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CLINICAL RESEARCH REPORT			
R- number:	R064766	Non-proprietary name:	Risperidone
EDMS:	USTI-2329591	Report Date:	2 November 2000
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. An interim analysis of 319 patients.		
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Trial number:	RIS-INT-41	Clinical phase:	III
Trial dates:	Start: 18 March 1997 – end: 3 May 2000		
Investigator:	Multicentre		

ABSTRACT

Design and subjects: In this international, multicentre, open trial, the long-term safety and efficacy of risperidone (0.02 to 0.06 mg/kg/day) were assessed in children with borderline intellectual functioning or mild to moderate mental retardation, suffering from conduct or other disruptive behaviour disorders. In order to provide the regulatory authorities with long-term safety and efficacy data in a sufficient number of subjects (ie, 300 subjects with 6 months exposure, 100 subjects with 1 year exposure) an interim analysis was carried out. All 319 subjects that entered the study before 31 July 1999 were included in the interim analysis. Out of these 319 subjects, 300 subjects newly entered the study, and 19 subjects came from RIS-CAN-19.

Overall, 83.4% of the subjects were male, and the mean age was 9.6 years (median 10 years, range 4-14 years). Seventy-nine subjects (24.8%) were adolescents (12 years or older). For the subjects with available Axis I diagnosis information at the time of the interim analysis (N=309), 45.8% had conduct disorder, 35.0% had oppositional defiant disorder and 16.3% had disruptive behaviour disorder not otherwise specified. For subjects with available Axis II diagnosis information (N=317), 44.5% had mild mental retardation, 20.8% had moderate mental retardation and 34.7% had borderline intellectual functioning. The overall mean mode daily dosage was 1.64 ± 0.04 mg/day (0.021 ± 0.001 mg/kg/day), and the mean treatment duration was 261.0 ± 7.2 days (range 1-498 days). Out of the 319 subjects, 230 subjects were treated for 6 months or more, and 181 of these 230 subjects were treated for 12 months or more. Sixty subjects (18.8%) dropped out before trial completion. The most common reason was adverse event (n=22, 6.9%), followed by insufficient response (n=10, 3.1%). Major protocol deviations, mainly forbidden intercurrent therapy, were noted in 27 subjects (8.5%).

Pharmacokinetic results: The overall plasma concentrations of risperidone, the active moiety and 9-hydroxy-risperidone remained fairly constant over the entire trial period. The

mean plasma levels of active moiety (dose-normalized to 0.04 mg/kg/day) were 11.8 ng/ml at visit 7, 13.5 ng/ml at visit 12 and 12.4 ng/ml at endpoint.

Efficacy results: The primary efficacy parameter was the change in behaviour from open label baseline to endpoint as measured on the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF). The mean score dropped from 32.7 (± 0.4) at baseline to 17.0 (± 0.6) at endpoint. The improvement was especially observed during the first 4 weeks of treatment. Scores remained stable thereafter. The mean change at endpoint was -15.6 ($p < 0.001$). A subgroup analyses by DSM-IV Axis I (diagnosis group) and Axis II (degree of mental retardation) was performed for the primary efficacy parameter. There were no differences between diagnosis groups. There were also no differences at endpoint between subjects with different levels of intellectual functioning.

The results from the secondary efficacy analysis showed a similar profile as for the primary efficacy parameter. A statistically significant ($p<0.001$) improvement at endpoint was observed on all subscales of the N-CBRF (compliant/ calm +3.2 (± 0.2); adaptive/ social +2.0 (± 0.2); insecure/ anxious -5.4 (± 0.5); hyperactive -7.0 (± 0.4); self-injury/ stereotyped -1.1 (± 0.2); self-isolated/ ritualistic -1.6 (± 0.2); overly sensitive -2.1 (± 0.2)), on the total score of the Aberrant Behaviour Checklist (-28.2 (± 1.8)) and on the Visual Analogue Scale of the most troublesome symptom (-40.5 (± 1.6)). The improvements were especially observed during the first 4 weeks of treatment. Scores remained stable thereafter. The ratings of the investigators' Clinical Global Impression showed 204 (65.6%) subjects with no, very mild or mild symptoms at endpoint compared to 21 (6.9%) at baseline.

Safety results: The most commonly reported adverse events (AEs) were somnolence (28.2%), rhinitis (24.5%), headache (17.2%) and pharyngitis (17.2%). The majority of all AEs was mild. Extrapyramidal symptom (EPS)-like AEs were reported by 22.3% of all subjects. Seven subjects (2.2%) had serious EPS-like AEs and 5 subjects discontinued treatment due to EPS-like AEs. Reversible tardive dyskinesia was reported by 2 subjects (0.6%). The overall level of EPS was very low. The majority of subjects did not show any scores on the extrapyramidal symptoms rating scale (ESRS) different from zero at any time point during the trial.

Except for an increase in prolactin, there were no consistent or clinically relevant changes in routine laboratory safety parameters. There was an increase in mean prolactin levels from screening to Week 4. Mean levels of male subjects increased from 8.3 ng/ml to 29.0 ng/ml, and levels of female subjects increased from 9.3 ng/ml to 37.0 ng/ml. Thereafter, the mean levels decreased, but they were still elevated at endpoint: 18.2 ng/ml in the male subjects, and 27.6 ng/ml in the female subjects. Sixteen subjects (5.0%) reported physical symptoms that could be related to elevated prolactin levels.

There were small changes in vital signs during the trial, which were not clinically relevant. There were no clinically relevant mean changes in ECG parameters.

Body weight increased by an average 6.3 kg (± 0.3) from baseline to endpoint, of which 4.1 kg might be expected in growing children (National Centre of Health Statistics, NCHS). The increase in body mass index (BMI) was 1.7 kg/m^2 at endpoint, of which 0.6 kg/m^2 might be attributed to a natural increase in BMI (NCHS). The increase in BMI was especially observed during the first 3 months of treatment. The BMI remained stable thereafter. There was no indication that risperidone had a negative effect on growth or sexual maturation.

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

Conclusion: The interim results from this one-year, multicentre, open trial demonstrate that risperidone was effective in the treatment of conduct and other disruptive behaviour disorders

in children 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 shows that long-term treatment with risperidone was safe and well tolerated.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ABC:	Aberrant Behaviour 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 ID:	CRF Identification
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
HR:	Heart Rate
ICH:	International Conference on Harmonization
IQ:	Intelligence Quotient
JRF:	Janssen Research Foundation
LDH:	Lactate Dehydrogenase
N-CBRF:	Nisonger Child Behaviour Rating Form
PRI:	Pharmaceutical Research Institute
QA:	Quality Assurance
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

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 performed in accordance with the declaration of Helsinki and its subsequent revisions.

Subject information and consent

At the first visit, the subjects 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.

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1. INTRODUCTION

Conduct and other disruptive behaviour 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 behaviour that involves persistent pattern of dissocial, aggressive or defiant behaviour that involves major violations of age-appropriate expectations or norms. Examples of the behaviours 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 about a 5-fold increased risk of presenting with severe behaviour problems, including Conduct and other disruptive behaviour 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 subjects.[3,4]

There have been many different approaches to the treatment of conduct and other disruptive behaviour disorders, including drug therapy, behavioural 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. Whilst 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 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 Risperdal® may be useful in treating symptoms such as aggression, self-injury and stereotypes. Van den Borre et al.[9] demonstrated that Risperdal®, as add-on therapy, brought about significant improvement in the conduct of mentally retarded adult and adolescent subjects compared to placebo as measured on the Aberrant Behaviour 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 trial,[11] autistic children who all had a degree of mental retardation with the exception of 1 subject, Risperdal® 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 subjects 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 Risperdal® 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 favourably to Risperdal®.[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 Risperdal® for 3 to 15 months in a dose range of 1-4 mg daily. This dosage was well tolerated. Two subjects 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 subjects with dementia showed that at low doses (1 mg/day), risperidone had beneficial effects on disruptive behaviour 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 behaviour 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 behavioural disturbances and was not associated with an increase in EPS in mentally retarded children.[14]

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

addition to this trial, 2 double-blind placebo controlled trials were being conducted.

2. TRIAL OBJECTIVES

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

In order to provide the regulatory authorities with long-term safety and efficacy data in a sufficient number of subjects (ie, 300 subjects with 6 months exposure, 100 subjects with 1-year exposure) an interim analysis was carried out. All subjects that entered the study before 31 July 1999 were included in the interim analysis. The interim analysis is the subject of this clinical report.

