: Patients could be inpatients or outpatients.

Main selection criteria (continued)

- Exclusion criteria:
  - Patients who had a diagnosis of Pervasive Development Disorder (299.00; 299.80; 299.10).
  - Patients who had a diagnosis of Schizophrenia and Otber Psychotic Disorders (295.xx; 297.xx; 298.8; 293.xx).
  - Head injury as a cause of mental impairment.
  - Note: Head injury attributed to birth trauma was not excluded. Birth trauma was defined as any event occurring before delivery of tbe placenta.
  - Seizure disorder currently requiring medication.
  - Use of disallowed concomitant therapy.
  - Females of childbearing potential engaging in sexual activity who were not on medically validated birth control method (e.g., double barrier, intrauterine device, oral contraceptives, Norplant,® DepoProvera®).
  - Participation in an investigational drug trial within 30 days before the start of the trial, except those patients who had participated in RIS- CAN-19.
  - Laboratory values outside the normal range. If the results of tbe biochemistry, hematology tests and the urinalysis testing were not within the laboratory's reference ranges, the patient could be included only on condition that the principal investigator judged that the deviations were not clinically relevant.
  - Known sensitivity to risperidone.
  - Serious or progressive illnesses, including, but not limited to: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal or endocrine disturbances.
  - History of tardive dyskinesia, neuroleptic malignant syndrome or known hypersensitivity to neuroleptics.
  - Patients known to be HIV-positive.
  - Patients who had previously received risperidone for Conduct Disorder for less than 3 weeks and discontinued use of risperidone due to lack of efficacy or due to adverse events. Patients who had completed at least 2 weeks of RIS-CAN-19 treatment and who were discontinued due to lack of efficacy were allowed to enter RIS-INT-41.
  - Patients who had previously been successfully treated with risperidone for this condition, except those patients who had participated in RIS-CAN-19.
  - Patients who experienced a bypersensitivity reaction or suspected hypersensitivity reaction to the trial medication administered in RIS-CAN-19.
  - The time elapsed since completing or discontinuing from RIS-CAN-19 exceeded 3 weeks.

Treatment	
Form – dosing route	solution – oral
Medication	Risperidone 1.0 mg/mL
Batch number	96I24/321, 96J01/F71, 97A24/F71, 97A29/956, 97F24/918, 97F25/917, 97F25/919, 98H14/799, 98L16/F71, 99A18/672, 99F07/588, 99H09/391
Dosage	0.02 to 0.06 mg/kg/day once daily in the morning or afternoon
Duration of treatment	1 year
Duration of trial	18 March 1997 – 10 July 2001

Treatment (continued)	
Disallowed medication	- All antipsychotics (other than risperidone), antidepressants, lithium, carbamazepine and valproic acid were prohibited. - Psychostimulants (e.g., methylphenidate, pemoline, dexedrine) were allowed for the treatment of ADHD. Other medication to treat ADHD, including but not limited to drugs such as clonidine or guanfacine, were prohibited. - All anticholinergic medication was to be discontinued at entry; introduction of anticholinergic medication during the trial was allowed in the case of emergent extrapyramidal symptoms. - Patients who were receiving a sedative/ hypnotic for sleep before the screening visit were allowed to continue; clonidine and other prescribed agents were not allowed to treat sleep difficulties. - It was permitted to use pre-medication, e.g., benzodiazepines, to facilitate the execution of medical procedures, where required. - Medication for organic disorders was to be kept as constant as possible during the trial period.

Assessments	Screen	Placebo run-in	Base-line	Week 1	2	3	4	Month 2	3	4	5	6	9	12
Day	-10 to -7	-7	1	7	14	21	28							
Visit	1*	2*	3	4	5	6	7	8	9	10	11	12	13	14
Informed Consent	x													
Medical History	x													
Physical Exam.	x								x			x		x
Weight			x				x		x			x		x
Psychiatric History	x													
IQ-Stanford Binet or Wechsler	x													
Vineland Adaptive Behavior Scale	x													
Vital signs	x		x	x	x	x	x	x	x	x	x	x	x	x
ECG	x								x‡			x		x
Lab safety, growth hormone, prolactin	x						x[a]		x[a]			x[a]	x[a]	x[a]
Tanner Staging			x									x		x
Child Symptom Inventory	x													
Nisonger Child Behavior Rating Form	x		x	x	x	x	x	x	x	x	x	x	x	x
Aberrant Behavior Checklist	x		x	x	x	x	x	x	x	x	x	x	x	x
Clinical Global Impression			x	x	x	x	x	x	x	x	x	x	x	x
Visual Analogue Scale			x	x	x	x	x	x	x	x	x	x	x	x
Extrapyramidal Symptom Rating Scale			x	x	x	x	x	x	x	x	x	x	x	x
Cognitive tests			x									x		x
Plasma level	x						x[b]					x[b]		x[b]
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x
Concomitant therapy			x	x	x	x	x	x	x	x	x	x	x	x
Dispense medication[c]		x	x	x	x	x	x	x	x	x	x	x	x	x

* Visits 1 and 2 did not need to be performed for patients who had participated in RIS-CAN-19. The evaluations from the Endpoint of RIS-CAN-19 could be used for the Baseline visit (Visit 3) if the time elapsed since the Endpoint of RIS-CAN-19 was ≤7 days.

‡ Only valid for the patients in the Hungarian centers Szeged and Baja

[a] Prolactin and Growth Hormone samples to be taken at trough level, i.e., 24 hours after previous dose or just before the next dose.

[b] Trough level, i.e., 24 hours after last dose or just before the next dose.

[c] Collect unused medication at each visit from Visit 3 to Visit 14.

Statistical methods	Intent-to-treat analysis. Descriptive statistics, paired t-test, Wilcoxon matched-pairs signed-ranks test.

Main features of the patient sample and summary of the results

Baseline characteristics – patient disposition	
Number of patients randomized (M/F)	419/85
Age: mean ±SE, yrs	9.7 ± 0.11
Age: median (min-max), yrs	10 (4; 14)
Height ±SE (cm):	139.8 ± 0.72
Weight ±SE (kg):	36.3 ± 0.61
Body mass index ±SE (kg/m^2):	17.9 ± 0.16
Axis I Diagnosis: n (%)	
Attention deficit hyperactivity disorder (ADHD)	10 (2.0%)
ADHD + Behavior disorder NOS	51 (10.1%)
ADHD + Conduct disorder	105 (20.8%)
ADHD + Oppositional defiant disorder	95 (18.8%)
Behavior disorder NOS	33 (6.5%)
Conduct disorder	120 (23.8%)
Oppositional defiant disorder	90 (17.9%)
Axis II Diagnosis: n (%)	
Borderline intellectual functioning	189 (37.6%)
Mild mental retardation	217 (43.1%)
Moderate mental retardation	97 (19.3%)
Discontinuation of treatment – reason: n (%)	
- Adverse event	43 (8.5%)
- Patient lost to follow-up	26 (5.2%)
- Patient withdrew consent	22 (4.4%)
- Insufficient response	18 (3.6%)
- Patient non-compliant	17 (3.4%)
- Other	8 (1.6%)
- Patient ineligible to continue trial	2 (0.4%)
- Patient asymptomatic/ cured	1 (0.2%)

NOS: not otherwise specified

Exposure	
Mean mode daily dose ±SE (min-max)	1.69 ± 0.04 mg/day (0.1 – 4.8 mg/day) or 0.02 ± 0.0007 mg/kg/day
Mean treatment duration ±SE (min-max)	307.3 ± 5.0 days on drug (1-505 days)

Min-max: minimum-maximum

Drug concentrations: Final pharmacokinetic data will be provided in an amendment to this report.

Efficacy	Risperidone ITT[a] patients (N=496)				
			Change from open-label baseline		
	n	Mean ± SE	Mean ± SE[b]	95% CI[c]	p-value[d]
Primary variable					
• Conduct Problem Subscale of the Nisonger-Child Behavior Rating Form (N-CBRF)					
Baseline	487	32.9 ± 0.3			
Endpoint	496	17.0 ± 0.5	-15.8 ± 0.5	(-16.8 ; -14.8)	<0.001
Secondary variables					
• Other subscales of the N-CBRF at Endpoint					
Compliant/calm	496	8.6 ± 0.2	3.4 ± 0.2	(3.1 ; 3.8)	<0.001
Adaptive/social	496	6.4 ± 0.1	1.9 ± 0.1	(1.6 ; 2.2)	<0.001
Insecure/anxious	496	10.4 ± 0.3	-5.7 ± 0.4	(-6.4 ; -4.9)	<0.001
Hyperactive	496	11.2 ± 0.3	-6.8 ± 0.3	(-7.4 ; -6.2)	<0.001
Self-injury/stereotyped	496	1.5 ± 0.1	-1.0 ± 0.2	(-1.3 ; -0.7)	<0.001
Self-isolated/ritualistic	496	3.4 ± 0.2	-1.7 ± 0.2	(-2.0 ; -1.3)	<0.001
Overly sensitive	496	5.4 ± 0.2	-2.1 ± 0.2	(-2.4 ; -1.8)	<0.001
• Aberrant Behavior Checklist (ABC) at Endpoint					
Total ABC	453	37.4 ± 1.3	-28.3 ± 1.4	(-31.0; -25.6)	<0.001
Irritability	475	11.5 ± 0.4	-7.9 ± 0.5	(-8.8 ; -7.1)	<0.001
Lethargy/social withdrawal	471	5.0 ± 0.3	-2.5 ± 0.3	(-3.2 ; -1.9)	<0.001
Stereotypic behavior	482	1.8 ± 0.2	-1.3 ± 0.2	(-1.7 ; -0.9)	<0.001
Hyperactivity	469	17.3 ± 0.5	-14.0 ± 0.6	(-15.2 ; -12.9)	<0.001
Inappropriate speech	493	2.4 ± 0.1	-1.5 ± 0.1	(-1.7 ; -1.2)	<0.001
• Visual Analogue Scale of the most troublesome symptom at Endpoint	480	33.9 ± 1.1	-40.3 ± 1.3	(-42.8 ; -37.8)	<0.001

Efficacy (continued) • Clinical Global Impression of change in patients' condition	The number of patients with no or mild symptoms increased over time. Three hundred twenty patients (66.3%) showed no, very mild or mild symptoms at Endpoint compared with 28 (5.8%) with very mild or mild symptoms at Baseline. Changes were mostly observed during the first 4 weeks of treatment, thereafter the scores remained stable.				
	ITT[a] patients				
			Change from open-label baseline		
Efficacy	n	Mean ± SE	Mean ± SE[b]	95% CI[c]	p-value[d]
• Subgroup analyses of N-CBRF Conduct Problem subscale score					
- Subgroup analyses by DSM-IV Axis I (diagnosis group) at Endpoint					
Conduct disorder	221	17.1 ± 0.8	-15.8 ± 0.8	(-17.4 ; -14.2)	<0.001
Oppositional defiant disorder	183	17.4 ± 0.8	-16.3 ± 0.9	(-18.1 ; -14.6)	<0.001
Disruptive behavior disorders not otherwise specified	82	16.4 ± 1.2	-14.6 ± 1.1	(-16.9 ; -12.3)	<0.001
- Subgroup analyses by Axis II diagnosis (degree of mental retardation)					
Mild mental retardation	214	17.1 ± 0.8	-15.7 ± 0.8	(-17.3 ; -14.1)	<0.001
Moderate mental retardation	96	14.0 ± 1.1	-18.0 ± 1.1	(-20.1 ; -15.8)	<0.001
Borderline intellectual functioning	185	18.5 ± 0.8	-14.9 ± 0.9	(-16.6 ; -13.2)	<0.001
- Subgroup analyses by patients who took/did not take psychostimulants					
Took psychostimulants	81	17.0 ± 1.3	-14.9 ± 1.4	(-17.7 ; -12.2)	<0.001
Did not take psychostimulants	415	17.0 ± 0.5	-16.0 ± 0.6	(-17.1 ; -14.9)	<0.001

[a]ITT: intent-to-treat, [b]SE: standard error; [c]CI: confidence interval; [d]Two-sided p-value for paired t-test on change from open-label Baseline.

Safety (n = number of patients with data)	
Adverse events (AE)	N=504
Most frequently reported AE: n (%)	
• Somnolence	149 (29.6%)
• Rhinitis	137 (27.2%)
• Headache	110 (21.8%)
• Weight increase	87 (17.3%)
• Upper respiratory tract infection	83 (16.5%)
No. (%) with one or more AE	462 (91.7%)
No. (%) of deaths	0 (0.0)
No. (%) with one or more serious AE (SAE)	67 (13.3%)
No. (%) treatment stopped due to AE	43 (8.5%)
No. (%) with one or more severe AE	74 (14.7%)
No. (%) with one or more EPS-related AE	108 (21.4%)

Safety (continued)	
Extrapyramidal symptoms (EPS)-like AEs	EPS-related AEs were reported by 21.4% of all patients. Eight patients had serious EPS-related AEs and 6 patients discontinued treatment due to EPS-related AEs. Reversible tardive dyskinesia was reported by 2 patients. Few patients took anti-EPS medication (n=5).
Extrapyramidal Symptom Rating Scale (ESRS)	The overall level of EPS was very low. The majority of patients did not show any ESRS scores different from zero at any time point during the trial. The mean total score at Baseline was 1.2. The mean total ESRS score decreased during treatment and was 0.8 at Endpoint (p=0.024).
Clinical laboratory parameters	Except for a transient increase in prolactin, there were no consistent changes in routine laboratory safety parameters.
Prolactin	There was an increase in mean prolactin levels from Screening to Week 4. Mean levels increased from 7.7 ng/mL to 28.2 ng/mL in males, and from 10.4 ng/mL to 35.4 ng/mL in females. The levels decreased from Week 4 onward, close to the normal range in boys and within the normal range in girls: 16.1±0.6 ng/mL in boys (laboratory upper limit of normal 13 ng/mL), and 21.6±2.7 ng/mL in girls (laboratory upper limit of normal 23 ng/mL). Thirty-three patients (6.6%) reported physical symptoms that could be related to elevated prolactin levels.
Vital signs	Overall, there were small changes in vital signs during the trial but these were not clinically relevant.
ECG	There were no clinically relevant changes in ECG results.
Body weight	Body weight increased by an average of 7.0±0.2 kg from Baseline to Endpoint, of which 4.8 kg might be expected in growing children (National Center of Health Statistics, NCHS). The increase in body mass index (BMI) was 1.8±0.1 kg/m^2 at Endpoint, of which 0.6 kg/m^2 might be attributed to a natural increase in BMI (NCHS). The greatest increase in BMI was observed during the first 3 months of treatment and remained stable thereafter. Obesity was reported for 4 patients (0.8%). Weight increase led to permanent discontinuation in 9 patients (1.8%).
Physical examination	No clinically relevant changes were observed.
Tanner staging	No deviations from normal were observed.
Changes in cognitive function - Modified verbal learning test - Continuous performance task	There were no negative effects on cognitive function. There were small increases in the number of items recalled in the short and long delay free recall tests and the overall number of items correctly recognized and correctly not recognized at Week 12 and Endpoint (p<0.001). There were increases in the total number of hits from Baseline to the end of the trial, and decreases in the total number of false alarms and misses, both in the easy and in the hard version of the task (p<0.001). The changes were of minor clinical relevance and indicated improvement rather than deterioration in cognitive function.

Conclusions

The results of the present trial demonstrate that risperidone was effective in the treatment of conduct and other disruptive behavior disorders in children and adolescents 5 to 14 years of age with borderline intellectual functioning or mild to moderate mental retardation. A review of all adverse events, extrapyramidal symptoms, laboratory parameters, vital signs and body weight showed that long-term treatment was safe and well tolerated.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ABC:	Aberrant Behavior Checklist
ADHD:	Attention Deficit/Hyperactivity Disorder
AE:	Adverse event
ALT:	Alanine transaminase
AST:	Aspartate transaminase
ATC:	Anatomic Therapeutic Chemical
BMI:	Body mass index
bpm:	Beats per minute
CI:	Confidence interval
CGI:	Clinical Global Impression
CRF:	Case report form
CSI:	Child Symptom Inventory
DBP:	Diastolic blood pressure
DSM-IV:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG:	Electrocardiogram
EDTA:	Ethylenediaminetetraacetic acid
EPS:	Extrapyramidal symptom
ESRS:	Extrapyramidal symptom rating scale
γ-GT:	Gamma glutamyltranspeptidase
GCP:	Good Clinical Practice
GH:	Growth hormone
HIV:	Human immune deficiency virus
ICH:	International Conference on Harmonization
ITT:	Intent-to-treat
IQ:	Intelligence quotient
JRF:	Janssen Research Foundation
LDH:	Lactate dehydrogenase
N-CBRF:	Nisonger Child Behavior Rating Form
PRI:	Pharmaceutical Research Institute
QTcB:	QT interval corrected according to Bazett's formula
QTcF:	QT interval corrected according to Fridericia's formula
QTcL:	Linear correction of QT interval according to Sagie
QTcL-2:	Linear correction of QT interval according to Sagie, using estimated slope
RBC:	Red blood cell
SAE:	Serious adverse event
SBP:	Systolic blood pressure
SE:	Standard error
SGOT:	Serum glutamic oxaloacetic transaminase
SGPT:	Serum glutamic pyruvic transaminase
SOP:	Standard operating procedure
VAS:	Visual Analogue Scale
WBC:	White blood cell

Definitions of terms

Tables referenced in text are either in-text tables, with the title format Table #, or SAS source tables, with the title format, e.g., Display SUB.# INT-41 and are provided as supporting data in Section 11. All listings are available in Appendix 3. Individual data for serious adverse events and for laboratory values beyond the predefined values are also provided in Annex 2 (Listing SAF.AE.3) and Annex 3 (SAF.LAB.2A and SAF.LAB.2B), respectively.

ETHICS

Ethics Committee / Institutional Review Board

The trial protocol and its amendments were reviewed by an independent Ethics Committee/ Institutional Review Board.

Ethical conduct of the trial

The trial was conducted in accordance with the declaration of Helsinki and its subsequent revisions.

Patient information and consent

At the first visit, the patients, or their legal representatives, gave their consent to participate in the trial after having been informed about the nature and purpose of the trial, participation and termination conditions, and risks and benefits.

INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

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- Trial co-ordination: A. Schotte, Ph.D., S. Gelerstein, Ph.D.

Clinical Operations

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1. INTRODUCTION

Conduct and other disruptive behavior disorders are among the most common and severe psychiatric disorders of childhood, with a prevalence of 6% in children and adolescents. Their main characteristic is a repetitive and persistent pattern of dissocial, aggressive or defiant behavior that involves major violations of age-appropriate expectations or norms. Examples of the behaviors on which the diagnoses are based include excessive levels of physical fighting, theft, vandalism, fire-setting, running away, truancy, frequent and severe temper tantrums, and disobedience. These children often traverse multiple social services, from mental health agencies, through special educational services to the juvenile justice system.[1,2]

Children with an intelligence quotient (IQ) below 85 have approximately a 5-fold increased risk of presenting with severe behavior problems, including Conduct and other disruptive behavior disorders. The prevalence of these disorders increases in inverse proportion to intellectual level, with estimates of the prevalence increasing up to 20-50% in mentally retarded patients.[3,4]

There have been many different approaches to the treatment of conduct and other disruptive behavior disorders, including drug therapy, behavioral treatment, psychotherapy, cognitive and social learning. The first report of the use of a neuroleptic drug for conduct disorder appeared in 1955 when chlorpromazine was prescribed for this purpose.[5] Since then virtually every available psychotropic drug has been administered to people with developmental disabilities, and numerous drug trials have been conducted. While a body of promising evidence exists indicating that neuroleptics may be beneficial in treating conduct disorder in mental retardation, the evidence is not conclusive as most of the studies have been open-label in design. There is a need to conduct placebo controlled, double-blind, randomized trials, using validated instruments to assess drug effect.[5,6,7,8]

Results from a number of small trials and anecdotal information indicate that risperidone may be useful in treating symptoms such as aggression, self-injury and stereotypes. Van den Borre et al.[9] demonstrated that risperidone, as add-on therapy, brought about significant improvement in the conduct of mentally retarded adult and adolescent patients compared to placebo as measured on the Aberrant Behavior Checklist (ABC) and Clinical Global Impression (CGI). Findling reported a superior effect of risperidone over placebo in the treatment of conduct disorder in a group of children with normal IQ.[10] In a small (n=7) open-label trial,[11] autistic children who all had a degree of mental retardation with the exception of 1 patient, risperidone showed positive results in modifying conduct disorder as measured on the Ritvo-Freeman Real Life Rating Scale,[12] the ABC, CGI and Visual Analogue Scale (VAS) of the most troublesome target symptom. The mean dose was 0.035 mg/kg/day with a range of 0.014 to 0.072 mg/kg/day. Four of these

7 patients were followed-up over a period of 12 months.[13] The treatment effect was sustained throughout the 12 months without apparent ill effect. In another small, double-blind, placebo controlled trial, similar results were attained in a population of mentally retarded children and adolescents.[14] The dose of risperidone ranged from 0.03 to 0.06 mg/kg/day. Sabaratnam reported on a series of 7 adult cases with varying degrees of learning disabilities and autistic spectrum disorders that responded favorably to risperidone.[15]

Mandoki has questioned whether children and adolescents may be more sensitive to extrapyramidal side effects; however, controlled data is lacking. He emphasized the need to generate reliable data in children and adolescents.[16] Simeon et al., treated 7 children 11 to 17 years of age with risperidone for 3 to 15 months in a dose range of 1 to 4 mg daily. This dosage was well tolerated. Two patients experienced sedation and drowsiness when given 6 mg daily. The symptoms resolved when the dose was reduced.[17]

The dosing information obtained in several trials was taken into consideration in selecting a dose range of 0.02 to 0.06 mg/kg/day for further evaluation. Studies in elderly patients with dementia showed that at low doses (1 mg/day), risperidone had beneficial effects on disruptive behavior and was associated with few extrapyramidal symptoms (EPS).[18,19] The results of study RIS-BEL-21 showed that the pharmacokinetics of risperidone are similar in adults and children,[20] and that no dose adaptations were needed. A Phase II program was set up to assess the efficacy and tolerability of relatively low doses of risperidone in the treatment of children with conduct and other disruptive behavior disorders. Two Phase II trials have been carried out in children who received oral risperidone 0.01 to 0.1 mg/kg/day. In RIS-BEL-22, an open-label dose-titration study, risperidone (0.01-0.12 mg/kg/day) treatment (0.03 mg/kg/day at Endpoint, range 0.01-0.06 mg/kg/day) resulted in clinically relevant improvement in children with Autistic Disorder.[11] In RIS-BEL-24, a double-blind placebo-controlled study, risperidone (0.05 mg/kg/day at Endpoint, range 0.03-0.06 mg/kg/day) was significantly more effective than placebo in controlling behavioral disturbances and was not associated with an increase in EPS in mentally retarded children.[14]

The objective of this open-label trial was to accumulate safety and efficacy data on the long-term (1 year) use of low-dose risperidone in conduct and other disruptive behavior disorders in children and adolescents 5 to 14 years of age with mild to moderate mental retardation or borderline intellectual functioning. Conduct and other disruptive behavior disorders are characterized in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).