3. SUBJECTS AND METHODS

3.1. Trial design

3.1.1. OVERALL TRIAL DESIGN AND PLAN

This was an open trial to investigate the safety and efficacy of 0.02 to 0.06 mg/kg/day of oral Risperdal® in conduct and other disruptive behaviour disorders in children 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 subjects had to score 24 or more on the Conduct Problem Subscale of the Nisonger Child Behaviour Rating Form (N-CBRF). This score of 24 approximates the 70th percentile according to the norms published by Tassé et al.[21] A substantial number of children referred to clinics with conduct disorder also have Attention Deficit/Hyperactivity Disorder (ADHD).[2] Subjects with ADHD were eligible for entry into the trial if they scored 24 or more on the Conduct Problem subscale of the N-CBRF.

Subjects underwent a 1-week placebo run-in period in order to identify placebo responders. Subjects had to score ≥ 24 on the conduct subscale of N-CBRF and ≤ 84 on the Vineland Adaptive Behaviour Scale[22] at baseline to qualify for the trial, *except those subjects who had participated in RIS-CAN-*

19.[1] All subjects who qualified for participation at baseline were given open 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 subscales of the N-CBRF, and change versus baseline on the VAS of the most troublesome symptom. 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.

Safety assessments included Extrapyramidal Symptom Rating Scale (ESRS),[23] adverse event monitoring and laboratory assessments including determination of prolactin and growth hormone (GH) levels.

3.1.2. DISCUSSION OF TRIAL DESIGN

There is no recognized pharmacological treatment for conduct and other disruptive behaviour 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.[5,8,7,8]

Results from a few small pilot trials and anecdotal information indicate that Risperdal® 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). Bearing in mind that conduct and other disruptive behaviour disorders are chronic conditions, the safety and efficacy of long-term treatment needs to be determined. The purpose of this open 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):

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

- 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.

3. A local amendment, dated 16 September 1998 that was valid for the USA and RSA was issued to allow US and South African subjects 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 subjects and sites who were participating in RIS-CAN-19. Any subject 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 3.4.1.

4. A local amendment, dated 31 August 1999 that was valid for 2 Hungarian centres (Szeged and Baja) was issued on request of the Regional Ethics Committee of the 2 centres after they had received the Correction to Amendment 3 of Investigator's Brochure (dated 15 April 1999). The protocol amendment specified that all subjects 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 ECG record, a cardiologist was to determine whether echocardiography was necessary or not (see section 3.4.1, 3.4.5.4 and 3.4.5.5).

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 subjects who entered the trial before 31 July 1999 were included. This date was chosen as a cut-off date based on the numbers of subjects required by the authorities (300 subjects with 6 months exposure, 100 subjects with 1-year exposure), and based on the number of subjects that were already included in RIS-USA-97 (ie, the long term follow-up of trial RIS-USA-93). The results from the interim analysis is the subject of this clinical report.

3.2. Subject sample

3.2.1. SAMPLE SIZE

During a period of 24 months, 500 subjects were to be recruited into the trial. This multicentre trial was to be conducted in Europe, *in the US and the Republic of South Africa*[2]. Each centre had to make every effort to include a minimum of 10 subjects.

3.2.2. INCLUSION CRITERIA

Subjects who met all of the following criteria were eligible for this trial:

1. Subjects with a DSM-IV, Axis I diagnosis of Conduct Disorder (312.8); or Oppositional Defiant Disorder (313.81); or Disruptive Behaviour Disorder not otherwise specified (312.9); and a total rating of ≥ 24 in the Conduct Problem subscale of the Nisonger Child Behaviour Rating Form (parent version), as assessed at Visits 1 and 3. Subjects 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 subjects who had participated in RIS-CAN-19 was to be waived for inclusion into this trial.*[2]
2. ***Subjects 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.***
3. Subjects with a Vineland Adaptive Behaviour Scale score of ≤ 84, *except those subjects who had participated in RIS-CAN-19.*[2]
4. ***Between 5 and 14 years of age (extremes included).***
5. Informed consent form had been signed.
6. Subject was healthy on the basis of a pre-trial physical examination, medical history and electrocardiogram (ECG).
7. A responsible person was available to accompany the subject 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.
8. *Subjects who had participated in RIS-CAN-19 should have completed at least 2 weeks (14 days) of double blind medication.*[2]
9. *Current symptoms requiring antipsychotic treatment in the opinion of an independent investigator.*[3]

Note: Subjects could be inpatients or outpatients.

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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.

3.2.3. EXCLUSION CRITERIA

Subjects meeting one or more of the following criteria could not be selected:

1. Subjects who had a diagnosis of Pervasive Development Disorder (299.00; 299.80; 299.10).
2. Subjects who had a diagnosis of Schizophrenia and Other Psychotic Disorders (295.xx; 297.xx; 298.8; 293.xx).
3. 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 prior to delivery of the placenta.
4. Seizure disorder currently requiring medication.
5. Use of disallowed concomitant therapy (see section 3.3.6)
6. Females of childbearing potential engaging in sexual activity who were not on medically validated birth control method (eg, double barrier, IUD, oral contraceptives, Norplant, DepoProvera).
7. Participation in an investigational drug trial within 30 days prior to the start of the trial, *except those subjects who had participated in RIS- CAN-19.*[4]
8. Laboratory values outside the normal range. If the results of the biochemistry, haematology tests and the urinalysis testing were not within the laboratory's reference ranges, the subject could be included only on condition that the principal investigator judged that the deviations were not clinically relevant.
9. Known sensitivity to Risperdal®
10. Serious or progressive illnesses, including, but not limited to: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal or endocrine disturbances.
11. History of tardive dyskinesia, neuroleptic malignant syndrome or known hypersensitivity to neuroleptics.
12. Subjects known to be HIV positive.
13. Subjects who had previously received Risperdal® for Conduct Disorder for less than 3 weeks and discontinued use of Risperdal® due to lack of efficacy or due to adverse events. *Subjects 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]
14. Subjects who had previously been successfully treated with Risperdal® for this condition, *except those subjects who had participated in RIS-CAN-19.* [4]
15. *Subjects who experienced a hypersensitivity reaction or suspected hypersensitivity reaction to the trial medication administered in RIS-CAN-19.* [4]
16. *The time elapsed since completing or discontinuing from RIS-CAN-19 exceeded 3 weeks.* [4]

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

3.2.4. PROHIBITIONS AND RESTRICTIONS

Not applicable.

3.2.5. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects were to be withdrawn from the trial if:

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

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

The date and the reason for discontinuation was to be recorded on the Case Report Form (CRF). All subjects 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 on the next pages. The investigator was allowed the following flexibility in scheduling and conducting visits:

- Subjects 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 subject 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 subject needed not be re-tested. The previously ascertained IQ rating could be recorded in the CRF. If the investigator judged the prior score did not accurately reflect the current status of the subject, a re-test could be given and the new score was to be recorded in the CRF.

- If a Vineland Adaptive Behaviour Scale score was available from the year prior to the trial, the subject needed not be re-tested. The previously ascertained score could be recorded on the CRF. If the investigator judged the prior score did not accurately reflect the current status of the subject, 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 subject would be more amenable to the procedure of blood sampling. Should it prove impossible to obtain a blood sample despite several attempts, the subject was to be withdrawn from the trial.

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

Table 3-1: 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 Behaviour Scale	x						
Vital signs	x		x	x	x	x	x
ECG	x						
Laboratory safety, GH, prolactin	x						x[1]
Tanner Staging			x				
CSI[2]	x						
N-CBRF	x		x	x	x	x	x
ABC	x		x	x	x	x	x
CGI[3]			x	x	x	x	x
VAS[4]			x	x	x	x	x
ESRS			x	x	x	x	x
Cognitive tests			x				
Plasma level	x						x[5]
Adverse events			x	x	x	x	x
Concomitant therapy			x	x	x	x	x
Dispense medication[6]		x	x	x	x	x	x

* Visits 1 and 2 needed not be performed for subjects 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.

1 Prolactin and Growth Hormone samples to be taken at trough level ie, 24 hours after previous dose or just prior to the next dose.

2 Child Symptom Inventory.

3 Overall severity at each assessment.

4 VAS of most troublesome symptom.

5 Trough level ie, 24 hours after last dose or just prior to the next dose.

6 Collect unused medication at each visit from Visit 3 to Visit 14.

Table 3-1: 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 Behaviour Scale							
Vital signs	x	x	x	x	x	x	x
ECG		x*			x		x
Laboratory safety, GH, prolactin		x[1]			x[1]	x[1]	x[1]
Tanner Staging					x		x
CSI[2]							
N-CBRF	x	x	x	x	x	x	x
ABC	x	x	x	x	x	x	x
CGI[3]	x	x	x	x	x	x	x
VAS[4]	x	x	x	x	x	x	x
ESRS	x	x	x	x	x	x	x
Cognitive tests					x		x
Plasma level					x[5]		x[5]
Adverse events	x	x	x	x	x	x	x
Concomitant Therapy	x	x	x	x	x	x	x
Dispense medication[6]	x	x	x	x	x	x	x

* Only valid for the subjects in the Hungarian centres Szeged and Baja

1 Prolactin and Growth Hormone samples to be taken at trough level ie, 24 hours after previous dose or just prior to the next dose.