An interim analysis of this study included all patients who entered the study before 31 July 1999.[21] The present report deals with the results of the final analysis of the total patient sample.

2. TRIAL OBJECTIVES

The primary objective of the present trial was to assess the long-term (1-year) safety of 0.02 to 0.06 mg/kg/day of an oral solution of risperidone in conduct and other disruptive behavior disorders in children and adolescents 5 to 14 years of age (inclusive) with borderline intellectual functioning or mild to moderate mental retardation. Long-term efficacy was also explored.

3. PATIENTS AND METHODS

3.1. Trial design

3.1.1. OVERALL TRIAL DESIGN AND PLAN

This was an open-label trial to investigate the safety and efficacy of 0.02 to 0.06 mg/kg/day of an orally administered liquid solution of risperidone in conduct and other disruptive behavior disorders in children and adolescents 5 to 14 years of age (inclusive) with borderline intellectual functioning or mild to moderate mental retardation (defined as an IQ of 35 to 84).

At Screening, patients had to score 24 or more on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF). A score of 24 approximates the 70th percentile according to the norms published by Tassé et al.[22] A substantial number of children referred to clinics with conduct disorder also have Attention Deficit/Hyperactivity Disorder (ADHD).[2] Patients with ADHD were eligible for entry into the trial if they scored 24 or more on the Conduct Problem subscale of the N-CBRF, and if they met all other selection criteria.

Patients underwent a 1-week placebo run-in period in order to identify placebo responders. Patients had to score ≥24 on the conduct subscale of N-CBRF and ≤84 on the Vineland Adaptive Behavior Scale[23] at Baseline to qualify for the trial, *except those patients who had participated in RIS-CAN-19.*[1] All patients who qualified for participation at Baseline were given open-label treatment with risperidone for 1 year.

The primary efficacy parameter was the change versus Baseline on the Conduct Problem subscale of the N-CBRF. Secondary efficacy parameters were CGI severity, change versus Baseline on the total score of the ABC and the irritability subscale of the ABC, change versus Baseline on the other

[1] Text in italics was added following protocol amendment dated 16 September 1998.

subscales of the N-CBRF, and change versus Baseline on the VAS of the most troublesome symptom.

Safety assessments included Extrapyramidal Symptom Rating Scale (ESRS),[24] adverse event monitoring, ECG, vital signs, body weight and laboratory assessments including determination of prolactin and growth hormone (GH) levels. In addition, the impact of the treatment on attention and verbal memory was assessed via a verbal learning test based on the California Learning Test-Children's Version and the Continuous Performance Task.

The flow chart in section 3.4.1 shows the timing of assessments.

3.1.2. DISCUSSION OF TRIAL DESIGN

There is no recognized pharmacologic treatment for conduct and other disruptive behavior disorders. Data from poorly designed trials plus anecdotal information has led to the use of various classes of medication for this condition, including antipsychotics, alpha-blockers, beta-blockers, lithium, carbamazepine, antihistamines and stimulants. Antipsychotics are among the most frequently prescribed drugs for this condition, however, few well-designed trials have been conducted and thus the perceived benefits have not been proven.[5,7,8]

Results from a few small pilot trials and anecdotal information indicate that risperidone may be effective in positively modifying conduct disorder in mild, moderate and borderline mental retardation.[9,11,13,14,15,16] Placebo controlled, double-blind trials to test this hypothesis were in progress at the time that the protocol of the present trial was being written (RIS-USA-93, RIS-CAN-19[25,26]). Bearing in mind that conduct and other disruptive behavior disorders are chronic conditions, the safety and efficacy of long-term treatment needs to be determined. The purpose of this open-label trial was to gather such data.

3.1.3. CHANGES IN THE CONDUCT OF THE TRIAL OR PLANNED ANALYSES

The following protocol amendments were made:

1. A local amendment, dated 20 January 1997, that was valid for Germany only, was issued to add the following inclusion criterion (see section 3.2.2):

- Current symptoms requiring antipsychotic treatment in the opinion of an independent investigator.

2. An international amendment, dated 21 February 1997, described a change in the Adverse Event reporting procedure in order to be compliant with the internationally implemented JRF/PRI-GCP-SOPs. In this amendment, the wording of the definitions of "adverse event," "serious adverse event,"

"unlisted (unexpected) adverse event," "life-threatening adverse event" and "adverse event associated with the use of the drug" was changed according to ICH guidelines. In addition, the attribution definitions of drug relatedness of adverse events "not related," "doubtful," "possible," "probable" and "very likely" were added. Finally, the reporting time frame was changed from "between signing of the Informed Consent and last dose administration" to "between first and last dose administration."

3. A local amendment, dated 16 September 1998 that was valid for the USA and the Republic of South Africa, was issued to allow USA and South African patients who had completed at least 2 weeks of trial medication in the double-blind trial RIS-CAN-19 to be eligible for the present trial. This amendment affected only those patients and sites who were participating in RIS-CAN-19. Any patient from these sites who had not participated in RIS-CAN-19 had to meet the eligibility requirements and had to follow the procedures as stated in the original protocol and international amendments. The following sections were amended: 3.1.1, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.5, and 3.4.2.

4. A local amendment, dated 31 August 1999 that was valid for 2 Hungarian centers (Szeged and Baja) was issued on request of the Regional Ethics Committee of the 2 centers after they had received the Correction to Amendment 3 of Investigator's Brochure (dated 15 April 1999). The protocol amendment specified that all patients were to be seen by cardiologist at the start of the trial, at the end of Month 3, Month 6 and Month 12. Based on physical examination and electrocardiogram (ECG) record, a cardiologist was to determine whether echocardiography was necessary or not (see section 3.4.2, 3.4.6.4, and 3.4.6.5).

5. A local amendment, dated 31 January 2000 that was valid for Belgium, was issued because the names of the local designees to be contacted in case of serious adverse events, were changed.

Details are given in the respective sections.

In order to provide the regulatory authorities with long-term safety and efficacy data, an interim analysis was carried out. All patients who entered the trial before 31 July 1999 were included. This date was chosen as a cut-off date based on the numbers of patients required by the authorities (300 patients with 6 months exposure, 100 patients with 1-year exposure), and based on the number of patients that were already included in RIS-USA-97 (i.e., the long-term extension of trial RIS-USA-93). The results of the interim analysis are presented in a separate report.[21]

3.2. Patient sample

3.2.1. SAMPLE SIZE

During a period of 24 months, 500 patients were to be entered (see section 3.6.1). This multicenter trial was to be conducted in Europe, *in the US and the Republic of South Africa.*[2] Each center had to make every effort to include a minimum of 10 patients.

3.2.2. INCLUSION CRITERIA

- Patients with a DSM-IV, Axis I diagnosis of Conduct Disorder (312.8); or Oppositional Defiant Disorder (313.81); or Disruptive Behavior Disorder not otherwise specified (312.9); and a total rating of ≥ 24 in the Conduct Problem subscale of the N-CBRF (parent version), as assessed at Visits 1 and 3. Patients who fulfilled this criterion, and, in addition, had ADHD (314.xx; 314.9), were eligible for entry. *The Conduct Problem subscale score for those patients who had participated in RIS-CAN-19 was to be waived for inclusion into this trial.*[2]
- Patients with a DSM-IV, Axis II diagnosis of Mild Mental Retardation (317), Moderate Mental Retardation (318.0) or Borderline Intellectual Functioning (V62.89). These 3 diagnoses represent IQs ranging from 84 to 35 inclusive.
- Patients with a Vineland Adaptive Behavior Scale score of ≤ 84, *except those patients who had participated in RIS-CAN-19.*[2]
- Patients between 5 and 14 years of age (extremes included).
- Informed consent form had been signed.
- Patient was healthy based on a pre-trial physical examination, medical history and ECG.
- A responsible person was available to accompany the patient to the investigator site on each assessment day as scheduled in the flow chart, was able to provide reliable information for the rating scales and was able to reliably and accurately dispense the trial medications as directed.
- *Patients who had participated in RIS-CAN-19 should have completed at least 2 weeks (14 days) of double-blind medication.*[2]
- *Current symptoms requiring antipsychotic treatment in the opinion of an independent investigator.*[3]

Note: Patients could be inpatients or outpatients.

3.2.3. EXCLUSION CRITERIA

- Patients who had a diagnosis of Pervasive Development Disorder (299.00; 299.80; 299.10).

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[2] Text in italics was added following protocol amendment dated 16 September 1998.

[3] For Germany only. This criterion was added following the local protocol amendment dated 20 January 1997.

- Patients who had a diagnosis of Schizophrenia and Other Psychotic Disorders (295.xx; 297.xx; 298.8; 293.xx).
- Head injury as a cause of mental impairment.
  Note: Head injury attributed to birth trauma was not excluded. Birth trauma was defined as any event occurring before delivery of the placenta.
- Seizure disorder currently requiring medication.
- Use of disallowed concomitant therapy (see section 3.3.6).
- Females of childbearing potential engaging in sexual activity who were not on medically validated birth control method (e.g., double barrier, intrauterine device, oral contraceptives, Norplant,® DepoProvera®).
- Participation in an investigational drug trial within 30 days before the start of the trial, *except those patients who had participated in RIS-CAN-19.*[4]
- Laboratory values outside the normal range. If the results of the biochemistry, hematology tests and the urinalysis testing were not within the laboratory's reference ranges, the patient could be included only on condition that the principal investigator judged that the deviations were not clinically relevant.
- Known sensitivity to risperidone.
- Serious or progressive illnesses, including, but not limited to: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal or endocrine disturbances.
- History of tardive dyskinesia, neuroleptic malignant syndrome or known hypersensitivity to neuroleptics.
- Patients known to be HIV-positive.
- Patients who had previously received risperidone for Conduct Disorder for less than 3 weeks and discontinued use of risperidone due to lack of efficacy or due to adverse events. *Patients who had completed at least 2 weeks of RIS-CAN-19 treatment and who were discontinued due to lack of efficacy were allowed to enter RIS-INT-41.*[4]
- Patients who had previously been successfully treated with risperidone for this condition, *except those patients who had participated in RIS-CAN-19.*[4]
- *Patients who experienced a hypersensitivity reaction or suspected hypersensitivity reaction to the trial medication administered in RIS-CAN-19.*[4]
- *The time elapsed since completing or discontinuing from RIS-CAN-19 exceeded 3 weeks.*[4]

3.2.4. PROHIBITIONS AND RESTRICTIONS

Not applicable.

3.2.5. REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were to be withdrawn from the trial if:

[4] Text in italics was added following protocol amendment dated 16 September 1998.

- a serious adverse event occurred;
- the investigator considered it in the best interest of the patient that he/she be withdrawn;
- the patient no longer met the requirements of inclusion criterion 1, after completion of the placebo run-in period, when evaluated at the baseline visit.

Patients had to be withdrawn from the trial if consent was withdrawn.

The date and the reason for discontinuation were to be recorded on the Case Report Form (CRF). All patients prematurely discontinuing the trial were to be seen for a final evaluation and the Trial Termination Form was to be completed.

3.3. Treatments

3.3.1. Overview

The flow chart showing trial phases and timing of treatment and assessments is given in Section 3.4.1. The investigator was allowed the following flexibility in scheduling and conducting visits:

- Patients could be assessed within plus or minus 2 days of the scheduled visit.
- The screening visit (Visit 1) and the placebo run-in visit (Visit 2) could be conducted on the same day if desired.
- *If the patient had participated in RIS-CAN-19, the evaluations for Visits 1 and 2 did not need to be performed. The evaluations from the Endpoint of RIS-CAN-19 could be used for the baseline visit (Visit 3). The pertinent data from the RIS-CAN-19 database were to be electronically transferred into the RIS-INT-41 database, obviating the need to transcribe any evaluations from the RIS-CAN-19 CRFs into the RIS-INT-41 CRFs.*
- *If the time elapsed since the Endpoint of RIS-CAN-19 was less than or equal to 1 week, the Endpoint evaluations could serve as the Baseline of RIS-INT-41. If the time elapsed since the Endpoint visit of RIS-CAN-19 was greater than 1 week but less than 3 weeks, the evaluations for Baseline (Visit 3) were to be repeated.*[5]
- If an IQ test had been performed with either the Wechsler or Stanford Binet test, during the year preceding entry to the trial, the patient needed not be re-tested. The previously ascertained IQ rating could be recorded in the CRF. If the investigator judged that the prior score did not accurately reflect the status of the patient, a re-test could be given and the new score was to be recorded in the CRF.

[5] Text in italics was added following protocol amendment dated 16 September 1998.

- If a Vineland Adaptive Behavior Scale score was available from the year before the trial, the patient did not need to be re-tested. The previously ascertained score could be recorded on the CRF. If the investigator judged that the prior score did not accurately reflect the status of the patient, a re-test could be given, and the new score was to be recorded in the CRF.
- In the event of the rater changing during the course of the trial, the new rater was to be shown a copy of the most recent ratings performed by the rater who was being replaced. This served to "anchor" the second rater in order to reduce the inter-rater variability.
- If extreme difficulty was experienced in obtaining blood samples at a particular visit, the procedure could be rescheduled to a time when the patient would be more amenable to the procedure of blood sampling. Should it prove impossible to obtain a blood sample despite several attempts, the patient was to be withdrawn from the trial.

3.3.2. IDENTITY OF INVESTIGATIONAL PRODUCTS

Medication batches used are given in Table 3-1.

Table 3-1: Identity of investigational product(s)

Product	Strength	Lot number	Expiry date
Placebo	--	97A24/F71	Jan 2000
Placebo	--	98L16/F71	Dec 2001
Placebo	--	96J01/F71	December, 1999
Risperidone	1 mg/mL	97F25/917	Jun 2000
Risperidone	1 mg/mL	99F07/588	June 2001
Risperidone	1 mg/mL	98H14/799	Aug 2001
Risperidone	1 mg/mL	99F07/588	June 2001
Risperidone	1 mg/mL	97F24/918	June 2000
Risperidone	1 mg/mL	97F25/919	June 2000
Risperidone	1 mg/mL	99H09/391	August 2002
Risperidone	1 mg/mL	96I24/321	December 1999
Risperidone	1 mg/mL	97A29/956	January 2000

All the trial medication was to be returned from the sites before the expiration date in all instances.

Each patient was provided with 100-mL bottles of solution containing risperidone 1mg/mL. Each bottle was supplied with a milliliter pipette to facilitate accurate dispensing of the dosage. The option of using a dropper (instead of the pipette) to dispense the dosage was offered for use in small children. All trial medication was labeled with the protocol number, medication number, lot number and expiry date. The medication number was to be recorded in the CRF on the first page.

During the 7-day single-blind, placebo run-in period, patients *except those who had participated in RIS-CAN-19* received risperidone placebo solution, which was identical in taste, smell and appearance to the solution containing active medication. *Those patients who had participated in RIS-CAN-19 would forego the placebo run-in period and were dispensed open-label medication immediately upon the last visit in RIS-CAN-19 and were to follow the titration schedule as per protocol.*[6]

3.3.3. METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

All patients admitted to the trial were screened for eligibility according to the inclusion and exclusion criteria (section 3.2.2 and section 3.2.3). Except for patients who were participants in the RIS-CAN-19, eligible patients received placebo treatment for 1 week in a single blinded manner to identify placebo responders. Patients who responded to placebo were removed from the trial. The patients, who remained eligible after this 1-week placebo run-in period, received open-label treatment with risperidone. Patient numbers were assigned in consecutive order at each center.

3.3.4. SELECTION AND TIMING OF DOSE

The liquid trial medication was administered once daily in the morning or afternoon. The medication was administered by means of a graduated pipette and could be diluted in water, fresh orange juice, low-fat milk or black coffee. No other beverages were to be used to dilute the trial medication. The responsible person administering the medication was to ensure that the entire volume of diluted medication was ingested.

The dosing range was 0.02 to 0.06 mg/kg/day. The dosing information obtained in several trials was taken into consideration in selecting a dose range of 0.02 to 0.06 mg/kg/day for further evaluation. The similar pharmacokinetics of risperidone in adults and children[20] suggested that low-dose risperidone treatment would be effective in children. Phase II studies RIS-BEL-22[11] and RIS-BEL-24[14], with mean doses at Endpoint of 0.03 and 0.05 mg/kg/day, respectively, confirmed the efficacy and tolerability of low doses of risperidone in the treatment of behavioral disturbances in children.

The starting dose was 0.01 mg/kg/day for Day 1 and Day 2. On Day 3 the dose was increased to 0.02 mg/kg/day. Thereafter the dosage could be raised or lowered at weekly intervals as judged necessary by the clinician depending on the therapeutic response. Increments were not to exceed 0.02 mg/kg/day, and the maximum dosage permitted was 0.06 mg/kg/day. The dose was to be calculated based on the most recent weight. The rate at which the dosage could be lowered was not limited. If the patients exhibited

[6] Text in italics was added following protocol amendment dated 16 September 1998.

breakthrough symptoms, the regimen could be changed to twice daily dosing. Documentation of breakthrough behavior was to be made in the source documents.

At each visit, the dosage to be taken was recorded in the CRF. After Day 28 (Visit 7) the daily dose was, if possible, to remain unchanged until the end of the trial. However, drug was to be withheld on the day of Visits 7, 12 and 14 until blood for the trough level had been taken.

3.3.5. BLINDING

This was an open-label trial; therefore, blinding does not apply to this study.

3.3.6. PRIOR AND CONCOMITANT THERAPY

All medications (prescriptions or over-the-counter medications) were to be documented on the Concomitant Therapy page of the CRF.

Behavior Intervention Therapy
Any behavior intervention therapy must have been initiated at least 30 days before trial start. No new therapy could be initiated after this point.

Psychotropic medication
During the trial, other than risperidone, no other antipsychotics, antidepressants, lithium, carbamazepine or valproic acid could be administered. However, patients who were receiving psychostimulant medication for the treatment of ADHD were allowed to continue on the medication. Every attempt was to be made to keep the dosage constant throughout the trial. The use of such medication was to be recorded in the CRF (including trade name, dose and duration of administration).

Treatment for ADHD
Psychostimulants (e.g., methylphenidate, permoline, dexedrine) were allowed for the treatment of ADHD provided the patient had been stabilized on a constant dose for 30 days before trial start. Every attempt was to be made to keep the dosage constant throughout the trial. The use of such medication was to be recorded in the CRF, including generic name, trade name and dose. Other medication to treat ADHD, including but not limited to drugs such as clonidine or guanfacine, were prohibited.

Anticholinergic medication
All anticholinergic medication was to be discontinued at entry into the trial. During the trial, the dose of risperidone was to be reduced in the case of emergent EPS. If such a reduction in the dosage resulted in deterioration of conduct disorder symptoms or failed to bring about an improvement in the EPS, introduction of anticholinergic medication could be considered after completion of the ESRS. Administration of anticholinergic medication was

to be limited to the extent possible, and each dose was to be accurately recorded in the CRF.

Sedative/hypnotic medication

No medication for sleep or anxiety could be initiated during the trial, however, patients who were receiving a sedative/hypnotic for sleep before the screening visit were allowed to continue during the trial. Clonidine and other prescribed agents could not be administered to treat sleep difficulties. In addition, it was permitted to use pre-medication, e.g., a benzodiazepine, to facilitate the execution of medical procedures, where required (e.g., before a dental appointment or to facilitate blood sampling).

Medication for organic disorders

Medication for organic disorders was to be kept as constant as possible during the trial period.

All concomitant medication (prescription or non-prescription) that the patient received at any time during the trial was to be recorded in the CRF (including trade name, indication, dose and duration of administration). During the trial, any changes in dosage or new medication commenced was to be recorded in the CRF. Patients who had been prescribed special diets were to be stabilized on them before trial start per the investigator's judgment. It was the responsibility of the investigator to judge the appropriateness of over the counter medications for the treatment of any particular patient.

If any concomitant therapy was given as a treatment for a new condition or a worsening of an existing condition, the condition was to be documented on the Adverse Event Form of the CRF.

3.3.7. MEASURES OF TREATMENT COMPLIANCE

A record was kept of the drug dispensed and returned for each patient. Any unused drug was returned and inspected by the sponsor's representative to monitor compliance in taking trial drug.

3.4. Assessments

3.4.1. FLOW CHART

Table 3-2: Flow chart of study assessments

Assessment	Screen	Placebo run-in	Base-line	Wk1	Wk2	Wk3	Wk4
Day	-10 to -7	-7	1	7	14	21	28
Visit	1*	2*	3	4	5	6	7
Informed Consent	x						
Medical History	x						
Physical Exam.	x						
Weight			x				x
Psychiatric History	x						
IQ-Stanford Binet or Wechsler	x						
Vineland Adaptive Behavior Scale	x						
Vital signs	x		x	x	x	x	x
Electrocardiogram	x						
Laboratory safety, GH, prolactin	x						x[a]
Tanner Staging			x				
Child Symptom Inventory	x						
Nisonger Child Behavior Rating Form	x		x	x	x	x	x
Aberrant Behavior Checklist	x		x	x	x	x	x
Clinical Global Impression[b]			x	x	x	x	x
Visual Analogue Scale[c]			x	x	x	x	x
Extrapyramidal Symptom Rating Scale			x	x	x	x	x
Cognitive tests			x				
Plasma level	x						x[d]
Adverse events			x	x	x	x	x
Concomitant therapy			x	x	x	x	x
Dispense medication[e]		x	x	x	x	x	x

Table 3-2: Flow chart of study assessments (continued)							
Assessment Month	2	3	4	5	6	9	12
Visit	8	9	10	11	12	13	14
Informed Consent							
Medical History							
Physical Exam		x			x		x
Weight		x			x		x
Psychiatric History							
IQ-Stanford Binet or Wechsler							
Vineland Adaptive Behavior Scale							
Vital signs	x	x	x	x	x	x	x
Electrocardiogram		x*			x		x
Laboratory safety, GH, prolactin		x[a]			x[a]	x[a]	x[a]
Tanner Staging					x		x
Child Symptom Inventory[b]							
Nisonger Child Behavior Rating Form	x	x	x	x	x	x	x
Aberrant Behavior Checklist	x	x	x	x	x	x	x
Clinical Global Impression[b]	x	x	x	x	x	x	x
Visual Analogue Scale[c]	x	x	x	x	x	x	x
Extrapyramidal Symptom Rating Scale	x	x	x	x	x	x	x
Cognitive tests					x		x
Plasma level					x[d]		x[d]
Adverse events	x	x	x	x	x	x	x
Concomitant Therapy	x	x	x	x	x	x	x
Dispense medication[e]	x	x	x	x	x	x	x

* Only valid for the patients in the Hungarian centers Szeged and Baja

[a] Prolactin and Growth Hormone samples to be taken at trough level, i.e., 24 hours after previous dose or just before the next dose.

[b] Overall severity at each assessment.

[c] Visual analogue scale of most troublesome symptom.

[d] Trough level, i.e., 24 hours after last dose or just before the next dose.

[e] Collect unused medication at each visit from Visit 3 to Visit 14.

3.4.2. INITIAL PATIENT AND DISEASE CHARACTERISTICS

At the screening visit, the following data were to be recorded *(except for those patients who had participated in RIS-CAN-19)*[7]: informed consent, medical history, physical examination, psychiatric history, IQ test (Stanford Binet or Wechsler), Vineland Adaptive Behavior Scale, R064766 plasma level, vital signs, laboratory assessments including prolactin and growth

[7] Text in italics was added following protocol amendment dated 16 September 1998.

hormone, ECG[8], Child Symptom Inventory (CSI), N-CBRF, ABC. The CSI was used to record co-morbidity and thus was to be completed once only, at the screening visit.

At the baseline visit, the following were to be performed (for patients who had participated in RIS-CAN-19: *the results of the last visit of RIS-CAN-19 could be recorded onto this visit if done within the time period specified in section 3.3.1)*[7]: weight, vital signs, N-CBRF, ABC, CGI, VAS of the most troublesome symptom, ESRS, cognitive tests, Tanner Staging (see section 3.4.6.8), adverse events and concomitant therapy.

There is a tendency for raters to score extreme conduct disorders as less severe over successive ratings, especially between the first and second ratings, hence the need to rate patients at Screening and at Baseline.

All entry criteria were checked at the first visit.

3.4.3. PHARMACOKINETICS

Venous (5 mL) blood samples for drug analysis were taken at Screening and at trough level (just before the scheduled drug intake), at Visits 7 and 12, and at end-point. The exact date and time of blood sampling, as well as the date and time of the previous drug intake, were to be recorded in the CRF.

The blood samples were collected in heparinized tubes or in tubes containing EDTA. Tubes were inverted 6 to 8 times to ensure adequate mixing of blood and reagents. Blood samples were centrifuged for 10 minutes at 2,500 rpm (1,000 g) within 2 hours after collection. Separated plasma was aspirated with a disposable glass Pasteur pipette and transferred into 5-mL plastic (polyethylene or polypropylene) tubes. The tubes were stoppered by means of polyethylene stoppers, and labeled with the investigator's name, trial number, medication code number and patients' initials, time and date of sampling. Samples were stored at -20°C and kept frozen while transported by the trial monitor to the JRF.

Plasma concentrations of risperidone were determined at JRF by means of a validated liquid chromatography/ mass spectrometry/ mass spectroscopy method. The limit of quantification was 0.10 ng/mL. Plasma concentrations of active moiety (sum of risperidone and 9-hydroxy-risperidone) were determined by means of a validated radioimmunoassay method, with a limit of quantification of 0.20 ng/mL.

3.4.4. PHARMACODYNAMICS

Not applicable.

[8] Following the local protocol amendment dated 31 August 1999, the hearts from patients from the 2 Hungarian centers Szeged and Baja were also to be examined by a cardiologist by means of auscultation and palpation.

3.4.5. EFFICACY

The efficacy of the trial medication was evaluated using the following scales at every visit (except Visit 2):

- N-CBRF to be scored by a parent or caregiver under guidance of the investigator;
- ABC, to be scored by a parent or caregiver under guidance of the investigator;
- CGI severity ratings, to be scored by a trained investigator;
- An individual target symptom was defined for each patient, i.e., the symptom considered to be the most disturbing for the patient and his/her surroundings. This symptom was rated on a VAS and was scored by the parent or caregiver.

3.4.5.1. Primary efficacy variable

The primary efficacy parameter was the change versus Baseline in behavior at Endpoint as measured on the Conduct Problem subscale of the N-CBRF. The N-CBRF was measured at Visits 1 and 3 through 14.

The conduct problem subscale of the N-CBRF consists of the following 16 items of the problem behavior subscale of the N-CBRF:

- item numbers: 2, 4, 7, 8, 10, 12, 17, 26, 36, 40, 50, 54, 56, 57, 63, and 66.

The scores for each item range from 0 to 3; lower scores indicating a better condition:

0 = no occurrence or no problem
1 = occasionally or mild problem
2 = quite often or moderate problem
3 = a lot or severe problem.

3.4.5.2. Secondary efficacy variables

Changes versus Baseline as measured on:

- N-CBRF other subscales
- ABC total score and the irritability subscale of the ABC
- CGI severity
- VAS of most troublesome symptom

Although tests of cognitive function, including CPT and California Verbal Learning Test-Children's Version, are considered to be efficacy assessments

in the Protocol, they were performed only to confirm that risperidone has no negative effect on cognition. The results of cognitive tests, therefore, are discussed in the Safety section.

3.4.5.2.1. Other subscales of N-CBRF

Besides the conduct problem subscale, the N-CBRF consists of the following subscales:

1. Positive Social Behavior:
   - Compliant / Calm (6 items, range 0 – 18): 1, 3, 4, 6, 9 and 10
   - Adaptive Social (4 items, range 0 - 12): 2, 5, 7 and 8.

2. Problem Behavior Subscales:
   - Insecure / Anxious (15 items, range 0 - 45): 16, 21, 23, 30, 31, 34, 41, 42, 44, 45, 48, 52, 55, 60 and 65
   - Hyperactive (9 items, range 0 - 27): 9, 13, 19, 24, 33, 35, 38, 39 and 46
   - Self Injury / Stereotypical (7 items, range 0 - 21): 6, 11, 22, 32, 43, 53 and 58
   - Self-Isolated / Ritualistic (8 items, range 0 - 24): 1, 18, 25, 29, 37, 47, 49 and 64
   - Overly Sensitive (5 items, range 0 - 15): 3, 5, 14, 15 and 20.

Items 27, 28, 51, 59, 61 and 62 of the problem behavior subscale were not used in any problem behavior subscale of the parent version of the N-CBRF.

3.4.5.2.2. Aberrant Behavior Checklist (ABC)

The ABC was scored by a parent or caregiver (under guidance of the investigator) at all visits.

The ABC consists of 58 items, with scores ranging from 0 to 3, lower scores indicating better conditions. The total ABC score was the sum of the individual items.

The ABC scale has 5 subscales: irritability (15 items), lethargy, social withdrawal (16 items), stereotypic behavior (7 items), hyperactivity (16 items) and inappropriate speech (4 items).

3.4.5.2.3. Clinical Global Impression (CGI)

CGI was measured at Visit 3 to Visit 14. At each visit, the investigator gave an impression about the severity of the patient's disorder at that time. It was measured on a 7-point scale: absent, very mild, mild, moderate, marked, severe, and extremely severe.

3.4.5.2.4. Visual Analogue Scale (VAS) of the most troublesome symptom

At Baseline, an individual target symptom was to be determined by the parent or caregiver for each patient. The target symptom was defined as the symptom considered the most disturbing for the patient and his/her surroundings. The severity of this symptom was to be rated on a VAS (ranging from 0 = not present, to 100 = extremely severe) and was scored by the parent or caregiver. The same symptom was to be evaluated at all visits.

3.4.6. SAFETY

3.4.6.1. Adverse events

Adverse events (AEs) were recorded at every visit, except Visits 1 and 2. All AEs occurring between the first and the last dose administration of trial medication were recorded by the investigator, and the following specifications were given: symptom(s), time of onset and subsidence, severity (mild, moderate, severe), drug-relatedness (none, doubtful, possible, probable, very likely), action taken (none, dose reduced, temporarily stopped, permanently stopped), and the patient outcome (patient recovered, AE still present, patient died).

Serious AEs were to be documented separately.

3.4.6.2. Clinical laboratory tests

Blood samples for biochemistry and hematology (including hormones) and a random urine sample for urinalysis were taken at the start of the trial, at Week 4, Months 3, 6, 9 and at the end of treatment The following tests were performed by the central laboratory (BARC):

Hematology (5 mL EDTA): hemoglobin, hematocrit, RBC, WBC with differential blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

Biochemistry (6 mL Blood): total protein, alkaline phosphatase, aspartate transaminase (AST, SGOT), alanine transaminase (ALT, SGPT), γ-GT, LDH, total bilirubin, urea, uric acid, creatinine, bicarbonate, sodium, potassium, chloride, calcium, prolactin and growth hormone. Sample for prolactin and growth hormone were taken at trough level, i.e., 24 hours after previous dose or just before the next dose. This did not apply to the sample taken at Visit 1, which was not a trough level, as no drug had been administered.

Urinalysis (10 mL random urine): urinalysis by dipstick for protein, glucose, occult blood. If abnormal, microscopic examination for WBC, RBC, and casts.

The sample tubes were labeled in such a way that the investigator's name, trial number, CRF identification, visit number, and date and time of sampling could be identified.

The laboratory values (or central laboratory report) was filed in the CRF, and a photocopy was left at the trial center. The laboratory report was interpreted by the investigator, any clinically relevant changes occurring during the trial were to be recorded on the AE Form of the CRF.

3.4.6.3. Vital signs and physical examination

Vital signs were recorded at each visit except Visit 2. Systolic and diastolic blood pressure were measured. All readings were taken on the same arm. Heart rate was recorded after each blood pressure measurement. Other vital signs (respiration and temperature) were also recorded.

Physical findings were recorded at Screening and at Visits 9, 12, and 14.

3.4.6.4. Electrocardiogram

A resting 12-lead ECG was recorded at a paper speed of 25 mm/s, (50 mm/s for the precordial leads). Recordings were performed at the start of the trial, at Visit 12 and at the end of the trial.[9] The investigator indicated whether the ECG was within normal limits or not by completing the appropriate page in the CRF. Any clinically relevant changes occurring during the trial were to be recorded on the AE Form of the CRF. A copy of the ECG was left at the investigator site and the original was filed in the CRF.

3.4.6.5. Cardiologic examination[10]

A cardiologist was to perform an examination of the heart by means of auscultation and palpation and review ECG records at Visit 9, at Visit 12 and at the end of the trial. Based on the findings he/she was to inform the investigator about the following in writing:

- *Presence of any abnormalities on ECG and in physical examination*
- *Echocardiography necessary or not, if yes, findings*
- *Presence of any contraindication to further risperidone treatment*

[9] An ECG was also to be recorded at Visit 9 for patients from the 2 Hungarian centers Szeged and Baja following the local protocol amendment dated 31 August 1999.

[10] Text in italics was added following the local protocol amendment dated 31 August 1999 and was only valid for the patients from the 2 Hungarian centers Szeged and Baja.

3.4.6.6. Body weight

Patients were weighed with outdoor clothing and footwear removed at Baseline and at Visits 7, 9 and 12 and at the end of the trial. The same amount of clothing was to be worn on each occasion, and the same scale was to be used at each visit.

3.4.6.7. Extrapyramidal Symptom Rating Scale (ESRS)

The presence and severity of EPSs was assessed at each visit (except Screening and Visit 2) and before the administration of anti-Parkinson medication by means of the ESRS. This rating instrument consisted of: a Questionnaire (12 items), Parkinsonian factor (8 items), Dystonia factor (2 items) and Dyskinesia factor (7 items) as well as a CGI of overall severity of Parkinsonism, dystonia and dyskinesia and staging of Parkinsonism.

3.4.6.8. Tanner Staging

The sexual maturity of the patient was rated on a scale of 1 to 5 by selecting one diagram (from a series of 5) thought to most closely resemble the sexual maturity of the patient. The number corresponding to the diagram selected was to be recorded in the CRF.

Tanner staging was conducted at Baseline and at Visits 12 and 14.

3.4.6.9. Cognitive tests

The following cognitive tests were performed at Visits 3, 12 and 14:

Modified verbal learning test
The modified verbal learning test consists of 2 parts: the 'short delay free recall' (trials 1-5) and the second part, which consists of 'long delay free recall' (trial 6) and 'recognition' (trial 7).

A list of 10 words is presented (orally or by pictures). For the 'short delay free recall' and the 'long delay free recall' trials, the patients were asked to enumerate the words they recalled. For the 'recognition trial' a list of 20 words was presented. The patient had to recognize the 10 words of the original list.

The following scores were calculated:

1 Total short delay free recall score (range 0-50, sum of 5 short delay free recall trials)
2 Total long delay free recall score (range 0-10, number of correctly recalled words of trial 6)
3 Recognition total (trial 7): total of correctly recognized and correctly not recognized items.

Continuous performance test
This test was performed on a computer and consisted of 2 trials, an easy test and a hard test. All 5 parameters (hits, misses, false alarm, reaction time for hits, reaction time for false alarm) were analyzed separately for both the easy and the hard test for the first half of the test, the second half of the test and the total test.

The scores are computer-generated. Where possible, the timing of testing had to remain constant for each respective patient. Thus, a patient who was tested at 10 a.m. on the first visit was to be tested at about that time throughout the trial.

3.4.7. OUTCOMES RESEARCH

Not applicable.

3.5. Data quality assurance

This trial was monitored according to the current JRF standard operating procedure for monitoring of clinical trials.

The trial monitor met with the investigator and staff involved in the trial and reviewed the procedures to be followed in conducting the trial and the procedures for recording the findings in the CRF. During the trial, the investigator permitted the trial monitor to verify the progress of the trial on-site as frequently as necessary. The investigator provided the CRFs and any corrected data. Key data were transcribed onto the CRFs, such as the patient's sex, date of birth, assessment dates, and test results, and were to be reviewed against source documents. All personal information from the patients was treated as strictly confidential and is not publicly available.

All numeric data, except laboratory safety data, vital signs, ECG data and plasma level data were entered from the CRF and verified by double data entry. CRF data were entered into an ORACLE database on a VAX computer. SAS data sets of the ORACLE database were created for processing within SAS. The data on vital signs and ECG were entered into an ORACLE database at the investigator's site. Laboratory data (including hormone levels) were supplied by BARC.

Drug-plasma concentration data were supplied by the bioanalytical laboratory (Department of Pharmacokinetics, JRF, Beerse), both as signed hard copy and as an Excel® spreadsheet computer file which was cross-checked with hard-copy before its use in the pharmacokinetic data analysis.

An independent Quality Assurance department and/or regulatory authorities could review this trial. This implied that auditors or inspectors had the right to inspect the trial centers at any time during and/or after completion of the trial and had access to source documents, including the patient's file. By participating in this trial, the investigators agreed to this requirement. Measures were undertaken to protect patient data handed over by the investigator to JRF and maintain confidentiality at all times.

An audit of randomly selected CRFs was performed. All CRFs were reviewed for AEs, trial medication, and trial discontinuation/ completion data.

3.6. Statistical methods and sample size determination

The analyses described in the following sections were performed as planned in the protocol, except where noted in sections 3.6.5.3, 3.6.6.1, and 3.6.6.3.2.

3.6.1. DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was performed for this open-label trial. The sample size of 500 patients was based on the regulatory requirements pertaining to long-term safety and efficacy trials.

3.6.2. GENERAL ANALYSIS SPECIFICATIONS

Statistical analyses were performed by or under the guidance of the JRF. All statistical tests were interpreted at the 5% 2-tailed significance level (unless otherwise noted). All statistical analyses and data listings were performed using SAS Version 6.12 on Windows® NT System.

Results were presented for all patients, and for patients who newly entered in this trial and patients from trial RIS-CAN-19 separately. Because of the small numbers of patients from RIS-CAN-19, these patients were not further grouped according to the treatment received during double-blind treatment.

For patients from RIS-CAN-19, Baseline assessments were not performed if the time elapsed since the Endpoint of RIS-CAN-19 was 1 week or less. In this case, the Endpoint evaluations of RIS-CAN-19 served as Baseline values for RIS-INT-41. However, if a Baseline evaluation was performed, this was used as Baseline assessment in the analysis. If the time elapsed since the Endpoint visit of RIS-CAN-19 was more than 1 week, the evaluations for the Baseline visit of RIS-INT-41 were repeated.

3.6.3. INITIAL CHARACTERISTICS OF PATIENT SAMPLE

Descriptive statistics and tabulations were generated for all demographic variables and Baseline characteristics.

3.6.4. PHARMACOKINETICS

3.6.4.1. Drug concentrations

Descriptive statistics were performed on the trough levels stratified according to daily dosage.

3.6.5. EFFICACY

An intent-to-treat (ITT) analysis was performed and included all patients who took at least one dose of trial medication during the open-label phase and who provided any follow-up data for the Conduct Problem Subscale of the N-CBRF.

The primary timepoint was Endpoint, i.e., the last observation during the open-label phase for each patient. Efficacy results were also analyzed per visit.

Imputation was performed for N-CBRF and ABC. Both non-imputed and imputed results for each parameter were analyzed. Missing items for N-CBRF and ABC were imputed as follows: if an item in one of the subscales of the N-CBRF or ABC was missing, it was imputed with the closest integer to the mean of the remaining items within the subscale at the timepoint at which the item was missing. If more than 15% of the items were missing, no imputation was performed and the total score remained missing.

3.6.5.1. Primary parameter

The primary parameter was the change from Baseline at Endpoint of the rating score for the Conduct Problem subscale of the N-CBRF.

Endpoint and Baselines (both Baseline [double-blind] and Baseline for patients from RIS-CAN-19) were compared using the paired t-test. This test was also performed to test for differences between Baseline and the other timepoints of the follow-on trial.

3.6.5.2. Secondary parameters

The secondary efficacy parameters included the remaining N-CBRF subscales, the ABC total score and the subscales of the ABC, the CGI, and the VAS of the most troublesome symptom. For continuous variables, Endpoint and open-label baseline scores were compared using the paired t-test. For CGI, only a frequency table was provided.

3.6.5.3. Subgroup analyses

Subgroup analyses was performed to assess the consistency in treatment effects as measured by the primary efficacy parameter. The categories of the subgroup variables were:

- diagnosis group: conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified;
- degree of retardation: borderline intellectual functioning, mild and moderate mental retardation;
- patients who took psychostimulants and patients who did not take psychostimulants. Psychostimulants include the following concomitant therapies: methylphenidate, methylphenidate hydrochloride, pemoline, amphetamine, pemoline magnesium, and dexamphetamine sulfate; and
- although the Statistical Analysis Plan specified 2 age groups, <12 years, ≥12 years, subgroup analyses by age group were performed for 3 age categories: ≤9 years, 10-11 years, and ≥12 years.

3.6.6. SAFETY

3.6.6.1. Adverse events

Type and incidence of AEs were tabulated. Special attention was paid to severe AEs; drug-related AEs; serious AEs; other significant AEs, e.g., those leading to the patient's withdrawal; and to any patients who died within 30 days of trial termination.

AEs were categorized by severity, relationship to trial medication, and by action taken regarding trial medication. Although tabulations of type and incidence of AEs were to be classified by 2 age groups (<12 years and ≥12 years), these tabulations were classified in 3 age categories, ≤9 years, 10-11 years, and ≥12 years.

3.6.6.1.1. EPS-related adverse events

Special attention was given to AEs that were related to EPS. Type and incidence of EPS-related AEs were tabulated. World Health Organization (WHO)-preferred AE terms defined as EPS-related were: tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, abnormal gait, ataxia, muscle contractions involuntary, hyporeflexia, akathisia, dyskinesia, dyskinesia tardive, tetany, tongue paralysis, bradykinesia, and extrapyramidal disorder.

3.6.6.1.2. Prolactin-related adverse events

Special attention was also given to AEs that were related to prolactin levels. WHO-preferred terms defined as prolactin-related were: gynecomastia, lactation nonpuerperal, breast discharge, impotence, libido decreased, breast pain male, breast pain female, anorgasmia, dysmenorrhea, ejaculation failure, hyperprolactinemia, amenorrhea, menorrhagia, vaginal bleeding, and breast enlargement.

The same analysis performed for EPS-related AEs was performed for prolactin-related AEs.