2 Child Symptom Inventory.

3 Overall severity at each assessment.

4 VAS of most troublesome symptom.

5 Trough level ie, 24 hours after last dose or just prior to the next dose.

6 Collect unused medication at each visit from Visit 3 to Visit 14.

3.3.2. IDENTITY OF INVESTIGATIONAL PRODUCT(S)

The trial medication was provided by the Janssen Research Foundation (JRF). The treatment consisted of Risperdal® oral solution 1.0 mg/ml solution.

The following batches of risperidone were used:

Batch number:	Expiry date:	Batch number:	Expiry date:
96I24/321	Sep 1999	97F25/919	Jun 2000
96J01/F71	Oct 1999	98H14/799	Aug 2001
97A24/F71	Jan 2000	98L16/F71	Dec 2001
97A29/956	Jan 2000	99A18/672	Jan 2002
97F24/918	Jun 2000	99F07/588	June 2002
97F25/917	Jun 2000	99H09/391	Aug 2002

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

3.3.3. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

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

3.3.4. SELECTION AND TIMING OF DOSE

The 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 allowed 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 - 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 behavioural 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 on the basis of the most recent weight. The rate at which the dosage could be lowered was not limited. If the subjects exhibited breakthrough symptoms the regimen could be changed to twice daily dosing. Documentation of breakthrough behaviour 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. Supply and Blinding

Each subject was provided with 100 ml bottles of solution containing Risperdal® 1mg/ml. Each bottle was supplied with a millilitre 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 labelled 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, subjects *except those who had participated in RIS-CAN-19* received Risperdal® placebo solution, which was identical in taste, smell and appearance to the solution containing active medication. *Those subjects 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]

3.3.6. Prior and Concomitant Therapy

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

Behaviour Intervention Therapy

Any behaviour intervention therapy must have been initiated at least 30 days prior to trial start. No new therapy could be initiated after this point.

Psychotropic medication

During the trial, other than the Risperdal®, no other antipsychotics, antidepressants, lithium, carbamazepine or valproic acid could be administered. However, subjects 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

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

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 (eg, methylphenidate, permoline, dexedrine) were allowed for the treatment of ADHD provided the subject had been stabilized on a constant dose for 30 days prior to 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 Risperdal® was to be reduced in the case of emergent extrapyramidal symptoms (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 and every 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, subjects who were receiving a sedative/hypnotic for sleep prior to 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, eg, a benzodiazepine, to facilitate the execution of medical procedures, where required (eg, prior to 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) which the subject 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. Subjects who had been prescribed special diets were to be stabilized on them prior to trial start per the investigator's judgement. It was the responsibility of the investigator to judge the appropriateness of over the counter medications for the treatment of any particular subject.

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. TREATMENT COMPLIANCE

A record was kept of the drug dispensed and returned for each subject. 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. INITIAL SUBJECT AND DISEASE CHARACTERISTICS

At the screening visit, the following data were to be recorded *(except for those subjects who had participated in RIS-CAN-19)*[7]: informed consent, medical history, physical examination, psychiatric history, IQ test (Stanford Binet or Wechsler), Vineland Adaptive Behaviour Scale, R064766 plasma level, vital signs, laboratory assessments including prolactin and growth hormone, ECG[8], 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 subjects 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 3.4.5.8), 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 subjects at screening and at baseline.

3.4.2. DRUG CONCENTRATION MEASUREMENTS

Venous (5 ml) blood samples for drug analysis were taken at screening and at trough level (just prior to 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 dosage of the previous drug intake, were to be recorded in the CRF.

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

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

The blood samples were collected in heparinized tubes or in tubes containing EDTA. Tubes were inverted 6-8 times to ensure adequate mixing of blood and reagents. Blood samples were centrifuged for 10 min at 2500 rpm (1000 g) within 2 h 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 labelled with the investigator's name, trial number, medication code number and subjects' initials, time and date of sampling. Samples were stored at -20°C and kept frozen during transport by the trial monitor to the JRF.

Plasma concentrations of risperidone were determined at JRF by means of a validated LC/MS/MS 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 RIA method, with a limit of quantification of 0.20 ng/ml. Descriptions of the assay validation data are included (see Annex PK.7).

3.4.3. PHARMACODYNAMICS

Not applicable.

3.4.4. EFFICACY

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

- Nisonger Child Behaviour Rating Form to be scored by a parent or caregiver under guidance of the investigator;
- Aberrant Behaviour Checklist, to be scored by a parent or caregiver under guidance of the investigator;
- Clinical Global Impression severity ratings, to be scored by a trained investigator;
- An individual target symptom was defined for each subject ie, the symptom considered to be the most disturbing for the subject and his/her surroundings. This symptom was rated on a Visual Analogue Scale and was scored by the parent or caregiver.

The same informant was, where possible, to perform all the assessments throughout the trial. Back-up informants were to be designated, if possible, who had to be available to attend at the time the baseline assessments were done, so that they became familiar with the rating scales.

3.4.4.1. Primary parameter

The primary efficacy parameter was the change versus baseline in behaviour at end point 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 behaviour 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.

3.4.4.2. Secondary parameters

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.

3.4.4.2.1. Other subscales of N-CBRF

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

1. Positive Social Behaviour:
   - 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 Behaviour 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 behaviour subscale were not used in any of the problem behaviour subscales of the parent version of the N-CBRF.

3.4.4.2.2. Aberrant Behaviour Checklist (ABC)

The Aberrant Behaviour Checklist (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 sore was the sum of the individual items.

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

3.4.4.2.3. Clinical Global Impression (CGI)

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

3.4.4.2.4. 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 subject. The target symptom was defined as the symptom considered to be the most disturbing for the subject 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.

3.4.5. SAFETY

3.4.5.1. 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 subject outcome (subject recovered, AE still present, subject died).

Serious adverse events were to be documented separately.

3.4.5.2. Clinical laboratory tests

Blood samples for biochemistry and haematology (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):

Haematology (5 ml EDTA): haemoglobin, haematocrit, RBC, WBC, white 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, ie, 24 hours after previous dose or just prior to 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 labelled in such a way that the investigator's name, trial number, CRF ID, 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 centre. 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.

3.4.5.3. 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.

3.4.5.4. 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.

3.4.5.5. Cardiological 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

3.4.5.6. Body weight

Subjects 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.

3.4.5.7. Extrapyramidal Symptom Rating Scale (ESRS)

The presence and severity of extrapyramidal symptoms 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 Clinical Global Impression of overall severity of Parkinsonism, dystonia and dyskinesia and staging of Parkinsonism.

3.4.5.8. Tanner Staging

The sexual maturity of the subject 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 subject. The number corresponding to the diagram selected was to be recorded in the CRF.

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[9] An ECG was also to be recorded at Visit 9 for subjects from the 2 Hungarian centres 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 subjects from the 2 Hungarian centres Szeged and Baja.

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

3.4.5.9. 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 subjects were asked to enumerate the words they recalled. For the 'recognition trial' a list of 20 words was presented. The subject 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 recognised 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 subject. Thus, a subject who was tested at 10 a.m. on the first visit was to be tested at about that time throughout the trial.

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 subject's sex, date of birth, assessment dates, test results etc., and were to be reviewed against source documents. All personal information from the subjects 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 hormones) 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 prior to 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 centres at any time during and/or after completion of the trial and had access to source documents, including the subject's file. By participating in this trial, the investigators agreed to this requirement. Measures were undertaken to protect subject 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 adverse events, trial medication, and trial discontinuation/ completion data. All database corrections were completed prior to the final interim statistical analysis.

3.6. Statistical methods - sample size

3.6.1. DETERMINATION OF SAMPLE SIZE

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

3.6.2. STATISTICAL METHODS

Statistical analysis was done by the JRF.

All statistical tests were interpreted at the 5% significance level (2-tailed).

Analysis results were presented for all subjects, as well as for the subjects who newly entered in this trial and the subjects coming from the preceding RIS-CAN-19 trial separately. Because of the small numbers of subjects in the latter group, this group was not further split according to the treatment received during the preceding double-blind phase of RIS-CAN-19.

For subjects coming from RIS-CAN-19, baseline assessments did not need to be performed if the time elapsed since the end point of RIS-CAN-19 was less than or equal to 1 week. In this case the end point evaluations of RIS-CAN-19 served as baseline values for RIS-INT-41. However, if a baseline evaluation was performed anyway, this was used as baseline assessment in the interim analysis. If the time elapsed since the end point visit of RIS-CAN-19 was more than 1 week, the evaluations for the baseline visit of RIS-INT-41 had to be repeated.