3.6.6.1.3. Glucose-related adverse events

Special attention was also given to AEs related to glucose levels. WHO-preferred terms defined as glucose-related were: acidosis, acidosis lactic, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus reactivated, glucose tolerance abnormal, glycosuria, hyperglycemia, hypoglycemia, hypoglycemic reaction, ketosis, coma diabetic, hypoglycemia neonatal, phenylketonuria, plasma osmolality increased, coma hypoglycemic, blood glucose false positive, breath odor ketones.

3.6.6.2. Clinical laboratory tests

For the clinical laboratory data, descriptive statistics in change from Baseline and pre- versus post-treatment cross-tabulations (with classes for below, within and above normal range) were generated for all tests performed. Important abnormalities, as determined by the occurrence of pathological values, were tabulated. Pathologic values were values that were outside the pathologic limits: for most hematological and biochemical tests, pathologic limits were defined by Lippert and Lehmann[27]; for enzymes, the lower pathologic limit was defined as zero, and the upper pathological limit as twice the upper normal limit; for leukocyte differential count, no pathologic limits were defined; if a value was outside the pathologic limits but not outside the normal limits for the particular laboratory, it was not considered pathologic. The type of important abnormality depended on the time of occurrence of the pathologic value, i.e., before (reference value of the parameter), during or after treatment (e.g., non-pathologic before, pathologic during treatment).

Different types of 'Important abnormalities' were determined based on the following definitions (codes-1 to 5). Code-0 means that no pathologic values are found at any timepoint for any particular test.

Code 1: reference value is pathologic; values during the observation period are not pathologic

Code 2: reference value is pathologic (high/low); at least one value during the observation period is pathologic (high/low)
Code 3: reference value is not pathologic; only one value - but not the last one - during the observation period is pathologic
Code 4: reference value is not pathologic; at least two values - or the last one - during the observation period are pathologic
Code 5: reference value is pathologically high (low); at least two values - or the last one - during the observation period are pathologically low (high)

Codes 4 and 5 are considered the most relevant.

3.6.6.3. Other safety parameters

3.6.6.3.1. Extrapyramidal symptom rating scale (ESRS)

The change from Baseline to the Endpoint was calculated for the total ESRS and ESRS subscale totals (questionnaire, parkinsonism, dystonia, dyskinesia, CGI of severity of dystonia, CGI of severity of parkinsonism, CGI of severity of dyskinesia, bucco-linguo-masticatory, choreoathetoid movements of limbs, hypokinetic and hyperkinetic symptoms), the individual parkinsonism items and the parkinsonism staging. The change from Baseline at other timepoints was also calculated, and the change from the maximum score determined.

The changes from Baseline were evaluated using the Wilcoxon Signed Rank Test.

The shifts versus Baseline at all timepoints were analyzed descriptively. The number of patients requiring anti EPS-medication was quantified and summarized.

Imputation was performed for ESRS. Missing items for ESRS were imputed as follows: if a patient did not allow the rater to assess the ESRS questionnaire, the items were left missing. Other ESRS scores (except for CGI of severity of dyskinesia, CGI of severity of parkinsonism, the CGI of severity of dystonia and stage of parkinsonism) were imputed by zero. If more than 25% of the items were missing, no imputation was performed and the total score remained missing. Missing ESRS scores were not included in the analyses. The same analyses were performed for the imputed results.

3.6.6.3.2. Vital signs, ECG and body weight

Intragroup tests (paired t-test) were performed to evaluate changes over time. Descriptive statistics and tabulations indicating abnormal values and/or changes were provided.

Changes in heart rate, diastolic blood pressure (DBP), and systolic blood pressure (SBP) were classified as follows:

Table 3-3: Criteria for classification of vital signs

Parameter	Abnormally high	Abnormally low
SBP (mmHg)	≥180 mmHg and increase ≥20	≤90 mmHg and decrease ≥20
DBP (mmHg)	≥105 mmHg and increase ≥15	≤50 mmHg and decrease ≥15
Pulse (bpm)	≥120 bpm and increase ≥15	≤50 bpm and decrease ≥15

The parameters heart rate, PQ and QRS were also categorized into normal, abnormal and pathological using the following boundaries:

Heart rate (bpm): below normal ≤55 < normal ≤ 100 < above normal
PQ (msec): below normal ≤ 120 < normal ≤ 200 < above normal
QRS (msec): normal < 120 ≤ abnormal

No calculations, e.g., of QT interval corrected according to Fridericia's or Bazette's formalae (QTcF and QTcB, respectively) were made. However, the expert's (child cardiologist, Charles Berul, see section 7.4) readings of QTcF and QTcB were used and changed from seconds to milliseconds.

Additional ECG parameters were calculated as follows: the linear correction of QT for heart rate according to Sagie, et al.[28] [QTcL = QT + 154*(1-RR)], and the linear correction of QT for heart rate according to new FDA recommendations [QTcL-2 = QT + slope*(1-RR)], where slope was estimated by fitting a linear model of QT = a + slope * RR of baseline data. For this parameter, slope=188 was used.

Changes from Baseline were calculated and analyzed with paired t-tests for each corrected QT interval. The percent of patients with clinically relevant changes in their ECG evaluations was summarized at each post-Baseline timepoint. The shifts in corrected QT intervals from baseline to post-Baseline were presented in cross-tabulations.

To fully evaluate ECG QTc interval changes, the following definition of normal/abnormal intervals were applied to the data:

	female	male
normal	≤450 ms	≤430 ms
borderline	451 through 470 ms	431 through 450 ms
prolonged	471 through 500 ms	451 through 500 ms
pathological	>500 ms	>500 ms

Changes in QTc intervals were also classified as follows:

- change from Baseline <30 ms (includes all decreases and the increases < 30 ms)
- increase from Baseline 30 – 60 ms
- increase from Baseline >60 ms

Body mass index (BMI) was calculated as weight in kg divided by the square of height in cm. Descriptive statistics were generated, and intragroup tests (paired t-test) were performed to evaluate changes over time for weight, height and BMI.

3.6.6.3.3. Tanner staging

The sexual maturity of the patients was rated on a scale of 1 to 5 by selecting one diagram (from a series of 5) thought to most closely resemble the sexual maturity of the patient. Tanner staging was conducted at Baseline and at Visits 12 and 14. Number and percent of patients in each category were generated at each visit.

3.6.6.3.4. Cognitive tests

Descriptive statistics were generated for the cognitive function parameters. The changes from Baseline were evaluated using the paired t-test.

4. RESULTS - PATIENT AND DISEASE CHARACTERISTICS

4.1. Patient disposition

The trial was run from 18 March 1997 to 10 July 2001. Eighty-nine physicians in 12 countries, primarily psychiatrists, psychologists and pediatricians who all were experienced in treating these types of patients participated in the trial (Listing SUB.INV.1). In total, 589 patients were recruited. Eighty-five of these patients received no treatment (Listing SUB.DV.2). Reasons that these patients did not receive trial medication were ineligibility to continue the trial (60), withdrawal of consent (11), loss to follow up (8), noncompliance (3), other reasons (2), or because they were asymptomatic/cured (1).

Of the 504 patients who entered the trial and received study medication, 481 newly entered the trial and 23 came from RIS-CAN-19 (Display SUB.PD.1). Enrollment by center is presented in Display SUB.INV.

The discontinuation summary is presented in Table 4-1. Listing SUB.TT lists each patient by study completion or discontinuation, their reason for discontinuation, and the number of days in the trial.

Table 4-1: Summary of reasons for premature discontinuation

	Newly entered patients (n=481)	Patients who received risperidone in RIS-CAN-19 (n=23)	Total (N=504)
	n (%)	n (%)	n (%)
Number of patients who were treated	481 (100.0)	23 (100.0)	504 (100.0)
Number of patients who completed	351 (73.0)	16 (69.6)	367 (72.8)
Number discontinued	130 (27.0)	7 (30.4)	137 (27.2)
Reason for discontinuation			
Adverse event	42 (8.7)	1 (4.3)	43 (8.5)
Patient lost to follow-up	25 (5.2)	1 (4.3)	26 (5.2)
Patient withdrew consent	22 (4.6)	0 (0.0)	22 (4.4)
Insufficient response	16 (3.3)	2 (8.7)	18 (3.6)
Patient non-compliant	16 (3.3)	1 (4.3)	17 (3.4)
Other	7 (1.5)	1 (4.3)	8 (1.6)
Patient ineligible to continue trial	2 (0.4)	0 (0.0)	2 (0.4)
Patient asymptomatic/ cured	0 (0.0)	1 (4.3)	1 (0.2)

Source: Display SUB.TT

One hundred thirty-seven patients (27.2%) dropped out before trial completion. The most common reason for discontinuation from the trial was adverse event (43 patients, 8.5%), followed by loss to follow-up (26 patients, 5.2%), withdrawal of consent (22 patients, 4.4%), insufficient response (18 patients, 3.6%), noncompliance (17 patients, 3.4%), other (8 patients, 1.6%), ineligibility to continue the trial (2 patients, 0.4%), and lack of symptoms (1 patient, 0.2%).

4.2. Protocol deviations

A summary of major protocol deviations is presented in Table 4-2, and details are presented in Display SUB.DV. Patients with major protocol deviations are individually listed in Listing SUB.DV.1.

Table 4-2: Summary of major protocol deviations

	Newly entered patients (n=481)	Patients who received risperidone in RIS-CAN-19 (n=23)	Total (N=504)
	n (%)	n (%)	n (%)
Number (%) of patients with deviations	58 (12.1)	9 (39.1)	67 (13.3)
Investigator mistake[a]	0 (0.0)	2 (8.7)	2 (0.4)
Intercurrent forbidden therapy	53 (11.0)	6 (26.1)	59 (11.7)
Selection criteria not met	6 (1.2)	3 (13.0)	9 (1.8)
Abnormal laboratory values	0 (0.0)	1 (4.3)	1 (0.2)
Age out of limits	1 (0.2)	0 (0.0)	1 (0.2)
Baseline disease condition out of limits	4 (0.8)	2 (8.7)	6 (1.2)
Selection criteria not met (NOS)[b]	1 (0.2)	0 (0.0)	1 (0.2)

[a] Interval between termination of RIS-CAN-19 and entry into RIS-INT-41 was >3 weeks.
[b] Not otherwise specified
Note that a patient can have more than one deviation
Source: Display SUB.DV

Apart from early withdrawals, described in Section 4.1 above, protocol deviations, mainly forbidden intercurrent therapy, were noted in 67 patients (13.3%). Fifty-nine patients (11.7%) took forbidden intercurrent therapy, the most frequent of which was Ritalin® (methylphenidate hydrochloride), taken by 18 patients (Listing SUB.DV.1). Although allowed by the protocol, Ritalin was taken at doses that had not been stabilized at a constant dosage 30 days before the start of the study.

4.3. Demographic and other baseline characteristics

Of the 23 patients who participated in RIS-CAN-19, 10 had been randomized to treatment with risperidone and 13 to placebo (Listing SUB.INV.4). The median number of days between the last medication intake in trial RIS-CAN-19 and the first intake in trial RIS-INT-41 was 2 days (range 1-50 days, Display SUB.PD.4).

Display SUB.DM gives the demographic data of the patients newly entered in the trial and of the patients who participated in trial RIS-CAN-19, and these data are summarized in Table 4-3.

Table 4-3: Summary of demographic and baseline characteristics

	Newly entered patients (n=481)[a]	Patients who received risperidone in RIS-CAN-19 (n=23)[b]	Total (N=504)
Sex (n, %)			
Female	81 (16.8)	4 (17.4)	85 (16.9)
Male	400 (83.2)	19 (82.6)	419 (83.1)
Race (n, %)			
Black	32 (6.7)	5 (21.7)	37 (7.3)
Caucasian	407 (84.6)	18 (78.3)	425 (84.3)
Hispanic	6 (1.2)	0 (0.0)	6 (1.2)
Oriental	2 (0.4)	0 (0.0)	2 (0.4)
Other	34 (7.1)	0 (0.0)	34 (6.7)
Domiciliary status (n, %)			
n	476	23	499
Lives with other	87 (18.3)	6 (26.1)	93 (18.6)
Lives with parents	389 (81.7)	17 (73.9)	406 (81.4)
Age (years)			
Mean ± SE[c]	9.7 ± 0.11	8.8 ± 0.45	9.7 ± 0.11
Median (min;max[d])	10 (4; 14)	9 (5; 12)	10 (4; 14)
Age class			
Children (<12 years)	355 (73.8)	20 (87.0)	375 (74.4)
Adolescents (≥12 years)	126 (26.2)	3 (13.0)	129 (25.6)
Weight (kg)			
N	480	23	503
Mean ± SE	36.5 ± 0.63	31.0 ± 1.85	36.3 ± 0.61
Median (min;max)	34 (13.6; 87.8)	31.8 (19.6; 51.9)	33.3 (13.6; 87.8)
Height (cm)			
N	463	23	486
Mean ± SE	140.1 ± 0.74	133.4 ± 2.84	139.8 ± 0.72
Median (min;max)	139.7 (101.6; 192)	134.9 (109; 154.9)	139 (101.6; 192)
Body mass index (kg/m^2)			
N	463	23	486
Mean ± SE	18.0 ± 0.17	17.7 ± 0.53	17.9 ± 0.16
Median (min;max)	17.2 (11.9; 35.3)	16.8 (13.9; 23.4)	17.2 (11.9; 35.3)
IQ			
n	480	23	503
Mean ± SE	64 ± 0.62	68.1 ± 2.2	64.2 ± 0.6
Median (min;max)	66 (35; 84)	70 (49; 83)	66 (35; 84)
Vineland score			
Mean ± SE	52.3 ± 0.62	60 ± 1.93	52.7 ± 0.6
Median (min;max)	52 (19; 83)	65 (40; 71)	53 (19; 83)
CSI score			
n	453	23	476
Mean ± SE	101.2 ± 1.4	109.3 ± 4.4	101.6 ± 1.4
Median (min; max)	99 (28; 212)	112 (60; 143)	100 (28; 212)

Table 4-3: Summary of demographic and baseline characteristics (continued)

	Newly entered patients (n=481)[a]	Patients who received risperidone in RIS-CAN-19 (n=23)[b]	Total (N=504)
Tanner staging (n, %)			
n	470	23	493
1	326 (69.4)	19 (82.6)	345 (70.0)
2	72 (15.3)	1 (4.3)	73 (14.8)
3	39 (8.3)	2 (8.7)	41 (8.3)
4	26 (5.5)	0 (0.0)	26 (5.3)
5	7 (1.5)	1 (4.3)	8 (1.6)
DSM-IV			
Axis I[c] (n, %)			
ADHD[e]	10 (2.1)	0 (0.0)	10 (2.0)
ADHD+BD NOS	49 (10.2)	2 (8.7)	51 (10.1)
ADHD+CD	96 (20.0)	9 (39.1)	105 (20.8)
ADHD+ODD	90 (18.7)	5 (21.7)	95 (18.8)
BD NOS	32 (6.7)	1 (4.3)	33 (6.5)
CD	118 (24.5)	2 (8.7)	120 (23.8)
ODD	86 (17.9)	4 (17.4)	90 (17.9)
Axis II (mental retardation) (n, %)			
N	480	23	503
Borderline	178 (37.1)	11 (47.8)	189 (37.6)
Mild	206 (42.9)	11 (47.8)	217 (43.1)
Moderate	96 (20.0)	1 (4.3)	97 (19.3)
Axis III (n, %)			
n	25	1	26
Asthma	0 (0.0)	1 (100.0)	1 (3.8)
Unspecified	25 (100.0)	0 (0.0)	25 (96.2)

[a]Newly entered patients. [b]Patients who came from RIS-CAN-19. [c]SE: standard error. [d]min;max: minimum – maximum.
[e]ADHD: Attention Deficit/Hyperactivity Disorder; BD NOS: Disruptive Behavior Disorder not otherwise specified; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder
Source: Display SUB.DM, Display SUB.DM.2, Display SAF.VS.3B, and Display SAF.TAN.1

Overall, 83.1% of the patients were male, and the median age was 10 years (range 4-14 years). One hundred twenty-nine patients (25.6%) were adolescents (12 years or older). Mean weight and height at Baseline were 36.3 kg and 139.8 cm, respectively.

There were 225 patients (44.6%) with conduct disorder alone or combined with ADHD. One hundred eighty-five patients (36.7%) had oppositional defiant disorder alone or combined with ADHD, and 84 patients (16.7%) had behavior disorder not otherwise specified alone or combined with ADHD. Ten patients (2.0%) were diagnosed with ADHD only.

There were 217 patients (43.1%) with mild mental retardation, 189 patients (37.6%) with borderline intellectual functioning, and 97 patients (19.3%) with moderate mental retardation.

4.4. Concomitant diseases and treatments

A wide range of concomitant diseases were reported across the treatment groups, none of which was thought to have any influence on the course of the trial (See Display SUB.DS and Listing SUB.DS). Four hundred thirty patients (85.3%) had at least one past or currently active medical condition at Baseline. The most frequently reported conditions were those involving ear, nose, and throat (70, 13.9% with currently active condition, 130, 25.8% with history/not active condition).

Three hundred seventy-six patients (74.6%) received concomitant medications. Display SUB.CT.1 lists all concomitant therapies by anatomic therapeutic chemical (ATC) class and generic name. A listing of all concomitant therapies with dosing details and indication is given in Listing SUB.CT.1. Listing SUB.CT.4 includes concomitant medications taken during the pre- and post-trial period.

A summary of all concomitant medications taken by 2% or more patients is presented in Table 4-4, while a detailed overview for the classes of psychoanaleptic and psycholeptic drugs is given in Table 4-5.

Table 4-4: Concomitant therapy taken by ≥2% of all patients

Generic name	Risperidone (N=504) n (%)
Paracetamol	134 (26.6)
Methylphenidate hydrochloride	62 (12.3)
Clavulin	41 (8.1)
Amoxicillin	32 (6.3)
Bactrim®	27 (5.4)
Ibuprofen	27 (5.4)
Acetylsalicylic acid	25 (5.0)
Ambroxol hydrochloride	19 (3.8)
Mebendazole	18 (3.6)
Salbutamol	18 (3.6)
Amoxicillin trihydrate	17 (3.4)
Ambroxol®	15 (3.0)
Acetylcysteine	14 (2.8)
Loratadine	14 (2.8)
Aminophenazone	13 (2.6)
Oxymetazoline hydrochloride	13 (2.6)
Dimetapp®	12 (2.4)
Pyrantel embonate	11 (2.2)
Fluticasone propionate	11 (2.2)
Cefuroxime axetil	11 (2.2)
Xylometazoline hydrochloride	10 (2.0)
Methylphenidate	10 (2.0)

Source: Display SUB.CT.1

Table 4-5: Concomitant therapy: psychoanaleptic and psycholeptic ATC classes

Concomitant psychoanaleptic and psycholeptic therapy	Risperidone (N=504) n (%)
Psychoanaleptics	
Amphetamine	1 (0.2)
Dexamphetamine sulfate	6 (1.2)
Dosulepin	1 (0.2)
Methylphenidate	10 (2.0)
Methylphenidate hydrochloride	62 (12.3)
Pemoline	1 (0.2)
Pemoline magesium	1 (0.2)
Piracetam	3 (0.6)
Trazodone	1 (0.2)
Psycholeptics	
Chloral hydrate	3 (0.6)
Clonazepam	3 (0.6)
Clotiapine	1 (0.2)
Diazepam	1 (0.2)
Euvegal-Tropfen N	1 (0.2)
Hydroxyzine	1 (0.2)
Hydroxyzine hydrochloride	2 (0.4)
Levomepromazine	1 (0.2)
Lithium carbonate	1 (0.2)
Lorazepam	4 (0.8)
Midazolam maleate	2 (0.4)
Nitrazepam	1 (0.2)
Oxazepam	1 (0.2)
Pipamperone	4 (0.8)
Prochlorperazine maleate	1 (0.2)
Thioridazine hydrochloride	2 (0.4)
Valerian extract	2 (0.4)

Source: Display SUB.CT.1

The most frequently used medication was paracetamol (n=134, 26.6%). Paracetamol was taken mostly for common conditions such as headache, fever, and cold. Methylphenidate hydrochloride for the treatment of ADHD was taken by 62 patients (12.3%) during the trial. None of these medications was thought to have had any influence on the course or outcome of the trial.

Special attention was given in the analysis to drugs administered for the treatment of EPS. Five patients (1.0%) took anti-Parkinson medication in the course of the trial (Display SUB.CT.2). Four patients (0.8%) took biperiden hydrochloride and 1 patient (0.2%) took trihexyphenidyl hydrochloride. One patient who received biperiden hydrochloride also received metacycline, potassium chloride, and furosemide (Listing SUB.CT.2).

The number of patients who used lorazepam as rescue medication for symptoms related to conduct disorder was reported separately. Of 4 patients who received lorazepam during the study, 2 received it as a premedication for medical procedures (Listing SUB.CT.1). The 2 remaining patients received lorazepam as a rescue medication, of whom one was given lorazepam for psychic decompensation, and one was given lorazepam for aggressive behavior (Display SUB.CT.3 and Listing SUB.CT.3).

5. RESULTS - EXTENT OF EXPOSURE

5.1. Drug dose and duration

The trial medication was administered as described in section 3.3.4 'Selection and timing of dose.'