3.6.2.1. Initial characteristics of subject sample

3.6.2.1.1. Analyses planned

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

3.6.2.1.2. Analyses performed

The analyses were performed as planned.

3.6.2.2. Pharmacokinetics - pharmacodynamics

3.6.2.2.1. Analyses planned

Not applicable

3.6.2.2.2. Analyses performed

Not applicable

3.6.2.3. Drug concentrations

3.6.2.3.1. Analyses planned

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

3.6.2.3.2. Analyses performed (if applicable)

The analyses were performed as described in the protocol.

3.6.2.4. Efficacy

3.6.2.4.1. Analyses planned

An intent-to-treat analysis was performed, ie, all subjects with at least one assessment after the baseline visit were included in the analysis, unless no trial medication had been taken at all.

The primary time point was end point, ie, the last observation during treatment for each subject. Efficacy results were also analyzed per visit.

In case of non-normality appropriate non-parametric tests were applied (Wilcoxon matched-pairs signed-ranks test instead of paired T-test).

(i) Primary parameters

The primary parameter was the change versus baseline at end point of the Conduct Problem subscale score of the N-CBRF. The change versus baseline at end point was evaluated using the paired T-test. This test was also performed to test for differences between baseline and the other time points.

(ii) Secondary parameters

The secondary efficacy parameters were the remaining N-CBRF subscales, the ABC total score, the irritability subscale of the ABC, the investigators CGI, and the severity of an individual target symptom (ie, most troublesome symptom) on a VAS.

The change versus baseline was calculated for all secondary parameters, except the CGI. Each of these changes were evaluated by means of the paired T-test. For CGI, frequency tables were generated.

3.6.2.4.2. Analyses performed

In addition to the irritability subscale of the ABC, the following ABC subscales were also analyzed: lethargy/social withdrawal, stereotypic behaviour, hyperactivity and inappropriate speech.

As a secondary sensitivity analysis, 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 time point where the item was missing. If more than 15% of the items were missing, no imputation was performed and the total score remained missing.

(i) Subgroup analyses

Subgroup analyses were performed for the primary efficacy variable by

- diagnosis group: conduct disorder, oppositional defiant disorder, disruptive behaviour disorder not otherwise specified. Subjects who

reported more than one diagnosis of which one was conduct disorder were classified in the conduct disorder category.

- degree of retardation: borderline, mild, moderate.

3.6.2.5. Safety

3.6.2.5.1. Analyses planned

(i) Adverse events

Type and incidence of all AEs were tabulated. Special attention was given to those subjects who had discontinued the trial for an AE, or who experienced a severe or a serious AE.

(ii) Clinical laboratory tests

Descriptive statistics were generated for the clinical laboratory data (including hormones), and pre versus post treatment cross-tabulations (with classes for below, within and above normal range) for all tests performed.

Important abnormalities, as determined by the occurrence of pathological values, were to be tabulated for all laboratory safety parameters, except hormones. The type of important abnormality depends on the time of occurrence of the pathological value, ie, before (reference value of the parameter), during or after treatment (eg, non-pathological before, pathological during treatment).

Five types of important abnormalities were defined, indicated with codes 1 to 5:

- Code 1: reference value is pathological; values during the observation period are not pathological
- Code 2: reference value is pathological (high/low); at least one value during the observation period is pathological (high/low)
- Code 3: reference value is not pathological; only one value - but not the last one - during the observation period is pathological
- Code 4: reference value is not pathological; at least 2 values - or the last one - during the observation period are pathological
- Code 5: reference value is pathologically high (low); at least 2 values - or the last one - during the observation period are pathologically low (high)

Pathological values are values that are outside the pathological limits. For most haematological and biochemical tests, pathological limits were defined by Lippert and Lehmann[24] For enzymes, the lower pathological limit was defined as zero, and the upper pathological limit as twice the upper normal limit. For leukocyte differential count, no pathological limits were defined. If a value was outside the pathological limits but not outside the normal limits for the particular laboratory, it was not considered pathological.

(iii) Vital signs (blood pressure, heart rate, ECG, body weight

Intragroup tests (paired T-test or Wilcoxon signed rank test in case of non-normality) were performed to evaluate changes over time. Descriptive statistics and tabulations indicating abnormal values and/or changes were provided.

Changes in heart rate (HR), diastolic blood pressure (DBP) and systolic blood pressure (SBP) were classified in the following normality classes:

Table 3-2: 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 ECG parameters QTcB (ms), QTlc (ms), HR (bpm), PQ (ms) and QRS (ms) were calculated and categorized into normal, abnormal and pathological using the following definitions and boundaries:

$QTcB = QT * (HR/60)^{1/2}$

$QTlc = QT + 154 * (1 - 60/HR)$

Table 3-3: Criteria for potentially clinically important ECG values

HR (beats/min)	Below normal	≤55	
	Normal	55-100	
	Above normal	>100	
PR (ms)	Below normal	≤120	
	Normal	120-200	
	Above normal	>200	
QRS (ms)	Normal	<120	
	Above normal	≥120	
QTcB (ms) QTlc (ms)	Normal	Male ≤430	Female ≤450
	Borderline	431 - 450	451 - 470
	Prolonged	451-500	471-500
	Pathologic	>500	>500

Changes in QTcB and QTlc were classified in the following normality classes:

- unlikely to raise concern about potential risk: change vs. baseline < 30 ms (includes all decreases and the increases < 30 ms)
- concern about potential risk: increase vs. baseline ranging from 30 – 60 ms
- clear concern about potential risk: increase vs. baseline > 60 ms

(iv) Extrapyramidal Symptom Rating Scale (ESRS)

The change versus baseline to the end point score during treatment was calculated for the total ESRS and ESRS subscale totals (questionnaire, Parkinsonism, dystonia, dyskinesia, CGI of severity of Parkinsonism, CGI of severity of dyskinesia, CGI of severity of dystonia, bucco-linguo-masticatory, choreoatethoid movements of limbs, hypokinetic and hyperkinetic symptoms), staging of Parkinsonism and for the individual Parkinsonism items. The change versus baseline at other time points was also calculated, as well as the change versus the maximum score.

The changes versus baseline were evaluated by means of the Wilcoxon Signed Rank Test.

The number of subjects requiring anti-EPS medication was quantified and summarized.

(v) Tanner staging

Descriptive statistics were generated for the Tanner staging.

(vi) Cognitive tests

Descriptive statistics were generated for the cognitive function parameters. The changes versus baseline were evaluated by means of the paired t-test.

3.6.2.5.2. Analyses performed

For vital signs: 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 or Wilcoxon signed rank test in case of non-normality) were performed to evaluate changes over time.

For ECG: In addition to the QT correction according to Bazett's formula (QTcB), a QT correction was performed using the formula of Fridericia:

$$QTcF\ (ms) = QT\ (ms) * (HR/60)^{1/3}$$

Applying Fridericia's correction formula to the QT data results in a QTc value (QTcF) which is more independent from heart rate compared to Bazett's correction, especially for higher heart rates. QTcF values were classified in normality classes using the same criteria as for QTcB with Bazett's correction.

All other safety data were analyzed as planned.

EPS listed as AEs were displayed. Subjects were considered to have EPS if they experienced at least one of the following at any time during open-label treatment: tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia and EPS disorders.

Subjects were considered to possibly have prolactin-related adverse events if they experienced hyperprolactinaemia, gynaecomastia, galactorrhoea, amenorrhoea, menorrhagia, dysmenorrhoea, and vaginal bleeding.

Weight-related adverse events included weight increase, appetite increase, and obesitas.

4. RESULTS

This following sections describe the outcomes from the interim analysis.

4.1. Subject and treatment information

After the interim analysis was completed, it appeared that there was a mistake in the interim database for subject #3239. The drug administration page in the CRF of this patient showed that there was no placebo run-in medication since this patient was previously in RIS-CAN-19, and therefore only information on drug administration of risperidone was filled in in the CRF. However, the first week of the drug administration information for risperidone was wrongly entered in the database as being run-in phase, and therefore interpreted as placebo medication. As a result the first week of active medication for this patient was treated in the analysis as if it was placebo medication. This means that visits for this subject in the interim analysis are shifted with 1 week compared to what will be in the final analysis (ie, data at baseline are analysed as screening data in the interim analysis, data at Week 1 as baseline data, and so forth). It was decided that the database was not to be re-opened at this stage. The data will however be corrected before the overall final analysis is going to be performed.

4.1.1. SUBJECT DISPOSITION

Only subjects who had entered the trial before 31 July 1999 were included in the interim analysis. The trial duration for the interim analysis was from 18 Mar 1997 until 3 May 2000. Forty-five psychiatrists/psychologists participated in the trial (Display SUB.INV).

A total of 393 subjects were screened, of which 74 subjects did not meet the inclusion and exclusion criteria at entry. Ultimately, 319 subjects entered the trial, and they all received the trial medication. Out of these 319 subjects, 300 subjects newly entered the trial, and 19 subjects came from RIS-CAN-19 (Display SUB.PD.1).