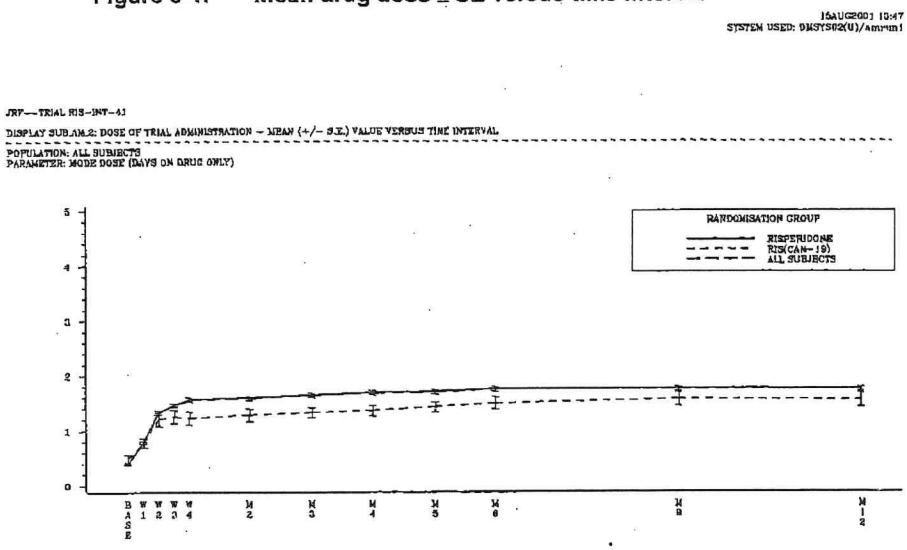
The mean, mode and maximum dose in mg/day at each timepoint are shown in Display SUB.AM.1A, and the duration of trial medication is shown in Display SUB.AM.1B. A summary of trial medication in mg/kg per day is given in Display SUB.AM.3, and a summary of trial medication in mg/day is given in Display SUB.AM.3A. These data are summarized in Table 5-1. The mean mode drug dose over time is shown in Figure 5-1.

Table 5-1: Mean, mode and maximum drug dose and duration (days on drug only)

	Risperidone (N=504)
Treatment duration (days on drug)	
Mean ± SE	307.3 ± 5.00
Median (min;max)	358 (1;505)
Dose (mg/day)	
Mode dose	
Mean ± SE	1.70 ± 0.04
Median (min;max)	1.60 (0.1; 4.8)
Mean dose	
Mean ± SE	1.59 ± 0.03
Median (min;max)	1.47 (0.1; 4.3)
Maximum dose	
Mean ± SE	1.89 ± 0.04
Median (min;max)	1.80 (0.1; 5.0)
Dose (mg/kg/day)	(N=502)
Mode dose	
Mean ± SE	0.02 ± 0.00
Median (min;max)	0.01 (0; 0.06)
Mean dose	
Mean ± SE	0.04 ± 0.00
Median (min;max)	0.04 (0.01; 0.08)

Source: Displays SUB.AM.1A, SUB.AM.1B, SUB.AM.3, and SUB.AM.3A

Figure 5-1: Mean drug dose ± SE versus time interval



Source: Display SUB.AM.2

The mean total trial duration was 314.2±4.83 days (range, 1-505 days, Display SUB.AM.1B). The mean treatment duration was 307.3±5.00 days (range, 1-505 days) when only days on drug were taken into account.

During dose titration in the initial 4 weeks of the trial, the mean mode daily dosage increased from 0.39±0.01 mg/day at Baseline to 1.54±0.03 mg/day at Week 4. The mean dose remained stable thereafter. The mean mode daily dosage overall (excluding days off drug) was 1.69±0.04 mg/day.

5.2. Treatment compliance

A record was kept of the drug dispensed and returned for each patient as described in section 3.3.4. Analyses of treatment compliance were not performed.

5.3. Pharmacokinetics

Final pharmacokinetic data will be provided in an amendment to this report.

6. RESULTS - EFFICACY EVALUATION

6.1. Data sets analyzed

The efficacy analysis included all patients who received trial medication and had at least one post-Baseline visit for the Conduct Problem subscale of the N-CBRF (ITT analysis).

The sample included in the ITT analysis is the one described under sections 4.1 'Patient disposition' and 4.3 'Demographic and other baseline characteristics.'

6.2. Analysis of efficacy

Only non-imputed efficacy results are discussed in the efficacy section of this report. The imputed and non-imputed results were similar.

6.2.1. PRIMARY EFFICACY VARIABLE

The primary efficacy parameter was the change in behavior from open-label Baseline to Endpoint as measured by the Conduct Problem subscale of the N-CBRF. The Conduct Problem subscale was measured at Screening, Baseline, and at each of the subsequent visits (Visits 4 to14). A lower score on the Conduct Problem subscale of N-CBRF indicates a better condition.

The results for the primary efficacy parameter at every timepoint are shown in Display EFF.NCBRF.1B, and are summarized in Table 6-1 and Figure 6-1.

Table 6-1: Conduct Problem subscale score: mean (± SE) and mean (± SE) change from open-label baseline at the different timepoints

	ITT Patients (N=496)			
			Change from open-label baseline	
Timepoint	n[a]	Mean ± SE	Mean[b] ± SE	95% CI
Screening	470	34.5 ± 0.3		
Baseline	487	32.9 ± 0.3		
Week 1	479	24.6 ± 0.5	-8.3 ± 0.4	(-9.1 ; -7.6)
Week 2	454	19.9 ± 0.5	-13.0 ± 0.5	(-13.9 ; -12.0)
Week 3	463	17.8 ± 0.5	-15.2 ± 0.5	(-16.2 ; -14.3)
Week 4	479	16.4 ± 0.5	-16.4 ± 0.5	(-17.4 ; -15.5)
Month 2	438	16.5 ± 0.5	-16.4 ± 0.5	(-17.3 ; -15.4)
Month 3	434	16.8 ± 0.5	-16.0 ± 0.5	(-17.0 ; -14.9)
Month 4	422	16.0 ± 0.5	-16.6 ± 0.5	(-17.7 ; -15.6)
Month 5	411	16.5 ± 0.6	-16.1 ± 0.5	(-17.2 ; -15.1)
Month 6	411	16.6 ± 0.6	-16.1 ± 0.6	(-17.2 ; -15.0)
Month 9	390	16.0 ± 0.5	-16.6 ± 0.6	(-17.7 ; -15.5)
Month 12	363	15.2 ± 0.5	-17.0 ± 0.6	(-18.2 ; -15.9)
Endpoint	496	17.0 ± 0.5	-15.8 ± 0.5	(-16.8 ; -14.8)

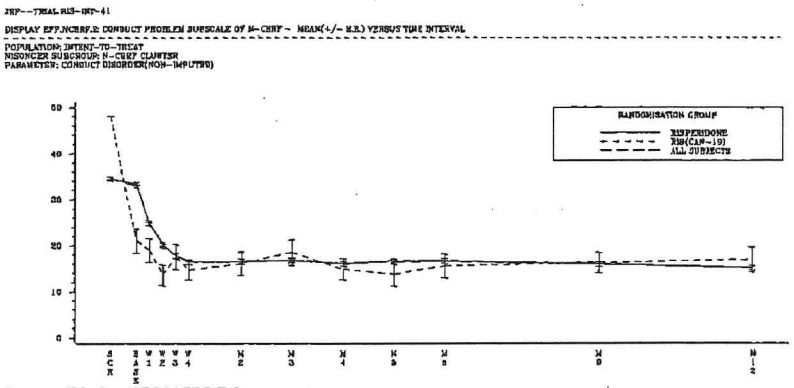
Non-imputed results

[a] Included in this table are data from only those patients with change-from-Baseline data at each given timepoint

[b] There were significant ($p<0.001$) changes from Baseline at every timepoint based on 2-sided paired t-test

Source: Display EFF.NCBRF.1B

Figure 6-1: Mean ± SE versus time interval on the Conduct Problem Subscale of N-CBRF



Source: Display EFF.NCBRF.2

The mean score dropped from 32.9±0.3 at the open-label Baseline to 17.0±0.5 at Endpoint, and to 15.2±0.5 at Month 12. The mean change from open-label Baseline at Endpoint and at Month 12 was -15.8 and -17.0, respectively. The improvement was highly statistically significant ($p<0.001$).

The improvement was observed especially during the first 4 weeks of treatment (Figure 6-1). Scores remained stable thereafter.

As shown in Display EFF.NCBRF.1B, the mean open-label Baseline score for patients who participated in RIS-CAN-19 (n=23, 21.0±2.7) was lower than those of the newly entered patients (n=464, 33.5±0.3). This suggests that the beneficial effects of treatment on the primary efficacy parameter for patients treated in trial RIS-CAN-19 were already partially obtained in the latter trial.

The mean change from the double-blind Baseline for all patients who participated in trial RIS-CAN-19 was -13.2±2.5 at Endpoint ($p<0.001$, Display EFF.NCBRF.1A).

6.2.2. SECONDARY EFFICACY VARIABLES

Secondary efficacy variables were the change from open-label Baseline on the other subscales of the N-CBRF, ABC total score, all subscales of the ABC, CGI severity, and VAS of most problematic symptom.

Because of the small numbers of patients (n=23), analyses of secondary efficacy variables were only performed for the all-patients population.

6.2.2.1.1. Other subscales of the Nisonger-Child Behavior Rating Form (N-CBRF)

In addition to the Conduct Problem subscale of the N-CBRF, the following subscales of N-CBRF were analyzed as secondary efficacy variables: the positive social behavior subscales (compliant/ calm, adaptive/ social) and the problem behavior subscales (insecure/ anxious, hyperactive, self-injury/ stereotyped, self-isolated/ ritualistic, overly sensitive). Lower scores indicate a better condition on all subscales except compliant/ calm and adaptive/ social, where higher scores imply improvement.

The results of the other subscales of the N-CBRF are given in Display EFF.NCBRF.3B. The scores at Month 12 and at Endpoint are summarized in Table 6-2.

Table 6-2: Other subscales of Nisonger Child Behavior rating form: mean (± SE) and mean (± SE) change from open-label baseline at Month 12 and at endpoint

	ITT Patients (N=496)			
			Change from open-label baseline	
N-CBRF subscale	n	Mean ± SE	Mean[a] ± SE	95% CI
Positive Social Behavior:				
Compliant/calm[b]				
Month 12	359	9.2 ± 0.20	3.9 ± 0.22	(3.5 ; 4.3)
Endpoint	496	8.6 ± 0.17	3.4 ± 0.19	(3.1 ; 3.8)
Adaptive/social[b]				
Month 12	361	6.7 ± 0.14	2.1 ± 0.15	(1.8 ; 2.4)
Endpoint	496	6.4 ± 0.12	1.9 ± 0.13	(1.6 ; 2.2)
Problem Behavior Subscales:				
Insecure/anxious				
Month 12	361	9.5 ± 0.37	-6.2 ± 0.44	(-7.1 ; -5.3)
Endpoint	496	10.4 ± 0.33	-5.7 ± 0.38	(-6.4 ; -4.9)
Hyperactive				
Month 12	361	10.4 ± 0.31	-7.8 ± 0.36	(-8.6 ; -7.1)
Endpoint	496	11.2 ± 0.28	-6.8 ± 0.31	(-7.4 ; -6.2)
Self-injury/ stereotyped				
Month 12	363	1.3 ± 0.15	-1.2 ± 0.19	(-1.6 ; -0.9)
Endpoint	496	1.5 ± 0.13	-1.0 ± 0.16	(-1.3 ; -0.7)
Self-isolated/ ritualistic				
Month 12	362	3.1 ± 0.19	-1.8 ± 0.22	(-2.2 ; -1.4)
Endpoint	496	3.4 ± 0.16	-1.7 ± 0.19	(-2.0 ; -1.3)
Overly sensitive				
Month 12	364	5.0 ± 0.17	-2.3 ± 0.19	(-2.7 ; -1.9)
Endpoint	496	5.4 ± 0.15	-2.1 ± 0.16	(-2.4 ; -1.8)

Non-imputed results

[a] There were significant ($p<0.001$) changes from Baseline to Month 12 and Endpoint based on 2-sided paired t-test

[b] Higher scores indicate better condition. For all other parameters, lower scores indicate a better condition

Source: Display EFF.NCBRF.3B

The other subscales of the N-CBRF showed a similar profile to the Conduct Problem Subscale. The mean changes from Baseline were statistically significant at all timepoints for all subscales of the N-CBRF: compliant/ calm, adaptive/ social, insecure/ anxious, hyperactive, self-injury/ stereotyped, self-isolated/ ritualistic and overly sensitive ($p<0.001$).

Improvement increased during the first 4 weeks and was maintained thereafter.

6.2.2.1.2. Aberrant Behavior Checklist (ABC)

The results for the total ABC score and the different subscales of the ABC are shown in Display EFF.ABC.1B. The change from the open-label Baseline at the different timepoints for the total ABC score is displayed graphically in Display EFF.ABC.2. The scores from the total ABC and its subscales at Month 12 and at Endpoint are summarized in Table 6-3. Lower scores indicate a better condition.

Table 6-3: Aberrant Behavior Checklist: mean (± SE) and mean change (± SE) from open-label baseline at Month 12 and at endpoint

	ITT Patients			
			Change from open-label baseline	
ABC	n	Mean ± SE	Mean[a] ± SE	95% CI
Total ABC				
Month 12	335	33.0 ± 1.35	-32.0 ± 1.52	(-35.0 ; -29.0)
Endpoint	453	37.4 ± 1.27	-28.3 ± 1.37	(-31.0 ; -25.6)
Irritability				
Month 12	349	10.0 ± 0.45	-8.8 ± 0.50	(-9.8 ; -7.9)
Endpoint	475	11.5 ± 0.42	-7.9 ± 0.45	(-8.8 ; -7.1)
Lethargy/social withdrawal				
Month 12	350	4.4 ± 0.33	-2.8 ± 0.36	(-3.6 ; -2.1)
Endpoint	471	5.0 ± 0.30	-2.5 ± 0.33	(-3.2 ; -1.9)
Stereotypic behavior				
Month 12	356	1.6 ± 0.17	-1.5 ± 0.24	(-2.0 ; -1.1)
Endpoint	482	1.8 ± 0.16	-1.3 ± 0.20	(-1.7 ; -0.9)
Hyperactivity				
Month 12	345	15.4 ± 0.58	-15.9 ± 0.67	(-17.2 ; -14.6)
Endpoint	469	17.3 ± 0.53	-14.0 ± 0.59	(-15.2 ; -12.9)
Inappropriate speech				
Month 12	363	2.3 ± 0.13	-1.7 ± 0.16	(-2.0 ; -1.4)
Endpoint	493	2.4 ± 0.12	-1.5 ± 0.13	(-1.7 ; -1.2)

Non-imputed results
[a] There were significant ($p<0.001$) changes from Baseline to Month 12 and Endpoint based on 2-sided paired t-test
Source: Display EFF.ABC.1B

The mean change from the open-label Baseline of the total ABC score ranged from -12.7 (Week 1) to -32.0 (Month 12), and was -28.3±1.4 at Endpoint ($p<0.001$). The improvement was especially observed during the

first 4 weeks of treatment and was statistically significant from Week 1 onward ($p<0.001$).

The scores on the individual subscales of the ABC showed a similar profile: Improvement increased during the first 4 weeks and was maintained thereafter.

6.2.2.1.3. Clinical Global Impression (CGI)

Display EFF.CGI.1 shows the distribution of the CGI of change of the patients' condition over time. The frequency distribution at the open-label Baseline, Month 12 and at Endpoint are summarized in Table 6-4.

Table 6-4: Frequency distribution of the Clinical Global Impression of change in patients' condition at Month 12 and at endpoint

	ITT Patients					
	Open-label baseline (n=485)		Month 12 (n=366)		Endpoint (n=483)	
CGI rating	n	(%)	n	(%)	n	(%)
Not ill	0	(0.0)	41	(11.2)	47	(9.7)
Very mild	3	(0.6)	117	(32.0)	128	(26.5)
Mild	25	(5.2)	118	(32.2)	145	(30.0)
Moderate	110	(22.7)	65	(17.8)	104	(21.5)
Marked	172	(35.5)	20	(5.5)	39	(8.1)
Severe	144	(29.7)	4	(1.1)	17	(3.5)
Extremely severe	31	(6.4)	1	(0.3)	3	(0.6)

Source: Display EFF.CGI.1

Overall, 320 (66.3%) patients showed no, very mild or mild symptoms at Endpoint (59, 12.2% marked to extremely severe) compared to 28 (5.8%) with very mild or mild symptoms at Baseline (347, 71.6% marked to extremely severe).

The number of patients with no or mild symptoms increased over time, while few patients had severe or extremely severe symptoms at the end of the trial. Changes were greatest during the first 4 weeks of treatment, and the scores remained stable thereafter.

6.2.2.1.4. Visual Analogue Scale (VAS) of the most troublesome symptom

The VAS score of the most troublesome symptom at the different timepoints is shown in Display EFF.VAS.1B and is graphically displayed in Display EFF.VAS.2. The scores at Month 12 and at Endpoint are summarized in Table 6-5. Lower scores indicate a better condition. The most frequent of the most troublesome symptoms included aggression, oppositional defiant behavior, and hyperactivity.

Table 6-5: Visual Analogue Scale: mean (± SE) and mean (± SE) change from open-label baseline at Month 12 and at endpoint

	ITT Patients			
			Change from open-label baseline	
	n	Mean ± SE	Mean[a] ± SE	95% CI
VAS score of the most troublesome symptom				
Month 12	366	28.8 ± 1.10	-45.1 ± 1.38	(-47.8 ; -42.4)
Endpoint	480	33.9 ± 1.10	-40.3 ± 1.27	(-42.8 ; -37.8)

[a] There were significant ($p<0.001$) changes from Baseline to Month 12 and Endpoint based on two-sided paired t-test.
Source: Display EFF.VAS.1B

There was substantial improvement in the VAS score from Week 1 (-11.9) to Month 12 (-45.1). The improvement at Endpoint was –40.3. Improvement increased during the first 4 weeks and was maintained thereafter. The improvement at Endpoint was -40.3±1.3. The change from Baseline was statistically significant at all timepoints ($p<0.001$). Improvement was greatest during the first 4 weeks of treatment and was maintained from Week 6 through Month 12.

6.2.2.2. Subgroup analyses

Subgroup analyses by DSM-IV Axis I (diagnosis group), Axis II diagnosis (degree of mental retardation) and patients who took/did not take psychostimulants were performed for the Conduct Problem subscale of the N-CBRF.

6.2.2.2.1. Subgroup analysis by diagnosis

Patients diagnosed with conduct disorder (DSM-IV 312.8) were analyzed separately from those diagnosed with oppositional defiant disorder (DSM-IV 313.81) and patients with disruptive behavior disorder not otherwise specified (DSM-IV 312.9). The results of this subgroup analysis are presented in Display EFF.STR.DIAG.NCBRF.1B and Display EFF.STR.DIAG.NCBRF.2. The results at Endpoint and Month 12 are summarized in Table 6-6.

Table 6-6: Conduct Problem subscale score: subgroup analysis by diagnosis

	ITT Patients			
			Change from open-label baseline	
Timepoint	n	Mean ± SE	Mean[a] ± SE	95% CI
Patients diagnosed with conduct disorder				
Month 12	162	15.3 ± 0.9	-16.7 ± 0.9	(-18.6 ; -14.9)
Endpoint	221	17.1 ± 0.8	-15.8 ± 0.8	(-17.4 ; -14.2)
Patients diagnosed with oppositional defiant disorder				
Month 12	127	15.5 ± 0.9	-17.6 ± 1.0	(-19.7 ; -15.6)
Endpoint	183	17.4 ± 0.8	-16.3 ± 0.9	(-18.1 ; -14.6)
Patients diagnosed with disruptive behavior not otherwise specified				
Month 12	65	14.4 ± 1.2	-16.6 ± 1.2	(-18.9 ; -14.3)
Endpoint	82	16.4 ± 1.2	-14.6 ± 1.1	(-16.9 ; -12.3)

Non-imputed results

[a] There were significant ($p<0.001$) changes from Baseline to Month 12 and Endpoint based on 2-sided paired t-test.

Source: Display EFF.STR.DIAG.NCBRF.1B

The mean change from the open-label Baseline for patients with conduct disorder ranged from -10.1 at Week 1 to -17.7 at Week 4. The improvement at Endpoint was -15.8.

The mean change from the open-label Baseline for patients with oppositional defiant disorder ranged from -7.2 at Week 1 to -17.6 at Month 12. The improvement at Endpoint was -16.3.

The mean change from the open-label Baseline for patients with disruptive behavior not otherwise specified ranged from -6.5 at Week 1 to -16.6 at Month 12. The improvement at Endpoint was -14.6.

The changes from open-label Baseline were statistically significant at all timepoints for all subgroups ($p<0.001$). The results were comparable for the three subgroups and similar to the overall results.

6.2.2.2.2. Subgroup analysis by degree of retardation

Patients diagnosed with borderline intellectual functioning (DSM-IV V62.89) were analyzed separately from patients diagnosed with mild (DSM-IV 317) or moderate (DSM-IV 318.0) mental retardation. The results are shown in Display EFF.STR.MR.NCBRF.1B and Display EFF.STR.MR.NCBRF.2. The degree of mental retardation was missing for 2 patients. Table 6-7 presents a summary of the results at Endpoint and Month 12.

Table 6-7: Conduct Problem subscale score: subgroup analysis is by degree of mental retardation

	ITT Patients			
			Change from open-label baseline	
Timepoint	n	Mean ± SE	Mean[a] ± SE	95% CI
Patients diagnosed with mild mental retardation				
Month 12	160	15.5 ± 0.9	-16.6 ± 0.9	(-18.4 ; -14.8)
Endpoint	214	17.1 ± 0.8	-15.7 ± 0.8	(-17.3 ; -14.1)
Patients diagnosed with moderate mental retardation				
Month 12	83	13.3 ± 1.1	-18.6 ± 1.1	(-20.7 ; -16.4)
Endpoint	96	14.0 ± 1.1	-18.0 ± 1.1	(-20.1 ; -15.8)
Patients diagnosed with borderline intellectual functioning				
Month 12	120	16.1 ± 0.9	-16.5 ± 1.0	(-18.5 ; -14.4)
Endpoint	185	18.5 ± 0.8	-14.9 ± 0.9	(-16.6 ; -13.2)

Non-imputed results
[a] There were significant ($p<0.001$) changes from Baseline to Month 12 and Endpoint based on 2-sided paired t-test.
Source: Display EFF.STR.MR.NCBRF.1B

The mean change from the open-label Baseline for patients with mild mental retardation ranged from -8.1 at Week 1 to -17.4 at Month 2. The improvement at Endpoint was -15.7.