The discontinuation summary is presented in Table 4-1 and in Display SUB.TT. Listing SUB.TT lists the individual subjects with their reason for discontinuation and the number of days that the subject has been in the trial.

Table 4-1: Summary of reasons for premature discontinuation

	Newly entered subjects (n=300)		Subjects who received risperidone in RIS-CAN-19 (n=19)		Total (n=319)	
	n	(%)	n	(%)	n	(%)
Number of subjects who were treated	300	(100.0)	19	(100.0)	319	(100.0)
Number of subjects who completed	169	(56.3)	3	(15.8)	172	(53.9)
Number of subjects ongoing[1]	72	(24.0)	15	(78.9)	87	(27.3)
Number discontinued	59	(19.7)	1	(5.3)	60	(18.8)
Reason for discontinuation						
Adverse event	22	(7.3)	0	(0.0)	22	(6.9)
Insufficient response	9	(3.0)	1	(5.3)	10	(3.1)
Subject non-compliant	9	(3.0)	0	(0.0)	9	(2.8)
Subject lost to follow-up	8	(2.7)	0	(0.0)	8	(2.5)
Subject withdrew consent	6	(2.0)	0	(0.0)	6	(1.9)
Other	4	(1.3)	0	(0.0)	4	(1.3)
Subject ineligible to continue the trial	1	(0.3)	0	(0.0)	1	(0.3)

[1] Number of subjects who had not yet completed the trial on 31 January 2000 (cut-off date for the interim analysis)
Source: Display SUB.TT

Sixty subjects (18.8%) dropped out before trial completion. The most common reason was adverse event (22 subjects, 6.9%), followed by insufficient response (10 subjects, 3.1%), non-compliance (9 subjects, 2.8%), lost to follow-up (eight subjects, 2.5%), consent withdrawal (6 subjects, 1.9%), other (4 subjects, 1.3%) and ineligibility to continue the trial (one subject, 0.3%).

4.1.2. PROTOCOL DEVIATIONS

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

Table 4-2: Summary of major protocol deviations

	Newly entered subjects (n=300)		Subjects who received risperidone in RIS-CAN-19 (n=19)		Total (n=319)	
	n	(%)	n	(%)	n	(%)
Number (%) of subjects with deviations	24	(8.0)	3	(15.8)	27	(8.5)
Intercurrent therapy	20	(6.7)	1	(5.3)	21	(6.6)
Intercurrent forbidden therapy	20	(6.7)	1	(5.3)	21	(6.6)
Selection criteria not met	5	(1.7)	3	(15.8)	8	(2.5)
Abnormal lab values	0	(0.0)	1	(5.3)	1	(0.3)
Age out of limits	1	(0.3)	0	(0.0)	1	(0.3)
Baseline disease conditions out of limits	3	(1.0)	2	(10.5)	5	(1.6)
Selection criteria not met (nos)[1]	1	(0.3)	0	(0.0)	1	(0.3)

[1] Not otherwise specified
Note that a subject can have more than one deviation
Source: Display SUB.DV

Apart from early withdrawals, described in Section 4.1.1 above, major protocol deviations, mainly forbidden intercurrent therapy, were noted in 27 subjects (8.5%). Twenty-one (6.6%) subjects took forbidden intercurrent therapy, the most frequent of which was Ritalin® (methylphenidate hydrochloride), taken by 11 subjects. Although allowed by the protocol, Ritalin was taken at doses that had not been stabilized at a constant dosage 30 days prior to the start of the study.

4.1.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Out of the 19 subjects who had previously been participating in RIS-CAN-19, 9 had been randomized to treatment with risperidone in RIS-CAN-19, and 10 to placebo (Listing SUB.INV.4). All subjects who had been randomized to risperidone had been effectively treated with risperidone in RIS-CAN-19 for at least 6 weeks. Treatment duration for subjects who had been randomized to placebo in RIS-CAN-19 was between 41 and 43 days in all cases, except for 2 subjects who had been treated for 23-29 days.

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).

The demographic data and other baseline characteristics for the subjects who newly entered the trial and for the subjects who had been participating in trial RIS-CAN-19 are presented in Display SUB.DM and Table 4-3.

Table 4-3: Summary of demographic and baseline characteristics

		Newly entered subjects (n=300)[1]	Subjects who received risperidone in RIS-CAN-19 (n=19)[2]	Total (n=319)
Sex (n, %)	Female	52 (17.3)	1 (5.3)	53 (16.6)
	Male	248 (82.7)	18 (94.7)	266 (83.4)
Race (n, %)	Black	15 (5.0)	3 (15.8)	18 (5.6)
	Caucasian	255 (85.0)	16 (84.2)	271 (85.0)
	Hispanic	3 (1.0)	0 (0.0)	3 (0.9)
	Oriental	1 (0.3)	0 (0.0)	1 (0.3)
	Other	26 (8.7)	0 (0.0)	26 (8.2)
Domiciliary status (n, %)	Lives with other	57 (19.2)	4 (21.1)	61 (19.3)
	Lives with parents	240 (80.8)	15 (78.9)	255 (80.7)
Age (years)	Mean ± SE[3]	9.7 ± 0.14	8.6 ± 0.5	9.6 ± 0.14
	Median (min;max[4])	10.0 (4;14)	9.0 (5;12)	10.0 (4;14)
Age class	Children (<12 years)	223 (74.3)	17 (89.5)	240 (75.2)
	Adolescents (≥12 years)	77 (25.7)	2 (10.5)	79 (24.8)
Weight (kg)	Mean ± SE	35.9 ± 0.8	29.9 ± 1.8	35.6 ± 0.7
	Median (min;max)	32 (14;82)	29.4 (20;46)	32.0 (14;82)
Height (cm)	Mean ± SE	140.3 ± 1.0	132.6 ± 3.0	139.8 ± 0.9
	Median (min;max)	139.0 (105;176)	134.9 (109;155)	138.0 (105;176)
Body mass index (kg/m^2)	Mean ± SE	17.7 ± 0.2	17.3 ± 0.5	17.7 ± 0.2
	Median (min;max)	17.0 (11.9; 35.3)	16.8 (13.9; 22.8)	16.9 (11.9;35.3)
IQ	Mean ± SE	63.0 ± 0.8	69.5 ± 2.4	63.4 ± 0.8
	Median (min;max)	64.0 (35;84)	72.0 (49;83)	65.0 (35;84)
Vineland score	Mean ± SE	52.0 ± 0.8	58.4 ± 2.2	52.4 ± 0.7
	Median (min;max)	51.5 (20;83)	60.0 (40;71)	52.0 (20;83)
CSI score	Mean ± SE	103.1 ± 1.8	113.5 ± 4.3	103.8 ± 1.7
	Median (min;max)	101.0 (28;212)	113.0 (74;143)	102.0 (28;212)
Tanner staging (n, %)	0	27 (9.3)	0 (0.0)	27 (8.7)
	1	169 (58.1)	17 (89.5)	186 (60.0)
	2	51 (17.5)	1 (5.3)	52 (16.8)
	3	21 (7.2)	1 (5.3)	22 (7.1)
	4	18 (6.2)	0 (0.0)	18 (5.8)
	5	5 (1.7)	0 (0.0)	5 (1.6)

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

		Newly entered subjects (n=300)[1]		Subjects who received risperidone in RIS-CAN-19 (n=19)[2]		Total (n=319)	
DSM-IV							
Axis I[5] (n, %)	ADHD	9	(3.0)	0	(0.0)	9	(2.8)
	ADHD+BD nos	28	(9.4)	2	(10.5)	30	(9.4)
	ADHD+CD	58	(19.4)	8	(42.1)	66	(20.8)
	ADHD+CD+BD nos	1	(0.3)	0	(0.0)	1	(0.3)
	ADHD+CD+ODD	6	(2.0)	0	(0.0)	6	(1.9)
	ADHD+ODD	57	(19.1)	3	(15.8)	60	(18.9)
	BD nos	21	(7.0)	1	(5.3)	22	(6.9)
	CD	68	(22.7)	2	(10.5)	70	(22.0)
	CD+ODD	3	(1.0)	0	(0.0)	3	(0.9)
	ODD	48	(16.1)	3	(15.8)	51	(16.0)
Axis II (mental retardation) (n, %)	Borderline	99	(33.2)	11	(57.9)	110	(34.7)
	Mild	134	(45.0)	7	(36.8)	141	(44.5)
	Moderate	65	(21.8)	1	(5.3)	66	(20.8)
Axis III (n, %)	Asthma	0	(0.0)	1	(100.0)	1	(5.0)
	Unspecified	19	(100.0)	0	(0.0)	19	(95.0)

[1]Newly entered subjects. [2]Subjects who came from RIS-CAN-19. [3]SE: standard error. [4]min;max: minimum – maximum.
[5]ADHD: Attention Deficit Hyperactivity Disorder; BD nos: Disruptive Behaviour 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, 83.4% of the subjects were male, and the median age was 10 years (range 4-14 years). Seventy-nine subjects (24.8%) were adolescents (12 years or older). Mean weight and height at baseline were 35.6 kg and 139.7 cm, respectively.