The mean change from the open-label Baseline for patients with moderate mental retardation ranged from -9.1 (Week 1) to -19.0 (Month 4). The improvement at Endpoint was -18.0.

The mean change from the open-label Baseline for patients with borderline intellectual functioning ranged from -8.3 at Week 1 to -16.5 at Month 12. The improvement at Endpoint was -14.9.

These changes were statistically significant at all timepoints for all subgroups ($p<0.001$). The results were comparable for the three subgroups and similar to the overall results.

6.2.2.2.3. Subgroup analysis by patients who took/did not take psychostimulants

Patients who took psychostimulants during the treatment were analyzed separately from patients who did not take psychostimulants. The results are shown in Display EFF.STR.PSY.NCBRF.1B and Display EFF.STR.PSY.NCBRF.2. Table 6-8 presents a summary of the results at Endpoint and Month 12.

Table 6-8: Conduct Problem subscale score: subgroup analysis by patients who took/did not take psychostimulants

	ITT Patients			
			Change from open-label baseline	
Timepoint	n	Mean ± SE	Mean[a] ± SE	95% CI
Patients who took psychostimulants				
Month 12	64	14.7 ± 1.3	-16.5 ± 1.5	(-19.5 ; -13.5)
Endpoint	81	17.0 ± 1.3	-14.9 ± 1.4	(-17.7 ; -12.2)
Patients who did not take psychostimulants				
Month 12	299	15.3 ± 0.6	-17.1 ± 0.6	(-18.4 ; -15.9)
Endpoint	415	17.0 ± 0.5	-16.0 ± 0.6	(-17.1 ; -14.9)

Non-imputed results
[a] There were significant ($p<0.001$) changes from Baseline to Month 12 and Endpoint based on 2-sided paired t-test.
Source: Display EFF.STR.PSY.NCBRF.1B

The mean change from the open-label Baseline for patients who took psychostimulants ranged from -6.4 at Week 1 to -16.5 at Month 12. The improvement at Endpoint was -14.9.

The mean change from the open-label Baseline for patients who did not take psychostimulants ranged from -8.7 (Week 1) and -17.1 (Month 12). The improvement at Endpoint was -16.0.

The changes from open-label Baseline were statistically significant at all timepoints for both subgroups ($p<0.001$). The results were comparable for the two subgroups and similar to the overall results.

6.3. Pharmacodynamics

Not applicable.

6.4. Pharmacokinetic - pharmacodynamic relationships

Pharmacokinetic results are provided separately.

6.5. Quality of life

Not applicable.

6.6. Efficacy conclusions

The efficacy results of this 1-year multicenter open-label trial in 504 children and adolescents (5 to 14 years of age) with conduct or other disruptive behavior disorders and borderline intellectual functioning or mild to moderate mental retardation showed that treatment with risperidone had a statistically significant beneficial effect, as measured by the primary efficacy variable (i.e., the change from open-label Baseline by the Conduct Problem

Subscale of the N-CBRF at Endpoint), and on all secondary efficacy parameters (i.e., other subscales of the N-CBRF, ABC, investigators' CGI and the VAS of the most troublesome symptom). The improvement increased to a stable level during the first 4 weeks of treatment and remained improved for 12 months.

The effect of treatment with risperidone was consistent across subsets of patients with different DSM-IV Axis I diagnosis (conduct disorder, oppositional defiant disorder and disruptive behavior disorder not otherwise specified), DSM-IV Axis II diagnosis (mild or moderate mental retardation or borderline intellectual functioning), and across subsets of patients who took/did not take psychostimulants during treatment.

7. RESULTS - SAFETY EVALUATION

All patients who received trial medication were included in the safety analysis.

7.1. Adverse events

7.1.1. ALL ADVERSE EVENTS

7.1.1.1. Incidence

An overview of all patients with AEs by WHO System-organ class and preferred term is presented in Display SAF.AE.1. Table 7-1 presents a summary of all AEs that were reported by 10% or more of the patients.

A listing of all AEs (verbatim) that were reported in this trial is given in Listing SAF.AE.1.

Table 7-1: Incidence of adverse events reported by 10% or more of all patients

System Organ Class Preferred term	Risperidone (N=504) n (%)
Patients with any adverse event	462 (91.7)
Psychiatric Disorders	
Somnolence	149 (29.6)
Appetite increased	53 (10.5)
Respiratory System Disorders	
Rhinitis	137 (27.2)
Upper respiratory tract infection	83 (16.5)
Pharyngitis	74 (14.7)
Coughing	67 (13.3)
Central & Peripheral Nervous System Disorders	
Headache	110 (21.8)
Metabolic and Nutritional Disorders	
Weight increase	87 (17.3)
Body as a Whole – General Disorders	
Fatigue	69 (13.7)
Fever	62 (12.3)
Injury	54 (10.7)
Gastrointestinal System Disorders	
Vomiting	60 (11.9)
Endocrine Disorders	
Hyperprolactinemia	56 (11.1)

Source: Display SAF.AE.1

Four hundred sixty-two patients (91.7%) reported AEs during the trial. Somnolence was the most common AE, reported by 149 patients (29.6%). The investigator considered the relationship with the trial medication to be possibly, probably or very likely in 130 patients (Display SAF.AE.3).

Other frequently reported AEs were rhinitis (n=137, 27.2%), headache (n=110, 21.8%), weight increase (n=87, 17.3%), and upper respiratory tract infection (n=83, 16.5%).

Rhinitis was considered to have a possible drug relationship in 4 cases (no probably or very likely related), and upper respiratory tract infection was never considered to be possibly, probably, or very likely drug related. Headache was considered drug-related in 34 patients. Weight increase was considered drug related in 81 patients (Display SAF.AE.3).

7.1.1.2. Severity

Investigators reported all AEs as "mild," "moderate," or "severe." Severe events were not necessarily classified as serious AEs (see section 7.1.2.2). The incidence of AEs by severity (mild, moderate, severe) is shown in Display SAF.AE.2. A tabulation of all severe AEs by relationship to trial medication is given in Display SAF.AE.7. A summary table of all severe

AEs that in the opinion of the investigator were possibly, probably or very likely related to treatment with the trial medication is presented in Table 7-2.

Table 7-2: Incidence of possibly, probably or very likely drug-related severe adverse events

System Organ Class Preferred term	Risperidone (N=504) n (%)
Patients with one or more severe adverse events that were possibly, probably or very likely drug related	38 (7.5)
Patients with one or more severe adverse event (related or not)	74 (14.7)
Central & Peripheral Nervous System Disorders	
Headache	2 (0.4)
Extrapyramidal disorder	2 (0.4)
Dizziness	1 (0.2)
Dyskinesia	1 (0.2)
Dyskinesia, tardive	1 (0.2)
Dystonia	1 (0.2)
Hypertonia	1 (0.2)
Muscle contractions, involuntary	1 (0.2)
Psychiatric Disorders	
Somnolence	4 (0.8)
Anxiety	1 (0.2)
Appetite increased	2 (0.4)
Anorexia	1 (0.2)
Apathy	1 (0.2)
Concentration impaired	1 (0.2)
Nervousness	1 (0.2)
Gastrointestinal System Disorders	
Abdominal pain	1 (0.2)
Constipation	1 (0.2)
Nausea	1 (0.2)
Saliva increased	1 (0.2)
Body as a Whole—General Disorders	
Condition aggravated	5 (1.0)
Fatigue	4 (0.8)
Fever	1 (0.2)
Leg pain	1 (0.2)
Metabolic and Nutritional Disorders	
Weight increase	11 (2.2)
Obesity	1 (0.2)
White Cell and RES Disorders	
Granulocytopenia	2 (0.4)
Leukopenia	1 (0.2)
Cardiovascular Disorders, General	
Hypertension	1 (0.2)
Heart Rate and Rhythm Disorders	
Tachycardia	1 (0.2)
Secondary Terms	
Medication error	1 (0.2)
Endocrine Disorders	
Hyperprolactinemia	1 (0.2)

Source: Display SAF.AE.7 and Listing SAF.AE.2

Most AEs were mild (Display SAF.AE.9). Overall, 74 patients (14.7%) experienced one or more severe AEs, and of these patients, 38 (7.5%) had one or more possibly, probably or very likely treatment–related AEs (Listing SAF.AE.2). Treatment-related severe AEs that were reported by more than one patient were weight increase (n=11, 2.2%), condition aggravated (n=5, 1.0%), somnolence (n=4, 0.8%), fatigue (n=4, 0.8%), headache, extrapyramidal disorder, appetite increase, and granulocytopenia (n=2 for each, 0.2%).

7.1.1.3. Drug-relatedness

The relationship of the AEs to the trial medication was classified as none, doubtful, possible, probable or very likely. The incidence of AEs by relationship to the trial medication is given in Display SAF.AE.3. The majority of the drug-related AEs were expected symptoms for this class of drug, i.e., headache, fatigue, somnolence, hyperprolactinemia, increased appetite and weight gain.

7.1.2. DEATHS, OTHER SERIOUS, AND OTHER SIGNIFICANT ADVERSE EVENTS

7.1.2.1. Deaths

No patient died during the trial.

7.1.2.2. All serious adverse events

An overview of all patients with serious AEs by WHO System-organ class and preferred term is presented in Display SAF.AE.8. Each subject with serious adverse events is identified in Listing SAF.AE.3 (Annex 2).

Sixty-seven patients (13.3%) had serious AEs while receiving treatment with risperidone. As shown in Display SAF.AE.8, serious AEs (drug-related or not) that were reported by more than one patient were condition aggravated (n=13, 2.6%), aggressive reaction (n=10, 2.0%), abdominal pain (n=4, 0.8%); fever, pharyngitis, and viral infection (n=3 for each, 0.6%); injury, depression, suicide attempt, dyskinesia, tardive dyskinesia, headache, hypertonia, oculogyric crisis, vomiting, asthma, bronchitis, and medication error (n=2 for each, 0.4%).

Serious AEs that were considered drug-related (i.e., possibly, probably or very likely related) by the investigator are shown in Display SAF.AE.10, and are summarized in Table 7-3.

Table 7-3: Incidence of possibly, probably or very likely drug-related serious adverse events during risperidone treatment

System Organ Class Preferred term	Risperidone (N=504) n (%)
Patients with one or more serious adverse events that were possibly, probably, or very likely drug related[a]	17 (3.4)
Patients with one or more serious adverse event (related or not)[a]	67 (13.3)
Central & Peripheral Nervous System Disorders	
Dyskinesia	1 (0.2)
Dyskinesia, tardive	2 (0.4)
Headache	2 (0.4)
Oculogyric crisis	2 (0.4)
Dystonia	1 (0.2)
Extrapyramidal disorder	1 (0.2)
Hypokinesia	1 (0.2)
Body as a Whole—General Disorders	
Condition aggravated	2 (0.4)
Fever	1 (0.2)
Asthenia	1 (0.2)
Fatigue	1 (0.2)
Pallor	1 (0.2)
Therapeutic response increased	1 (0.2)
Psychiatric Disorders	
Anorexia	1 (0.2)
Confusion	1 (0.2)
Somnolence	1 (0.2)
Gastrointestinal System Disorders	
Abdominal pain	1 (0.2)
Nausea	1 (0.2)
Saliva increased	1 (0.2)
Secondary Terms	
Medication error	1 (0.2)
Skin and Appendages Disorders	
Urticaria	1 (0.2)
Heart Rate and Rhythm Disorders	
Tachycardia	1 (0.2)
Red Blood Cell Disorders	
Pancytopenia	1 (0.2)
Vision Disorders	
Glaucoma	1 (0.2)
White Cell and RES Disorders	
Granulocytopenia	1 (0.2)

[a]One additional patient (A03108) had an aggressive reaction judged serious and possibly drug-related during the placeho run-in phase.
Source: Display SAF.AE.10, Listing SAF.AE.3

Seventeen patients (3.4%) reported 67 drug-related serious AEs during treatment with risperidone (Listing SAF.AE.3). One additional patient (A03108) had an aggressive reaction judged possibly drug-related during the run-in placebo phase. The majority of all drug-related serious AEs were

EPS-related AEs. All EPS-related AEs (serious or not) are discussed in section 7.1.2.4.

7.1.2.3. Adverse events leading to discontinuation

An overview of all AEs that led to permanent discontinuation of the trial medication is given in Display SAF.AE.14, and is summarized in Table 7-4.

Table 7-4: Incidence of adverse events leading to permanent discontinuation

System Organ Class Preferred term	Risperidone (N=504) n (%)
Patients with one or more adverse events leading to discontinuation	43 (8.5)
Central & Peripheral Nervous System Disorders	
Headache	3 (0.6)
Dyskinesia	2 (0.4)
Dyskinesia, tardive	2 (0.4)
Extrapyramidal disorder	2 (0.4)
Hypertonia	2 (0.4)
Convulsions	1 (0.2)
Dizziness	1 (0.2)
Fecal incontinence	1 (0.2)
Hyperkinesia	1 (0.2)
Hypokinesia	1 (0.2)
Vertigo	1 (0.2)
Psychiatric Disorders	
Appetite increased	4 (0.8)
Somnolence	3 (0.6)
Anorexia	2 (0.4)
Anxiety	2 (0.4)
Depression	2 (0.4)
Nervousness	2 (0.4)
Agitation	1 (0.2)
Concentration impaired	1 (0.2)
Hallucination	1 (0.2)
Body as a Whole—General Disorders	
Condition aggravated	2 (0.4)
Asthenia	1 (0.2)
Fatigue	1 (0.2)
Fever	1 (0.2)
Leg pain	1 (0.2)
Edema	1 (0.2)
Gastrointestinal System Disorders	
Abdominal pain	1 (0.2)
Diarrhea	1 (0.2)
Diarrhea, bloody	1 (0.2)
Dyspepsia	1 (0.2)
Gastroenteritis	1 (0.2)
Nausea	1 (0.2)
Saliva increased	1 (0.2)
Vomiting	1 (0.2)
Metabolic and Nutritional Disorders	
Weight increase	9 (1.8)
Obesity	1 (0.2)
System Organ Class Preferred term	**Risperidone (N=504) n (%)**
Urinary System Disorders	
Urinary incontinence	2 (0.4)
Face edema	1 (0.2)

Table 7-4: Incidence of adverse events leading to permanent discontinuation (continued)	
Endocrine Disorders Gynecomastia	3 (0.6)
Cardiovascular Disorders, General Hypertension	1 (0.2)
Platelet, Bleeding & Clotting Disorders Epistaxis	1 (0.2)
Resistance Mechanism Disorders Sepsis	1 (0.2)
Respiratory System Disorders Dyspnea	1 (0.2)
White Cell and RES Disorders Granulocytopenia	1 (0.2)

Note that a patient can have more than one adverse event that led to discontinuation
Source: Display SAF.AE.14

Forty-three patients (8.5%) had AEs that resulted in permanent discontinuation of the trial medication. Six patients had one or more EPS-related adverse events that led to permanent discontinuation (see section 7.1.2.4).

7.1.2.4. Other significant adverse events

The incidence of EPS-related AEs is presented in Display SAF.AE.11, and is summarized in Table 7-5. An individual patient listing is given in Listing SAF.AE.4.

Table 7-5: Incidence of EPS-related adverse events

System Organ Class Preferred term	Risperidone (N=504) n (%)
Patients with one or more EPS-related adverse event	108 (21.4)
Central & Peripheral Nervous System Disorders	
Extrapyramidal disorder	27 (5.4)
Tremor	22 (4.4)
Hypertonia	21 (4.2)
Hypokinesia	21 (4.2)
Hyperkinesia	20 (4.0)
Dyskinesia	15 (3.0)
Bradykinesia	14 (2.8)
Dystonia	9 (1.8)
Gait abnormal	9 (1.8)
Oculogyric crisis	5 (1.0)
Dyskinesia tardive	2 (0.4)

Source: Display SAF.AE.11

As shown in Listing SAF.AE.4, 8 patients (1.6%) had EPS-related AEs that were reported as serious: 2 patients had hypertonia, 1 patient had dyskinesia and tardive dyskinesia, 1 patient had tardive dyskinesia, 2 patients had oculogyric crisis, and 1 patient had hypokinesia, and 1 patient had dystonia.

Six patients (1.2%) permanently discontinued treatment because of EPS-related AEs, 4 patients discontinued treatment temporarily, and 30 patients had one or more dose adjustments.

Overall, most EPS-related AEs were mild and considered possibly, probably or very likely related to risperidone treatment.

Five patients required treatment with anti-EPS medication (Listing SUB.CT.2), including the anti-Parkinson medications biperiden hydrochloride (4 patients) and trihexyphenidyl hydrochloride (1 patient).

Two patients (0.4%) reported reversible tardive dyskinesia.

A 9-year-old female patient (A03233, 0.6 mg/day risperidone) had an unremarkable medical history. At the final visit, the patient was found to have abnormal movements of the lips. She also tossed her head back and occasionally jerked her shoulders back. The mother gave the last dose of study medication 30 hours before the examination. The mother stated that she noticed that the head and truncal movements had been going on for 2 months. The mouth involvement had not begun until approximately 12 hours after the study treatment had stopped (on Day 374). During a follow-up examination 10 days later, the patient's symptoms were improved and later resolved (the time to complete recovery was not recorded). The oral dyskinesia was diagnosed as tardive dyskinesia; another possible diagnosis put forward by the investigator was discontinuation dyskinesia.

A 7-year old male patient (A03278, 1 mg/day risperidone) had an unscheduled visit for urticarial rash 133 days after the start of treatment. Occasional movement of the lips was noted, and the risperidone dosage was reduced from 1.6 mg/day to 1.0 mg/day. One week later, no movements were noted. The following week, the patient presented with marked labial movements, diagnosed as moderate tardive dyskinesia, and medication was stopped. The patient recovered without treatment 2 weeks later. The relationship with the trial medication was judged as very likely. This adverse event was reported as serious.

Prolactin-related AEs are discussed in section 7.2.4. No patient had glucose-related AEs.

7.1.3. ANALYSIS AND DISCUSSION OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

Individual case reports on deaths, other serious AEs and AEs leading to discontinuation of treatment are given in Annex 1.

7.2. Clinical laboratory evaluation

7.2.1. LABORATORY VALUES OVER TIME

Clinical laboratory data were available for all patients. Four hundred eighty patients (95%) had paired laboratory data, i.e., both at Baseline and at least once during or at the end of treatment. Display SAF.LAB.1B describes the descriptive statistics and distribution of changes from open-label Baseline at each timepoint for hematology and biochemistry. Shift tables for each parameter are given in Display SAF.LAB.2B.

Overall, there were no consistent or clinically relevant changes in blood chemistry or hematology, with the exception of prolactin (see section 7.2.4).

7.2.2. INDIVIDUAL CHANGES

The numbers of patients with low, normal, or high values, with respect to laboratory normal ranges, at Screening and at each timepoint are given in Display SAF.LAB.2B.

7.2.3. INDIVIDUAL CLINICALLY SIGNIFICANT ABNORMALITIES

Two hundred seventy-nine patients (58%) showed potentially clinically important changes (see section 3.6.6.2) at some time during the trial. Of these patients, 118 (25%) had a 'code-4' important abnormality, i.e., non-pathological laboratory values before treatment but at least 2 values—or the last one—during the observation period were pathologic (Display SAF.LAB.4B). No patients had code-5 abnormalities.

Individual data on 'code-4' important abnormalities are given in Listing SAF.LAB.2B. The numbers of patients with 'code-4' important abnormalities are summarized in Table 7-6.

Table 7-6: Potentially clinically important changes in laboratory values

Laboratory test	Risperidone (N=504)		
	↑	↓	Total
Clinical chemistry			
Chloride	4	-	4
Potassium	5	-	5
Total protein	2	1	3
Urea	3	-	3
Total bilirubin	3	-	3
Alkaline phosphatase	25	-	25
γ-GT	1	-	1
AST	2	-	2
ALT	6	-	6
Bicarbonate	3	51	52[a]
Hematology			
Hemoglobin	-	14	14
Hematocrit	-	10	10
WBC	2	3	5
Platelet count	9	3	12

↑ increase to above upper pathological limit
↓ decrease to below lower pathological limit
Note: a patient could have more than one 'code-4' abnormality
[a]Patient A03310 had a code-4 increase (Week 4) and a code-4 decrease (Month 3). Patient A03273 had a code-4 increase (Month 6) and a code-4 decrease (Month 12).
Source: Display SAF.LAB.4B and Listing SAF.LAB.2B

There were 52 patients with pathologically low and, occasionally, high bicarbonate levels during the trial, but this was considered not clinically relevant. Transient fluctuations during the trial in alkaline phosphatase, γ-GGT, AST, ALT, hemoglobin, hematocrit, and platelet count were of no clinical relevance.

7.2.4. PROLACTIN LEVELS

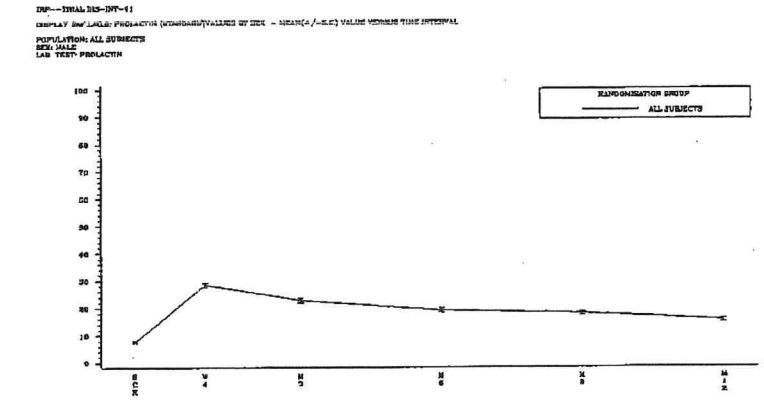
Descriptive statistics and distribution of changes in prolactin levels from the open-label Screening to the different timepoints are presented by sex in Display SAF.LAB.6B. Shift tables are shown in Display SAF.LAB.5B. The data at Endpoint and at Month 12 are summarized in Table 7-7. Graphical displays of prolactin levels versus time are shown by sex in Figure 7-1 and Figure 7-2.