With respect to the DSM-IV Axis I diagnosis, subjects whom reported more than one diagnosis, and one of which was conduct disorder, were classified in the conduct disorder category. As such, there were 146 subjects (45.8%) with conduct disorder (DSM-IV 312.8); 111 subjects (34.8%) with oppositional defiant disorder (DSM-IV 313.81) and 52 subjects (16.3%) with disruptive behaviour disorder not otherwise specified (DSM-IV 312.9). Ten subjects (3.1%) had a missing Axis I diagnosis at the time of the interim analysis, including 9 subjects (2.8%) with attention deficit/hyperactivity disorder (DSM-IV 314.xx; 314.9).

With respect to the DSM-IV Axis II diagnosis there were 141 subjects (44.5%) with mild mental retardation (DSM-IV 317), 66 subjects (20.8%) with moderate mental retardation (DSM-IV 318.0) and 110 subjects (34.7%) with borderline intellectual functioning (DSM-IV V62.89). Two subjects had a missing Axis II diagnosis at the time of the interim analysis.

4.1.4. CONCOMITANT DISEASES AND TREATMENTS

A wide range of concomitant diseases were reported, none of which were thought to have any influence on the course of the trial (see Display SUB.DS and Listing SUB.DS). A total of 268 subjects (84.0%) had at least one past or currently active medical condition at baseline. The most frequently mentioned diseases were related to body system 'ear, nose, throat'.

Concomitant medications were reported by 238 subjects (74.6%). Display SUB.CT.1 lists all concomitant therapies by anatomic therapeutic chemical (ATC) class and generic name. A listing of all concomitant therapies (including those that were taken during the pre and post trial period) with dosing details and indication is given in Listing SUB.CT.1.

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

Table 4-4: Concomitant therapy: summary data

Concomitant therapy	Risperidone (n=319)	
Generic name	n	(%)
Paracetamol	88	(27.6)
Methylphenidate hydrochloride	37	(11.6)
Clavulin	28	(8.8)
Amoxicillin	22	(6.9)
Bactrim	18	(5.6)
Acetylsalicylic acid	14	(4.4)
Mebendazole	14	(4.4)
Salbutamol	13	(4.1)
Ibuprofen	13	(4.1)
Ambroxol hydrochloride	13	(4.1)
Ambroxol	11	(3.4)
Pyrantel embonate	10	(3.1)
Loratadine	10	(3.1)
Oxymetazoline hydrochloride	9	(2.8)
Aminophenazone	8	(2.5)
Fluticasone propionate	8	(2.5)
Mefenamic acid	8	(2.5)
Acetylcysteine	7	(2.2)
Amoxicillin trihydrate	7	(2.2)
Loperamide hydrochloride	7	(2.2)

Source: Display SUB.CT.1

Table 4-5: Concomitant therapy: details for the classes of psychoanaleptics and psycholeptics

Concomitant psychoanaleptic and psycholeptic therapy		Risperidone (n=319)	
ATC class	Generic name	n	(%)
Psychoanaleptics	Amfetamine	1	(0.3)
	Dexamfetamine sulfate	3	(0.9)
	Dosulepin	1	(0.3)
	Methylphenidate	6	(1.9)
	Methylphenidate hydrochloride	37	(11.6)
	Pemoline	1	(0.3)
	Piracetam	2	(0.6)
Psycholeptics	Chloral hydrate	2	(0.6)
	Clonazepam	1	(0.3)
	Diazepam	1	(0.3)
	Euvegal-Tropfen N	1	(0.3)
	Hydroxyzine	1	(0.3)
	Levomepromazine	1	(0.3)
	Lorazepam	3	(0.9)
	Midazolam maleate	2	(0.6)
	Pipamperone	1	(0.3)
	Prochlorperazine maleate	1	(0.3)
	Thioridazine hydrochloride	2	(0.6)
	Valerian extract	1	(0.3)

Source: Display SUB.CT.1

The most frequently used medication was paracetamol (n=88, 27.6%). Paracetamol was most taken for common conditions like headache, fever and cold. Methylphenidate hydrochloride for the treatment of ADHD was taken by 37 subjects (11.6%) 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 that were administered for the treatment of EPS. Five subjects (1.6%) took anti-Parkinson medication in the course of the trial (Display SUB.CT.2). Four subjects (1.3%) took biperiden hydrochloride and 1 subject (0.3%) took trihyexyphenidyl hydrochloride. One of the subjects who received biperiden hydrochloride also received metacycline, potassium chloride, and furosemide.

The number of subjects who used lorazepam as rescue medication for symptoms related to conduct disorder was reported separately. One subject used lorazepam for sedation to facilitate a medical procedure and 2 subjects took lorazepam as rescue medication (Listing SUB.CT.3).

4.2. Treatment compliance

A record was kept of the drug dispensed and returned for each subject as described in section 3.3.7. Analyses of treatment compliance were not performed.

4.3. Drug dose and pharmacokinetics

4.3.1. DRUG DOSE

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

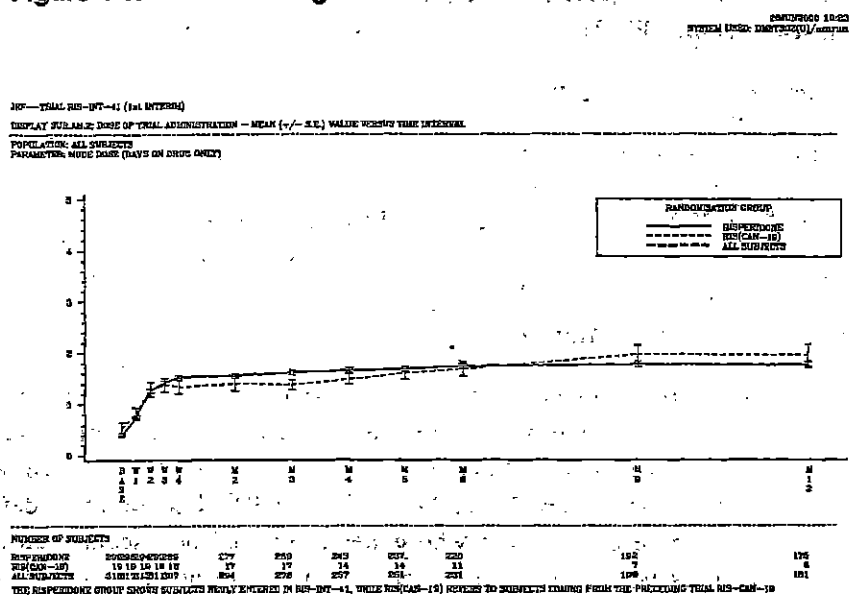
The mean, mode and maximum dose at each time point are shown in Display SUB.AM.1A. The mean mode drug dose over time is shown in Figure 4-1. The overall data are summarized in Table 4-6.

Table 4-6: Mean, mode and maximum drug dose (days on drug only)

Dose (mg/day)		Risperidone (N=319)	
Mode dose	Mean ± SE	1.64	± 0.04
	Median (min;max)	1.60	(0.2; 4.0)
Mean dose	Mean ± SE	1.54	± 0.04
	Median (min;max)	1.45	(0.2; 3.7)
Maximum dose	Mean ± SE	1.86	± 0.05
	Median (min;max)	1.80	(0.2; 5.0)
Dose (mg/kg/day)		(N=318)	
Mode dose	Mean ± SE	0.021	± 0.001
	Median (min;max)	0.011	(0;0.06)
Mean dose	Mean ± SE	0.04	± 0.001
	Median (min;max)	0.04	(0.01; 0.08)

[1] SE: standard error
[2] min;max: minimum-maximum
Source: Displays SUB.AM.1A and SUB.AM.3

Figure 4-1: Mean drug dose ± SE versus time interval



The mean mode daily dosage increased from 0.39 ± 0.01 mg/day at baseline to 1.52 ± 0.04 mg/day at Week 4, and remained stable thereafter. The overall mean mode daily dosage (excluding days off drug) was 1.64 ± 0.04 mg/day.

Exposure is discussed in section 4.5.1.

4.3.2. DRUG CONCENTRATION

4.3.2.1. Data accountability

Only samples received at the bioanalytical laboratory before May 11, 2000 were included in the actual interim analysis. Samples available after that date will be included in the final analysis and report.

A total of 1079 samples were available, from which 928 samples were included in the pharmacokinetic analysis.