Table 7-7: Mean (± SE) prolactin levels (ng/mL) by sex

	Risperidone (N=504)				
			Change from open-label baseline		
Timepoint	n	Mean ± SE	Mean ± SE	95% CI	p-value[a]
Males					
Screening	382	7.7 ± 0.4			
Week 4	348	28.2 ± 0.8	20.5 ± 0.8	(19.0; 22.0)	<0.001
Month 3	316	22.5 ± 0.9	14.8 ± 0.9	(12.9; 16.6)	<0.001
Month 6	287	19.0 ± 0.8	11.2 ± 0.9	(9.5; 12.8)	<0.001
Month 9	263	17.5 ± 0.7	9.5 ± 0.7	(8.1; 10.9)	<0.001
Month 12	251	15.2 ± 0.7	7.5 ± 0.7	(6.0; 8.9)	<0.001
Endpoint	371	16.1 ± 0.6	8.4 ± 0.7	(7.1; 9.7)	<0.001
Females					
Screening	75	10.4 ± 1.0			
Week 4	63	35.4 ± 2.4	25.4 ± 2.1	(21.3; 29.6)	<0.001
Month 3	54	29.6 ± 2.4	19.3 ± 2.2	(14.8; 23.8)	<0.001
Month 6	50	26.8 ± 2.5	15.9 ± 2.2	(11.6; 20.2)	<0.001
Month 9	51	23.6 ± 2.5	14.0 ± 2.4	(9.1; 18.8)	<0.001
Month 12	36	23.4 ± 4.4	13.9 ± 4.5	(4.8; 23.0)	0.004
Endpoint	68	21.6 ± 2.7	11.5 ± 2.7	(6.2; 16.8)	<0.001

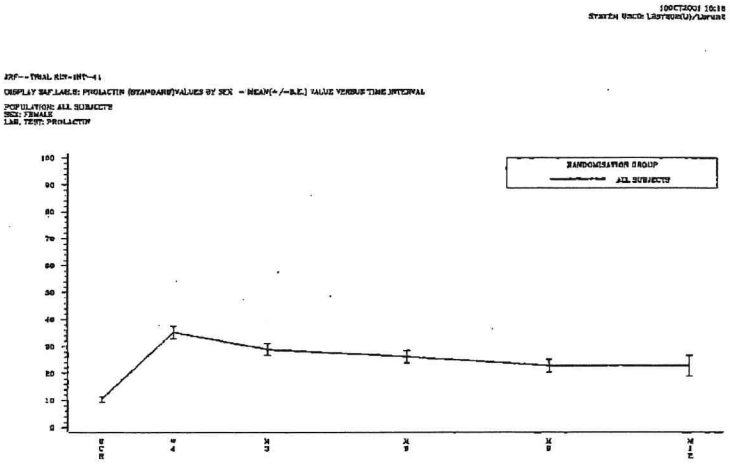
[a] Two-sided p-value for paired t-test on change from Screening at reassessment time.
Source: Display SAF.LAB.6B

Figure 7-1: Prolactin levels (mean ± SE) versus time
Male patients



Source: Display SAF.LAB.6

Figure 7-2: Prolactin levels (mean ± SE) versus time
Female patients



Source: Display SAF.LAB.6

There was an increase in mean prolactin levels from Screening to Week 4 in both sexes. Mean levels for male patients increased from 7.7 ng/mL to 28.2 ng/mL (upper normal limit for boys, 13 ng/mL), and levels for female patients increased from 10.4 ng/mL to 35.4 ng/mL (upper normal limit for girls, 23 ng/mL). Thereafter, the mean levels decreased and returned toward the normal range in boys and within the normal range in girls: to 16.1 ng/mL in the male patients, and to 21.6 ng/mL in the female patients.

There were no serious AEs that were related to the increased prolactin levels.

Fifty-six patients (11.1%) had hyperprolactinemia reported as an abnormal laboratory finding. In most cases, hyperprolactinemia was mild. In 16 cases, it was moderate, and in 1, it was severe. In most patients, hyperprolactinemia was a laboratory finding that had no clinical symptoms. There were 33 patients (6.6%) with symptoms that could be related to increased prolactin levels. WHO-preferred terms defined as prolactin-related are listed in section 3.6.6.1.2.

Gynecomastia or breast enlargement was reported in 25 patients, of whom 23 were boys; one patient with gynecomastia was an 8-year-old girl, and one patient with breast enlargement was a 9-year-old girl. Three patients discontinued due to gynecomastia. In 8 patients, the symptoms were transient, and the patients recovered during the trial. In 15 patients, gynecomastia was still present at the end of the trial.

Other AEs were amenorrhea (n=2), menorrhagia (n=4), dysmenorrhea (n=1), and galactorrhea (n=1). All of these AEs were transient, and the patients recovered during the trial.

All patients with prolactin-related AEs are identified in Table 7-8.

Table 7-8: Patients with prolactin-related adverse events

Patient ID Sex/race/age	Event	Days to onset/ Dose at onset	Total Duration (days)	Severity	Drug relationship	Action taken	Outcome	Treatment
A03004 C/M/9 yr	Gynecomastia	207/ 1.2 mg	>178	Moderate	Probably	None	Not Rcvd	None
A03025 C/M/14 yr	Gynecomastia	22/ 1 mg	>260	Moderate	Probably	None	Not Rcvd	None
A03030 C/M/10 yr	Gynecomastia	368/ 1.1 mg	>33	Mild	Very likely	Dose adjusted	Not Rcvd	None
A03357 C/M/7 yr	Gynecomastia	131 0.8 mg	>242	Moderate	Probably	Perm. Stop	Not Rcvd	None
A03366 C/M/10 yr	Gynecomastia	304 1 mg	>62	Moderate	Probably	None	Not Rcvd	None
A03374 C/F/8 yr	Gynecomastia	3/ 0.2 mg	27	Moderate	Very likely	Perm. Stop	Rcvd	None
A03483 C/M/13 yr	Gynecomastia	260/ 1.4 mg	53	Mild	Possibly	None	Rcvd	None
		313/ 1.4 mg	32	Mild	Possibly	None	Rcvd	None
A03489 C/M/11 yr	Gynecomastia	63/ 2.1 mg	105	Mild	Very likely	None	Rcvd	None
A03065 C/M/13 yr	Gynecomastia	118/ 1.2 mg	>249	Mild	None	None	Not Rcvd	None
A03299 C/M/14 yr	Gynecomastia	50/ 2.8 mg	>44	Mild	Probably	Dose adjusted	Not Rcvd	None
A03303 C/F/14 yr	Amenorrhea	18/ 2 mg	254	Mild	Very likely	None	Rcvd	Normensal®
A03329 C/M/5 yr	Gynecomastia	342/ 0 mg	>22	Mild	Doubtful	None	Not Rcvd	None
A03344 C/F/13 yr	Nonpuerperal lactation (galactorrhea)	92/ 3.1 mg	197	Moderate	Doubtful	None	Rcvd	None
A03350 C/M/10 yr	Gynecomastia	169/ 1.6 mg	>169	Moderate	Possibly	None	Not Rcvd	None
A03352 C/M/14 yr	Gynecomastia	84/ 4 mg	>1	Moderate	Possibly	None	Not Rcvd	None
A03737 C/M/12 yr	Gynecomastia	266 1.8 mg	90	Mild	Very likely	None	Rcvd	None
		356 1.7 mg	1	Moderate	Very likely	Dose adjusted	Not Rcvd	None
A03741 C/M/12 yr	Gynecomastia	170/ 2 mg	>183	Mild	Very likely	None	Not Rcvd	None

Table 7-8: Table patients with prolactin-related adverse events (continued)

Patient ID Sex/race/age	Event	Days to onset/ Dose at onset	Total Duration (days)	Severity	Drug relationship	Action taken	Outcome	Treatment
A03747 C/M/14 yr	Gynecomastia	87/ 3 mg	>194	Moderate	Probably	Perm. Stop	Not Rcvd	None
A03044 C/M/12 yr	Gynecomastia	38/ 1.6 mg	144	Mild	Possibly	None	Rcvd	None
		367/ 1.9 mg	>1	Mild	Very likely	None	Not Rcvd	None
A03464 C/F/10 yr	Vaginal hemorrhage (bleeding)	144/ 0 mg	4	Mild	None	Temp stop	Rcvd	None
	Menorrhagia	166/ 0.8 mg	3	Mild	None	None	Rcvd	None
A03565 C/M/13 yr	Gynecomastia	141/ 2.8 mg	>233	Mild	Very likely	None	Not rcvd	None
		202/ 2.8 mg	>172	Mild	Very likely	None	Not rcvd	None
A03245 O/M/12 yr	Gynecomastia	363/ 1.8 mg	>1	Mild	Doubtful	None	Not rcvd	None
A03780 C/M/11 yr	Gynecomastia	87/ 1.4 mg	120	Moderate	Very likely	None	Rcvd	None
A03190 C/M/7 yr	Gynecomastia	134/ 1.8 mg	33	Mild	None	None	Rcvd	None
A03922 B/M/13 yr	Gynecomastia	113/ 2.5 mg	259	Mild	Possibly	None	Rcvd	None
A03933 C/F/13 yr	Dysmenorrhea	33/ 2 mg	1	Mild	None	None	Rcvd	Anacin®
A03237 C/F/12 yr	Menorrhagia	48/ 1.3 mg	13	Mild	Doubtful	None	Rcvd	No
A03703 B/M/9 yr	Gynecomastia	24/ 2 mg	34	Mild	Very likely	None	Rcvd	No
A03907 C/M/12 yr	Gynecomastia	76/ 2 mg	92	Mild	Probably	None	Rcvd	No
A03237 C/F/12 yr	Menorrhagia	48/ 1.3 mg	13	Mild	Doubtful	None	Rcvd	No
A03294 O/F/14 yr	Menorrhagia	54/ 1.5 mg	10	Moderate	None	None	Rcvd	Eugynon® (biphasil)
A03060 C/F/13 yr	Amenorrhea	90/ 1.2 mg	8	Mild	Probably	None	Rcvd	None
A03384 C/F/9 yr	Breast enlargement	121/ 1.2 mg	244	Mild	Probably	None	Rcvd	None

C: Caucasian; B: black; O: Other; M: Male; F: female; yr: year(s); Rcvd: Recovered; Perm/Temp Stop: Risperidone treatment permanently or temporarily stopped.
*Indicates serious adverse event.
Source: Listings SAF.AE.1, SUB.DM.1, SUB.CT.1

7.3. Vital signs and physical findings

Vital signs were recorded at each visit except Visit 2.

Display SAF.VS.1B shows the descriptive statistics for body temperature, SBP, DBP, pulse rate and respiration rate at each visit. A summary of the data at Endpoint and at Month 12 is given in Table 7-9.

Table 7-9: Summary of vital signs: mean (± SE) and mean change (± SE) from open-label baseline at Month 12 and at endpoint

	Risperidone (N=504)				
			Change from open-label baseline		
	n	Mean ± SE	Mean ± SE	95% CI	p-value[a]
Body temperature (degrees Centigrade)					
Month 12	339	36.4±0.03	-0.03±0.03	(-0.09: 0.03)	0.380
Endpoint	474	36.4±0.02	-0.01±0.03	(-0.06; 0.04)	0.704
Systolic blood pressure (mmHg)					
Month 12	368	105.6±0.67	3.34±0.60	(2.17; 4.52)	<0.001
Endpoint	504	106.1±0.58	3.00±0.53	(1.96; 4.04)	<0.001
Diastolic blood pressure (mmHg)					
Month 12	367	67.3±0.54	1.99±0.60	(0.82; 3.17)	<0.001
Endpoint	504	67.6±0.46	1.84±0.50	(0.86; 2.82)	<0.001
Pulse rate (bpm)					
Month 12	368	80.2±0.62	-1.6±0.74	(-3.08; -0.18)	0.027
Endpoint	504	81.3±0.54	-0.6±0.64	(-1.87; 0.63)	0.330
Respiration rate (L/min)					
Month 12	363	20.6±0.20	-0.4±0.30	(-0.99; 0.17)	0.168
Endpoint	501	20.6±0.17	-0.3±0.25	(-0.78; 0.18)	0.221

SE: standard error
CI: confidence interval
[a]Two-sided p-value for paired t-test on change from open-label Baseline
Source: Display SAF.VS.1B

Overall, there were small changes during the trial that were not clinically relevant.

Blood pressure and pulse rates were classified as normal or abnormal according to the criteria in Table 3-3. The classification of the shift versus open-label Baseline is given in Display SAF.VS.2B and is summarized in Table 7-10.

Table 7-10: Classification of vital signs: frequency distribution of shift versus open-label baseline at Month 12 and at endpoint

	Risperidone (N=504)			
	Month 12 (n=364)		Endpoint (n=498)	
Vital signs	n	(%)	n	(%)
Systolic blood pressure (mmHg)				
Normal	357	(98.1)	489	(98.2)
Abnormal below	**7**	**(1.9)**	**9**	**(1.8)**
Diastolic blood pressure (mmHg)[a]				
Normal	354	(97.5)	488	(98.0)
Abnormal below	**9**	**(2.5)**	**10**	**(2.0)**
Pulse rate (bpm)				
Normal	361	(99.2)	493	(99.0)
Abnormal below	**1**	**(0.3)**	**1**	**(0.2)**
Abnormal above	**2**	**(0.5)**	**4**	**(0.8)**

[a]n=363
Source: Display SAF.VS.2B

Only very few patients had abnormal low (blood pressure) or high (pulse rate) values; one patient also had low pulse rate. Individual values for these patients can be found in Listing SAF.VSA and SAF.VSB.

A physical examination was performed at Screening and at Visits 9, 12, and 14. The data are shown in Display SAF.PE. Overall, there were no clinically relevant changes.

7.4. Electrocardiogram

ECG recordings were performed at the start of the trial, at Visit 12 and at the end of the trial. An additional ECG recording was performed at Visit 9 for patients from the 2 Hungarian centers Szeged and Baja.

Mean changes from the open-label Baseline in ECG results (axis, heart rate, JT interval, JTCB interval, PR interval, QRS complex, QT interval, RR interval, QTc intervals using Bazett's formula (QTcB) and Fridericia's formula (QTcF), and linear corrections of QT for heart rate (QTcL and QTcL-2) are presented in Display SAF.ECG.1B and summarized in Table 7-11.

Because of the physiologically higher heart rates in children and the increased heart rate associated with risperidone treatment, QT interval was also corrected using Fridericia's correction formula and two linear correction formulas. These formulas are considered more appropriate for the correction of QTc intervals in this pediatric population than is Bazett's formula in patients with heart rates above 60 ms.[29]

One linear correction of QT for heart rate was calculated according to new FDA recommendations: [QTcL-2 = QT + slope*(1-RR)], where slope was estimated to be 188 by fitting a linear model of QT = a + slope * RR of Baseline data. This new formula is recommended over the older Bazett's formula.

To ensure accurate interpretation, all ECGs were measured and interpreted by a third party (child cardiologist, Charles I. Berul, M.D., Department of Cardiology, Children's Hospital, Boston, Massachussetts), under the responsibility and according to the instructions of JRF.

Relative to Screening, there were statistically significant mean decreases in axis (-1.60 degrees, p=0.041) and heart rate (-4.1 beats/minute, p<0.001) and statistically significant mean increases in JT interval (+7.04 ms, p<0.001), JTCF interval (+3.61 ms, p<0.001), PR interval (+1.64 ms, p=0.031), QRS interval (+1.18, p=0.002), and QT interval (+8.22 ms, p<0.001), QTcL interval (+1.68, p=0.059), QTcF interval (+3.22 ms, p<0.001), and RR interval (+42.13 ms, p<0.001). These changes had no clinical relevance.

QTc intervals corrected using the different formulas are presented in Display SAF.ECG.1B. Statistically significant increases from Baseline in QTcF intervals were observed at Month 6 (+2.8 ms, p=0.008), Month 12 (+4.5 ms, p<0.001), and Endpoint (+3.2 ms, p<0.001). These changes were not clinically relevant. There were no statistically significant changes in QTcL-2 interval at any timepoint.

Table 7-11: **Summary of QTcL-2 and QTcF results at month 12 and endpoint**

	Risperidone (N=504)				
			Change from open-label baseline		
	n	Mean ± SE	Mean ± SE	95% CI	p-value[a]
QTcL-2					
Screening	474	399.9±0.7			
Month 6	392	400.6±0.9	0.86±1.0	(-1.1;2.8)	0.388
Month 12	340	401.0±1.0	0.97±1.1	(-1.2;3.1)	0.378
Endpoint	447	400.0±0.9	0.25±1.0	(-1.6;2.1)	0.789
QTcF interval (ms)					
Screening	475	386.5±0.9			
Month 6	392	389.1±1.0	2.8±1.0	(0.7;4.8)	0.008
Month 12	340	391.0±1.0	4.5±1.1	(2.3;6.7)	<0.001
Endpoint	447	389.5±0.9	3.2±1.0	(1.3;5.1)	<0.001

SE: standard error
CI: confidence interval
[a]Two-sided p-value for paired t-test on change from open-label Screening
Source: Display SAF.ECG.1B

The distribution of ECG data outside the normal range is presented in Display SAF.ECG.2.

The following criteria[30] were used to classify QTc intervals as abnormal or pathological in the Committee for Proprietary Medicinal Products (CPMP)-proposed categories:

Normal	Female: ≤450 ms	Male: ≤430 ms
Borderline	Female: 451-470 ms	Male: 431-450 ms
Prolonged	Female: >470-500 ms	Male: >450-500 ms
Pathological	>500 ms (female and male)	

The distribution of QTcF and QTcL-2 intervals is summarized in Table 7-12.

Table 7-12: Distribution of borderline and prolonged QTcL-2 and QTcF intervals

	Risperidone (N=504)				
	N	Normal n (%)	Borderline n (%)	Prolonged n (%)	Pathological n (%)
QTcL-2					
Screening	474	469 (98.9)	3 (0.6)	1 (0.2)	1 (0.2)
Month 6	392	378 (96.4)	12 (3.1)	2 (0.5)	0 (0.0)
Month 12	340	331 (97.4)	9 (2.6)	0 (0.0)	0 (0.0)
Endpoint	447	434 (97.1)	13 (2.9)	0 (0.0)	0 (0.0)
QTcF					
Screening	475	473 (99.6)	1 (0.2)	1 (0.2)	0 (0.0)
Month 6	392	388 (99.0)	3 (0.8)	1 (0.3)	0 (0.0)
Month 12	340	339 (99.7)	1 (0.3)	0 (0.0)	0 (0.0)
Endpoint	447	445 (99.6)	2 (0.4)	0 (0.0)	0 (0.0)

Source: Display SAF.ECG.2

As shown in Table 7-12 and Listing SAF.ECG.2, 4 male patients had a prolonged or pathological QTcL-2, but in only 2 patients did the abnormality occur during treatment. Patient 03001 had a prolonged QTcL-2 at Month 6 (493 ms) but had normal valnes at Screening (407 ms) and Month 12 (406 ms). Patient A03002 had a prolonged QTcL-2 at Screening (462 ms), followed at Month 6 by a borderline value (436 ms), and at Month 12 by a normal value (419 ms). Patient A03284 had a pathological QTcL-2 at Screening (508 ms), followed at Month 6 by a borderline value (441 ms, no further data available). Patient A03938 had a normal QTcL-2 at Screening (425 ms), followed at Month 6 by a prolonged value (456 ms). At Month 12, this patient's QTcL-2 had returned to normal (423 ms).

Two patients had prolonged QTcF: one at Screening and one during the trial. One male patient (A03284) had a QTcF interval that was prolonged at Screening (500 ms) but not during treatment (430 ms at Month 6, no further data). One male patient (A03001) had a QTcF interval that was prolonged (490 ms) at Month 6 but normal at Screening (390 ms) and at Month 12 (390

ms). No patient had pathological QTcF intervals at any time during the study.

Increases in QTc values from Baseline were expressed in the CPMP-proposed categories as follows:

Increase <30 ms
Increase 30-60 ms
Increase >60 ms

The distribution of increases in QTcF and QTcL-2 values is summarized in Table 7-13.

Table 7-13: Distribution of increases from open-label baseline in QTcL-2 and QTcF values

		Risperidone (N=504)		
		<30 ms	30-60 ms	>60 ms
	N	n (%)	n (%)	n (%)
QTcL-2				
Month 6	375	352 (93.9)	21 (5.6)	2 (0.5)
Month 12	324	307 (94.8)	16 (4.9)	1 (0.3)
Endpoint	421	401 (95.2)	19 (4.5)	1 (0.2)
QTcF				
Month 6	375	332 (88.5)	40 (10.7)	3 (0.8)
Month 12	324	278 (85.8)	46 (14.2)	0 (0.0)
Endpoint	422	372 (88.2)	50 (11.8)	0 (0.0)

Source: Display SAF.ECG.4B

Two patients (0.6%) had increases in QTcL-2 of >60 ms at Month 6, one of whom also had an increase >60 ms at Month 12. Three patients (0.8%) had increases in QTcF values of >60 ms at Month 6 only, not at Month 12 or Endpoint.

Patient A03001 an 8-year-old boy, had a normal QTcL-2 at Screening (407 ms). QTcL-2 increased by 86 ms at Month 6, to a prolonged interval of 493 ms, but decreased to normal (406 ms) at Month 12. The same patient had a QTcF increase of +100 ms, from a normal value at Screening (390 ms) to a prolonged value of 490 ms at Month 6. QTcF for this patient was normal at Month 12 (390 ms).