Samples taken at visit 1 (n=272) are listed separately in Annex PK.1. Ten of these samples had quantifiable plasma concentrations of active moiety and/or risperidone. For seven of these samples, all plasma levels were below 1 ng/ml. The active moiety concentrations of the three remaining samples were 22.7 ng/ml (#3706), 23.8 ng/ml (#3522) and 45.9 ng/ml (#3372), indicating that these subjects had been receiving risperidone before visit 1.

The following samples were excluded from the summary statistics for the following reasons (n=151; see also Annex PK.2):

- Samples from subjects not yet present in the interim CRF database (n=93) (not listed in Annex PK.2).
- Samples from subjects that did not receive any treatment (n=15).
- Missing information on dose and/or weight (n=18).
- Unscheduled samples with no dosing information (n=24).
- No drug intake before sampling (n=1).

4.3.2.2. Pharmacokinetics

Descriptive statistics of the plasma concentrations of risperidone, the active moiety and 9-hydroxy-risperidone were calculated for samples taken at visit 7 (3-10 weeks after treatment start) (n=236), visit 12 (23-46 weeks after treatment start) (n=231) and endpoint (n=184). Endpoint was defined as the last sample of a subject who either completed or discontinued in the trial. Samples from subjects that were still participating in the trial at the time of the interim analysis were allocated to their corresponding visit.

Summary statistics of the plasma concentrations of risperidone, the active moiety and 9-hydroxy-risperidone at visit 7, visit 12 and endpoint are listed in Table 4-7 (source: Display PK.1). The individual plasma concentrations are displayed in Annex PK.3, Annex PK.4 and Annex PK.5. Scatter plots of the dose-normalized concentrations *versus* the time after the first drug intake are enclosed in Display PK.2.

Table 4-7: Plasma concentrations (ng/ml) of risperidone, active moiety and 9-hydroxy-risperidone (dose-normalized to 0.04 mg/kg/day) at visit 7, visit 12 and endpoint

	N	Mean ± SD	Median (min-max)
Active moiety			
Visit 7	236	11.8 ± 9.8	8.46 (NQ – 54.0)
Visit 12	231	13.5 ± 12.6	10.9 (NQ – 111)
Endpoint	184	12.4 ± 11.2	9.11 (NQ – 64.7)
Risperidone			
Visit 7	236	2.40 ± 6.07	0.17 (NQ – 46.9)
Visit 12	231	2.53 ± 6.05	0.22 (NQ – 45.5)
Endpoint	184	2.02 ± 5.22	0.22 (NQ – 43.5)
9-hydroxy-risperidone			
Visit 7	236	9.44 ± 6.59	7.65 (NQ – 36.8)
Visit 12	231	11.0 ± 9.3	9.08 (NQ – 65.7)
Endpoint	184	10.4 ± 8.6	8.17 (NQ – 50.2)

NQ: <0.20 ng/ml for active moiety and <0.10 ng/ml for risperidone.

Source: Display PK.1

Plasma concentrations remained fairly constant over the entire trial period, and were in the same order of magnitude as in another long-term trial in children (RIS-USA-97).

To better reflect overall peak and trough concentrations of risperidone, summary statistics have been calculated on samples with a sampling time of 0-8 hours post-dose (reflecting more near peak plasma levels) and those with a sampling time of 8-30 hours (representative for trough levels). Summary statistics of the plasma concentrations of risperidone, the active moiety and 9-hydroxy-risperidone are listed in Table 4-8 (source: Display PK.3). Scatter plots of the dose-normalized concentrations *versus* the time relative to drug intake are provided in Display PK.4.

Basically, these plots show the disposition kinetics of the active moiety. The decline in the concentrations is in agreement with the half-life of the active moiety of approximately 24 hours. Based on the risperidone/active moiety plasma concentration ratio, 96.5% of the subjects were identified as apparent extensive metabolizers and 3.5% as apparent poor metabolizers (poor metabolizer if ratio >0.6; otherwise extensive).

Table 4-8: Plasma concentrations (ng/ml; mean ± SD) of risperidone, active moiety and 9-hydroxy-risperidone (dose-normalized to 0.04 mg/kg/day) for samples taken from 0 to 8 hours and from 8 to 30 hours post-dose

Relative time	Active moiety	Risperidone	9-hydroxy-risperidone
0-8 hours (N=55)	22.4 ± 15.8	6.16 ± 6.46	16.2 ± 12.0
8-30 hours (N=545)	12.2 ± 10.4	2.10 ± 5.84	10.1 ± 7.6

Source: Display PK.3

4.3.2.3. Pharmacokinetic correlations

Somnolence

Drug concentrations have been correlated to the occurrence of somnolence, which was the most common AE in this trial. For this purpose, the samples were divided into two subgroups: samples from subjects who experienced somnolence at one or more occasion during the trial (n=160) and from subjects not experiencing somnolence during the trial (n=491). The active moiety plasma concentrations of the group reporting somnolence (mean ± SD: 11.2 ± 10.4 ng/ml) were in the same order of magnitude as the concentrations of the subjects not reporting somnolence (12.8 ± 11.3 ng/ml).

Concomitant intake of methylphenidate

Except for paracetamol, methylphenidate was the most commonly taken medication in this trial (1.9 % of the subjects took methylphenidate and 11.6 % took methylphenidate hydrochloride). The mean active moiety concentrations in the methylphenidate comedication subgroup (n=80; mean ± SD: 11.0 ± 8.4 ng/ml) were comparable to those of the other subjects (n=571; 12.6 ± 11.4 ng/ml), indicating that the concomitant intake of

methylphenidate does not affect the plasma concentrations of the active moiety during long-term treatment with risperidone.

4.4. Efficacy evaluation

4.4.1. DATA SETS ANALYZED

The efficacy analysis included all subjects who had entered the trial before 31 July 1999 and who had received trial medication and had at least one post baseline visit for the primary efficacy parameter (intent-to-treat analysis).

The sample included in the intent-to-treat analysis is the one described under 'Subject disposition' (section 4.1.1) and 'Demographic and other baseline characteristics' (section 4.1.3).

4.4.2. ANALYSIS OF EFFICACY

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

4.4.2.1. Primary efficacy variable

The primary efficacy parameter was the change in behaviour from open label baseline to endpoint as measured on 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 4-14). A lower score on the Conduct Problem subscale of N-CBRF indicates a better condition.

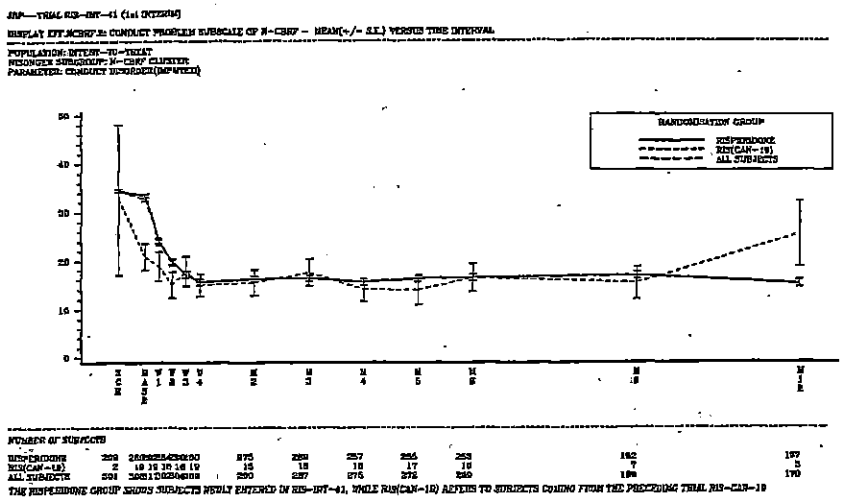
The results for the primary efficacy parameter at the different time points are shown in Display EFF.NCBRF.1B, and are summarized in Table 4-9 and Figure 4-2.