Patient A03364, a 9-year-old boy, had a normal QTcL-2 at Screening (361 ms), followed at Month 6 by a 64-ms increase (to 425 ms). The QTcL-2 interval was 422 ms at Month 12, representing a 61-ms increase from Screening, but this subject's QTcL-2 intervals remained within the normal range throughout the study.

For patient A03217, a 10-year-old girl, QTcF increased from 330 ms at Screening to 400 ms (+70 ms) at Month 6; at Month 12, QTcF was 390 ms (+60 ms increase). All values remained within the normal range.

Patient A03437, a 12-year-old boy, had a normal QTcF at Screening (330 ms). At Month 6, QTcF increased 80 ms (to 410 ms) and at Month 12, QTcF (370 ms) was still 40 ms above that at Screening. Despite these increases, QTcF for Patients A03217 and A03437 remained within the normal range throughout the study.

7.5. Other safety observations

7.5.1. Body weight

Patients were weighed at Baseline and at Visits 7, 9 and 12 and at the end of the trial.

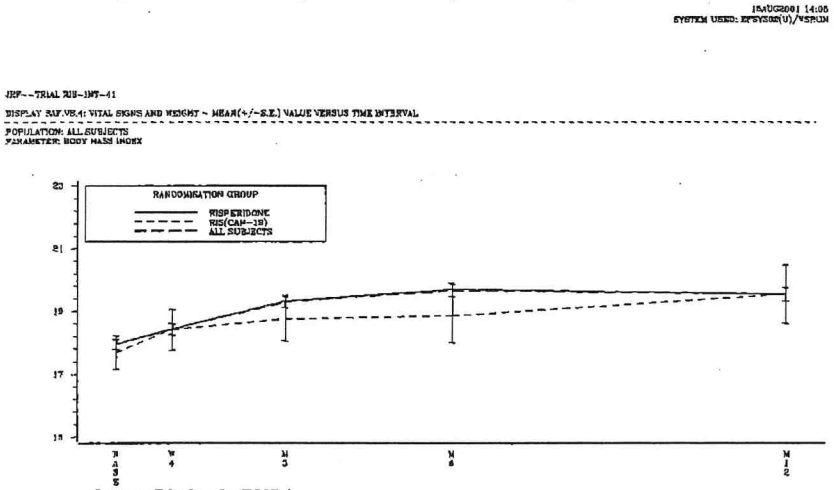
The descriptive statistics for body weight, height and the BMI are given in Display SAF.VS.3B. The data at Endpoint and at Month 12 are summarized in Table 7-14. BMI versus time is graphically displayed in Figure 7-3.

Table 7-14: Summary of body height, weight and BMI: mean (± SE) and mean change (± SE) from open-label baseline at Month 12 and at endpoint

	Risperidone (N=504)				
			Change from open-label baseline		
	n	Mean ± SE	Mean ± SE	95% CI	p-value[a]
Body weight (kg)					
Month 12	364	43.1±0.8	7.6±0.3	(7.1; 8.0)	<0.001
Endpoint	487	43.4±0.7	7.0±0.2	(6.6; 7.4)	<0.001
Body height (cm)					
Month 12	364	146.3±0.8	6.9±0.2	(6.6; 7.2)	<0.001
Endpoint	486	145.8±0.7	6.0±0.2	(5.6; 6.3)	<0.001
Body mass index (kg/m^2)					
Month 12	364	19.5±0.2	1.9±0.1	(1.7; 2.1)	<0.001
Endpoint	486	19.8±0.2	1.8±0.1	(1.6; 2.0)	<0.001

SE: standard error
CI: confidence interval
[a] Two-sided p-value for paired t-test on change from open-label Baseline
Source: Display SAF.VS.3B

Figure 7-3: Body Mass Index (mean ± SE) versus time



Source: Display SAF.VS.4

Body weight increased by an average 7.0 kg from Baseline to Endpoint. This increase was statistically significant ($p<0.001$). Since the patients were children and adolescents from 5 to 14 years of age, the effect of risperidone on body weight was confounded by growth. The height of the patients increased by 6.0 cm on average from Baseline to Endpoint. The typical child in the trial was a 10-year-old boy with a Baseline weight of 36.3 kg and a height of 139.8 cm. According to the National Center for Health Statistics (NCHS) percentiles,[31] the 75th percentile weight at age 10 years is 35.6 kg, similar to the average weight in the present study. As the 75th percentile weight at age 11 years is 40.4 kg, the average natural weight gain expected over a 1-year period would be 4.8 kg. This implies that, of the 7.0-kg weight gain during the trial, 4.8 kg might be attributed to natural weight gain and 2.2 kg to treatment with risperidone.

The increase in BMI was 1.8 kg/m^2 at Endpoint. This effect was statistically significant ($p<0.001$). The greatest increase in BMI was observed during the first 3 months of treatment. The average BMI at Baseline in the present study (17.9 kg/m^2) was close to the 50th percentile for BMI at age 10 years (17.2 kg/m^2).[32] Since the 50th percentile at age 11 years is 17.8 kg/m^2, the natural increase expected over a 1-year period would be 0.6 kg/m^2. This implies that of the 1.8 kg/m^2 increase during the trial, 0.6 kg/m^2 might be attributed to a natural increase and 1.2 kg/m^2 to treatment with risperidone.

Appetite increase was reported in 53 patients (10.5%). The severity was considered moderate in 29 cases and severe in 3 cases. Weight increase was reported in 87 patients (17.3%). The severity was moderate in 47 cases and

severe in 14 cases. Obesity was reported for 4 patients (0.8%), of whom 1 patient had severe and 3 had moderate obesity.

Weight increase led to permanent discontinuation of treatment in 9 patients (1.8%).

7.5.2. EXTRAPYRAMIDAL SYMPTOM RATING SCALE (ESRS)

The presence and severity of EPSs was assessed at each visit with the exception of Screening and Visit 2. The data are shown in Display SAF.ESRS.1B. The mean and median total score at the different timepoints and the mean and median maximum score are summarized in Table 7-15.

Table 7-15: Total ESRS score: mean (± SE), median (min, max) and mean (± SE) change from open-label baseline at the different timepoints

	Risperidone (N=504)				
				Change from open-label baseline	
Timepoint	n	Mean ± SE	Median (min; max)	Mean ± SE	p-value[a]
Baseline	497	1.2 ± 0.1	0.0 (0.0; 35.0)		
Week 1	484	1.0 ± 0.1	0.0 (0.0; 25.0)	-0.1 ± 0.1	0.157
Week 2	476	1.0 ± 0.1	0.0 (0.0; 25.0)	-0.0 ± 0.1	0.458
Week 3	470	0.9 ± 0.1	0.0 (0.0; 25.0)	-0.1 ± 0.1	0.502
Week 4	480	0.9 ± 0.1	0.0 (0.0; 16.0)	-0.1 ± 0.1	0.280
Month 2	441	0.9 ± 0.1	0.0 (0.0; 16.0)	-0.1 ± 0.1	0.735
Month 3	448	0.9 ± 0.1	0.0 (0.0; 16.0)	-0.2 ± 0.1	0.355
Month 4	426	0.8 ± 0.1	0.0 (0.0; 14.0)	-0.2 ± 0.1	0.108
Month 5	420	0.9 ± 0.1	0.0 (0.0; 14.0)	-0.2 ± 0.1	0.258
Month 6	417	0.8 ± 0.1	0.0 (0.0; 14.0)	-0.2 ± 0.1	0.291
Month 9	397	0.8 ± 0.1	0.0 (0.0; 12.0)	-0.3 ± 0.1	0.043
Month 12	367	0.7 ± 0.1	0.0 (0.0; 13.0)	-0.4 ± 0.2	<0.001
Endpoint	495	0.8 ± 0.1	0.0 (0.0; 16.0)	-0.3 ± 0.1	0.024
Maximum	495	2.3 ± 0.2	1.0 (0.0; 25.0)	1.3 ± 0.1	<0.001

SE: standard error
min, max: minimum, maximum
Nonimputed results
[a] Two-sided p-value for Wilcoxon signed rank test on change from open-label baseline
Source: Display SAF.ESRS.1B

The overall level of EPSs was very low. The median score was always 0.0: the majority of patients did not show any ESRS scores different from zero at any timepoint during the trial. The mean score at the open-label Baseline was 1.2. The mean ESRS score decreased during risperidone treatment and was 0.8 at Endpoint. The mean decrease ranged from -0.0 at Week 2 to -0.4 at Month 12. The mean decrease at Endpoint was -0.3. The decrease was statistically significant at Months 9 and 12 and at Endpoint.

The maximum value at Baseline was 35.0 and the maximum score on treatment was 25.0. The overall mean maximum score on treatment was 2.3, which was statistically significantly ($p<0.001$) higher than the score at Baseline.

7.5.3. TANNER STAGING AND GROWTH

Tanner staging was performed at Baseline and at Visits 12 and 14. The data are shown in Display SAF.TAN.1, and are summarized in Table 7-16.

Table 7-16: Frequency distribution of the change in patients' Tanner staging condition at Month 12 and at endpoint

	Risperidone (N=504)					
	Open-label baseline (n=493)		Month 12 (n=364)		Endpoint (n=451)	
Tanner staging	n	(%)	n	(%)	n	(%)
1	345	(70.0)	186	(51.1)	237	(52.5)
2	73	(14.8)	76	(20.9)	85	(18.8)
3	41	(8.3)	44	(12.1)	58	(12.9)
4	26	(5.3)	37	(10.2)	48	(10.6)
5	8	(1.6)	21	(5.8)	23	(5.1)

Source: Display SAF.TAN.1

Sexual maturation progressed during the trial. At entry, there were 345 (70.0%) children with a Tanner score of 1. At Endpoint, the number decreased to 237 (52.5%), while the number of patients in a higher Tanner stage increased.

7.5.4. CHANGES IN COGNITIVE FUNCTION

Cognitive tests were performed at Visits 3, 12 and 14.

7.5.4.1. Modified verbal learning test

The results of the modified verbal learning test (long delay free recall, short delay free recall, total correct recognized, total correct not recognized, and total correct) are shown in Display EFF.CT.1B. A summary of the scores at Endpoint and Month 12 is presented in Table 7-17.

Table 7-17: Modified verbal learning test: mean (± SE) and mean (± SE) change from open-label baseline at Month 12 and at endpoint

	Risperidone (N=504)				
			Change from open-label baseline		
Cognitive test	n	Mean ± SE	Mean ± SE	95% CI	p-value[a]
Modified verbal learning test					
Total long delay free recall					
Month 12	349	6.6±0.13	0.8±0.12	(0.6 ; 1.1)	<0.001
Endpoint	442	6.6±0.12	0.7±0.11	(0.5 ; 1.0)	<0.001
Total short delay free recall					
Month 12	349	32.4±0.49	2.9±0.43	(2.1 ; 3.8)	<0.001
Endpoint	442	32.3±0.44	2.9±0.39	(2.2 ; 3.7)	<0.001
Total correct					
Month 12	349	17.7±0.23	0.8±0.21	(0.4 ; 1.2)	<0.001
Endpoint	442	17.7±0.20	0.7±0.19	(0.3 ; 1.1)	<0.001

SE: standard error
CI: confidence interval
[a] Two-sided p-value for paired t-test on change from open-label Baseline
Source: Display EFF.CT.1B

Overall, there was a small increase in the total number of items that was recalled. The effect was statistically significant for the long delay free recall test at all timepoints ($p<0.001$). The effect for the short delay free recall test was statistically significant ($p<0.001$) at Endpoint and at Month 12 and borderline significant at Month 6 ($p=0.055$).

There was a small increase in the overall total number of items that was correctly recognized and correctly not recognized. The effect was statistically significant at Month 6 ($p=0.010$), Month 12, and Endpoint (both $p<0.001$).

The changes were of minor clinical relevance and indicated improvement rather than deterioration in cognitive function.

7.5.4.2. Continuous performance task

The results of the continuous performance task are shown in Display EFF.CT.2B, and are summarized in Table 7-17. Only the total scores are summarized, the scores for the first and second half can be found in Display EFF.CT.2B.

Table 7-17: Continuous performance task: mean (± SE) and mean (± SE) change from open-label baseline at Month 12 and at endpoint

Cognitive test	Risperidone (N=504)				
			Change from open-label baseline		
	n	Mean ± SE	Mean ± SE	95% CI	p-value[a]
Continuous performance test, easy					
Total hits					
Month 12	315	36.6±0.4	1.9±0.4	(1.2; 2.6)	<0.001
Endpoint	409	36.2±0.4	1.6±0.3	(1.0; 2.2)	<0.001
Total false alarm					
Month 12	314	4.8±0.6	-2.9±0.7	(-4.3; -1.5)	<0.001
Endpoint	409	5.3±0.5	-2.9±0.6	(-4.1; -1.7)	<0.001
Total misses					
Month 12	315	3.4±0.4	-1.8±0.4	(-2.5; -1.1)	<0.001
Endpoint	409	3.7±0.4	-1.5±0.3	(-2.1; -0.9)	<0.001
Continuous performance test, hard					
Total hits					
Month 12	296	36.6±0.3	2.0±0.4	(1.2; 2.7)	<0.001
Endpoint	380	36.0±0.3	1.6±0.4	(0.9; 2.3)	<0.001
Total false alarm					
Month 12	296	12.2±4.0	-3.5±0.8	(-5.1; -1.9)	<0.001
Endpoint	380	11.1±3.2	-4.2±0.7	(-5.6; -2.8)	<0.001
Total misses					
Month 12	295	3.8±0.5	-1.7±0.5	(-2.7; -0.8)	<0.001
Endpoint	380	4.2±0.4	-1.4±0.4	(-2.2; -0.6)	<0.001

SE: standard error
CI: confidence interval
[a] Two-sided p-value for paired t-test on change from open-label Baseline
Source: Display EFF.CT.2B

There were statistically significant ($p<0.001$) increases in the total number of hits from Baseline to Endpoint, and statistically significant decreases in the total number of false alarms and misses, both in the easy and in the hard version of the task. These increases and decreases also occurred at Months 6 and 12, and differences from Baseline were usually significant.

The changes were of minor clinical relevance and indicated improvement rather than deterioration in cognitive function.

7.6. Pharmacokinetic - pharmacodynamic relationships

Not applicable.

7.7. Safety conclusions

The results of the safety analysis show that long-term treatment with 0.02 to 0.06 mg/kg/day risperidone (mean treatment duration 307.3± 5.0 days) was safe and well tolerated.

The most commonly reported AEs were somnolence (29.6% of all patients), rhinitis (27.2%), headache (21.8%), weight increase (17.3%), and upper respiratory tract infection (16.5%). Most AEs were mild. EPS-related AEs were reported by 21.4% of all patients. The overall EPS-level was low. The majority of patients did not show any ESRS scores different from zero at any timepoint during the trial.

Mean prolactin levels increased from Screening to Week 4. Thereafter, the mean levels decreased to close to the normal range in boys and to within the normal range in girls at Endpoint. Female patients attained higher prolactin levels than did male patients. Increased prolactin levels led to clinical manifestations in 33 patients (6.6%).

An increase in body weight was especially observed during the first 3 months of treatment. According to the NCHS percentiles,[31] 4.8 kg (70% of the weight gain) might be attributed to natural weight gain and 2.2 kg (30% of the weight gain) to treatment with risperidone. The increase in BMI was 1.8 kg/m^2 at Endpoint. The natural increase in BMI during a 1-year period at age 10 years is 0.6 kg/m^2. Weight increase was reported as an AE during treatment by 87 patients (17.3%). Appetite increase was reported by 53 patients (10.5%).

Cognitive function was assessed by means of a modified verbal learning test and a continuous performance task. The mean scores on both tasks showed a small, but statistically significant improvement at Endpoint and at Month 12. There was no indication that risperidone had a negative effect on cognitive function.

8. SUMMARY AND DISCUSSION

Conduct and other disruptive behavior disorders are among the most common forms of psychopathology in children and adolescents. The reported prevalence of psychiatric consultations for these disorders, which include Conduct Disorder, Oppositional Defiant Disorder and Disruptive Behavior Disorder not otherwise specified, has varied from 20% to 64%. Factors that predispose individuals to greater severity and poorer outcome include ADHD and reduced intelligence.

There have been many different approaches to the treatment of conduct and other disruptive behavior disorders, including drug therapy, behavioral treatment, psychotherapy, cognitive and social learning. The efficacy of risperidone (mean dose 1.16 mg/day) for the treatment of this condition in mentally retarded children was demonstrated in a 6-week double-blind, placebo-controlled, randomized, parallel group trial (RIS-USA-93).[26] Statistically significant differences between the placebo and risperidone

group were observed as early as Week 1 on all primary and secondary parameters, and across all scales.

Because of the chronic nature of the conduct and other disruptive behavior disorders, pharmacotherapy is used on a long-term basis and is directed toward maintenance of the response achieved and prevention of a symptomatic and functional deterioration. Long-term therapy necessitates an effective, well-tolerated treatment with a high level of patient compliance. The purpose of this open-label trial was to examine the long-term effects of risperidone treatment.

The overall mean mode daily dosage was 1.69±0.04 mg/day or 0.02±0.0007 mg/kg/day, and the mean treatment duration was 307.3±5.0 days (range 1-505 days).

Efficacy

The primary efficacy parameter was the change in behavior from open-label Baseline to Endpoint as measured on the Conduct Problem subscale of the N-CBRF. The mean score improved from 32.9±0.3 at Baseline to 17.0±0.5 at Endpoint. The improvement increased to a stable level during the first 4 weeks of treatment and remained improved for 12 months. The mean change at Endpoint was -15.8 ($p<0.001$).

Subgroup analyses for the primary efficacy parameter revealed no differences between patients with conduct disorder, with oppositional defiant disorder and with disruptive behavior disorder not otherwise specified. There were also no differences between patients with different levels of intellectual functioning (mild mental retardation, moderate mental retardation or borderline intellectual functioning), or between those who did and did not take psychostimulants during treatment.

The results of the secondary efficacy analyses showed a profile similar to that of the primary efficacy parameter. A statistically significant improvement at Endpoint was observed on all subscales of the N-CBRF (compliant/ calm +3.4±0.2; adaptive/ social +1.9± 0.1; insecure/ anxious -5.7±0.4; hyperactive –6.8±0.3; self-injury/ stereotyped -1.0± 0.2; self-isolated/ ritualistic -1.7±0.2; overly sensitive -2.1±0.2), on the total score of the ABC (-28.3±1.4) and on the VAS of the most troublesome symptom (-40.3±1.3). The improvements were especially observed during the first 4 weeks of treatment. Scores remained stable thereafter. The ratings of the investigators' CGI showed 20 (4.1%) patients with severe or extremely severe symptoms at Endpoint compared to 175 (36.1%) at Baseline.

Safety

Risperidone was well tolerated. There were 17 patients (3.4%) who reported drug-related serious AEs. The discontinuation rate for AEs was 8.5% (43 patients). The most commonly reported AEs were somnolence (29.6%), rhinitis (27.2%), headache (21.8%), weight increase (17.3%), and upper respiratory tract infection (16.5%). Most AEs were mild.

EPS-related AEs were reported by 108 patients (21.4%). The majority of these events were mild. The overall incidence of EPS was low. The majority of patients did not show any ESRS scores different from zero at any timepoint during the trial. Only 5 patients had symptoms that required administration of anti-Parkinson medication.

The incidence of tardive dyskinesia is estimated to be between 7% and 12% in children and adolescents receiving long-term conventional treatment for less than 1.5 years.[33] There were 2 patients with reversible tardive dyskinesia (0.4%) in this trial. These results suggest that risperidone has a better safety profile with respect to tardive dyskinesia than that of typical neuroleptics.

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels. The mean prolactin levels in the present trial increased during the first 4 weeks of treatment, and decreased again thereafter, close to the normal range in boys and within the normal range in girls. The incidence of clinical manifestations in the present trial was low. There were 33 patients (6.6%) with clinical manifestations of prolactin increase. In most cases, symptoms related to increased prolactin levels were transient and did not require intervention.

Apart from the increase in prolactin levels, no consistent or clinically significant changes or trends in hematology, biochemistry or urinalysis were detected.

There were small changes in vital signs during the trial that were not clinically relevant. The ECG results did not show clinically relevant changes.

Body weight increased by an average 7.0 kg from Baseline to Endpoint. Antipsychotic-induced weight gain is a well-documented phenomenon, and the body weight increase in this trial is modest especially when it is taken into account that the patients were children and the effect on weight was confounded by growth. According to NCHS percentiles,[31] 4.8 kg (70% of the weight gain) might be attributed to natural weight gain and 2.2 kg (30% of the weight gain) to treatment with risperidone. The increase in BMI was 1.8 kg/m^2 at Endpoint. According to the NCHS percentiles,[32] 0.6 kg/m^2 might be attributed to natural weight gain and 1.2 kg/m^2 to treatment with risperidone. The increase was especially observed during the first 3 months of treatment, and remained stable thereafter.

There were no clinically relevant changes at the physical examination. The patients had grown by 6.0±0.2 cm at Endpoint ($p<0.001$), and sexual maturation had progressed, as determined by Tanner staging.

Cognitive function was assessed by means of a modified verbal learning test and a continuous performance task. The mean scores on both showed a small but statistically significant improvement at Endpoint. There is clearly no evidence indicating that risperidone has negative effects on cognitive function.

9. OVERALL CONCLUSIONS

The results of the present trial demonstrate that risperidone was effective in the treatment of conduct and other disruptive behavior disorders in children and adolescents 5 to 14 years of age with borderline intellectual functioning or mild to moderate mental retardation. A review of all adverse events, extrapyramidal symptoms, laboratory parameters, vital signs and body weight showed that long-term treatment with risperidone was safe and well tolerated.

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