Table 4-9: Conduct Problem subscale score: mean (± SE) and mean (± SE) change from open label baseline at the different time points

	Risperidone (n=319)				
			Change from open label baseline		
Time point	N[1]	Mean ± SE	Mean ± SE	95% CI	p-value[2]
Screening	298	34.4±0.4			
Baseline	308	32.7±0.4			
Week 1	306	24.1±0.6	-8.7 ± 0.5	(-9.7 ; -7.7)	< 0.001
Week 2	294	19.6±0.6	-13.1 ± 0.6	(-14.3 ; -12.0)	< 0.001
Week 3	303	17.1±0.6	-15.7 ± 0.6	(-16.9 ; -14.5)	< 0.001
Week 4	309	15.6±0.6	-16.8 ± 0.6	(-18.1 ; -15.6)	< 0.001
Month 2	286	16.0±0.6	-16.7 ± 0.6	(-17.9 ; -15.5)	< 0.001
Month 3	282	16.2±0.6	-16.2 ± 0.6	(-17.5 ; -14.9)	< 0.001
Month 4	273	15.5±0.6	-16.7 ± 0.6	(-17.9 ; -15.5)	< 0.001
Month 5	271	16.1±0.7	-16.2 ± 0.6	(-17.4 ; -14.9)	< 0.001
Month 6	267	16.4±0.7	-16.0 ± 0.7	(-17.4 ; -14.6)	< 0.001
Month 9	199	16.8±0.7	-16.0 ± 0.8	(-17.5 ; -14.5)	< 0.001
Month 12	168	15.1±0.8	-17.5 ± 0.9	(-19.3 ; -15.8)	< 0.001
Endpoint	319	17.0±0.6	-15.6 ± 0.7	(-16.9 ; -14.3)	< 0.001

Nonimputed results
SE: standard error
CI: confidence interval
[1] Included in this table are data from only those subjects with change-from-baseline data at each given time point
[2] Two-sided p-value for paired T-test on change from open label baseline
Source: Display EFF.NCBRF.1B

Figure 4-2: Mean change from open label baseline ± SE versus time interval on the Conduct Problem Subscale of N-CBRF



The mean score dropped from 32.7 (± 0.4) at the open label baseline to 17.0 (± 0.6) at endpoint, and to 15.1 (± 0.8) at Month 12. The mean change from open label baseline at endpoint and at Month 12 was -15.6 and -17.5, respectively. The effect was highly statistically significant (both $p < 0.001$).

The improvement was especially observed during the first 4 weeks of treatment. Scores remained stable thereafter.

As shown in Display EFF.NCBRF.1B, the open label baseline scores of the subjects who had previously participated in RIS-CAN-19 (N=19, mean ± SE 20.8 ± 2.78) were lower than the scores of the newly entered subjects (N = 289, 33.4 ± 0.38). This suggests that the beneficial effects of treatment on the primary efficacy parameter for subjects who were treated in trial RIS-CAN-19 were already partially obtained in the latter trial.

The mean change from the double-blind baseline for all subjects who had participated in trial RIS-CAN-19 was -13.6 (± 2.3) at endpoint ($p < 0.001$). Because of the small numbers of subjects (n=19), this group was not further split according to the treatment received during the preceding double-blind phase of RIS-CAN-19.

4.4.2.2. 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.

4.4.2.2.1. Other subscales of the Nisonger-Child Behaviour 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 behaviour subscales (compliant/ calm, adaptive/ social) and the problem behaviour 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 sub-scales of the N-CBRF are given in Display EFF.NCBRF.3B. The scores at Month 12 and at endpoint are summarized in Table 4-10.

Table 4-10: Other subscales of Nisonger Child Behaviour rating form: mean (± SE) and mean (± SE) change from open label baseline at Month 12 and at endpoint

	Risperidone (n=319)				
			Change from open label baseline		
N-CBRF subscale	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Positive Social Behaviour:					
Compliant/calm[2]					
Month 12	166	9.2±0.3	4.1±0.3	(3.4 ; 4.7)	< 0.001
Endpoint	319	8.5±0.2	3.2±0.2	(2.7 ; 3.6)	< 0.001
Adaptive/social[2]					
Month 12	168	7.0±0.2	2.5±0.2	(2.1 ; 2.9)	< 0.001
Endpoint	319	6.5±0.1	2.0±0.2	(1.6 ; 2.3)	< 0.001
Problem Behaviour Subscales:					
Insecure/anxious					
Month 12	167	9.4±0.5	-6.3±0.6	(-7.6 ; -5.0)	< 0.001
Endpoint	319	10.3±0.4	-5.4±0.5	(-6.3 ; -4.4)	< 0.001
Hyperactive					
Month 12	168	10.3±0.5	-8.5±0.5	(-9.5 ; -7.5)	< 0.001
Endpoint	319	11.2±0.4	-7.0±0.4	(-7.8 ; -6.2)	< 0.001
Self-injury/ stereotyped					
Month 12	168	1.2±0.2	-1.5±0.3	(-2.0 ; -1.0)	< 0.001
Endpoint	319	1.5±0.2	-1.1±0.2	(-1.4 ; -0.7)	< 0.001
Self-isolated/ ritualistic					
Month 12	167	3.2±0.3	-2.0±0.3	(-2.6 ; -1.3)	< 0.001
Endpoint	319	3.6±0.2	-1.6±0.2	(-2.0 ; -1.1)	< 0.001
Overly sensitive					
Month 12	169	5.0±0.3	-2.6±0.3	(-3.1 ; -2.1)	< 0.001
Endpoint	319	5.2±0.2	-2.1±0.2	(-2.5 ; -1.7)	< 0.001

SE: standard error
CI: confidence interval
[1] Two-sided p-value for paired T-test on change from open label baseline
[2] 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 time points for all subscales of the N-CBRF: compliant/ calm, adaptive/ social, insecure/ anxious, hyperactive, self-injury/ stereotyped, self-isolated/ ritualistic and overly sensitive (all $p < 0.001$).

The improvement was mainly observed during the first 4 weeks of treatment, and remained stable thereafter.

4.4.2.2.2. Aberrant Behaviour 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 time points for the total ABC score is graphically displayed in Display EFF.ABC.2. The scores from the total ABC and its subscales at Month 12 and at endpoint are summarized in Table 4-11. Lower scores indicate a better condition.

Table 4-11: Aberrant Behaviour Checklist: mean (± SE) and mean change (± SE) from open label baseline at Month 12 and at endpoint

	Risperidone (n=319)				
			Change from open label baseline		
ABC	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Total ABC					
Month 12	153	32.3±2.0	-36.1±2.3	(-40.5 ; -31.7)	< 0.001
Endpoint	291	38.0±1.7	-28.2±1.8	(-31.9 ; -24.6)	< 0.001
Irritability					
Month 12	160	10.1±0.7	-9.5±0.8	(-11.0 ; -8.0)	< 0.001
Endpoint	304	11.5±0.5	-8.0±0.6	(-9.2 ; -6.9)	< 0.001
Lethargy/social withdrawal					
Month 12	160	4.0±0.4	-3.3±0.5	(-4.4 ; -2.2)	< 0.001
Endpoint	300	5.2±0.4	-2.5±0.4	(-3.3 ; -1.6)	< 0.001
Stereotypic behaviour					
Month 12	163	1.6±0.2	-2.3±0.4	(-3.0 ; -1.5)	< 0.001
Endpoint	308	2.0±0.2	-1.3±0.3	(-1.8 ; -0.8)	< 0.001
Hyperactivity					
Month 12	157	15.0±0.9	-17.4±1.0	(-19.3 ; -15.5)	< 0.001
Endpoint	299	17.3±0.7	-14.3±0.8	(-15.8 ; -12.8)	< 0.001
Inappropriate speech					
Month 12	169	2.4±0.2	-1.8±0.2	(-2.3 ; -1.4)	< 0.001
Endpoint	317	2.5±0.2	-1.3±0.2	(-1.7 ; -1.0)	< 0.001

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

The mean change from the open label baseline of the total ABC score ranged between -12.2 (Week 1) and -36.1 (Month 12), and was -28.2 (± 1.8) at

endpoint ($p < 0.001$). The improvement was especially observed during the first 4 weeks of treatment and was statistically significant from Week 1 onwards (all $p < 0.001$).

The scores on the individual subscales of the ABC showed a similar profile: a statistically significant improvement that was observed mainly during the first 4 weeks of treatment and that remained stable thereafter (all p-values at all time points for all subscales < 0.001).

4.4.2.2.3. Clinical Global Impression (CGI)

Display EFF.CGI.1 and Display EFF.CGI.2 show the distribution of the clinical global impression of change of the subjects' condition over time. The frequency distribution at the open label baseline, Month 12 and at endpoint are summarized in Table 4-12.

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

	Risperidone (n=319)					
	Open label baseline (n=305)		Month 12 (n=170)		Endpoint (n=311)	
CGI rating	n	(%)	n	(%)	n	(%)
Not ill	0	(0.0)	26	(15.3)	35	(11.3)
Very mild	2	(0.7)	48	(28.2)	84	(27.0)
Mild	19	(6.2)	55	(32.4)	85	(27.3)
Moderate	70	(23.0)	33	(19.4)	71	(22.8)
Marked	104	(34.1)	5	(2.9)	20	(6.4)
Severe	92	(30.2)	3	(1.8)	15	(4.8)
Extremely severe	18	(5.9)	0	(0.0)	1	(0.3)

Source: Display EFF.CGI.1

Overall 204 (65.6%) subjects showed no, very mild or mild symptoms at endpoint compared to 21 (6.9%) with very mild or mild symptoms at baseline.

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

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

The VAS score of the most troublesome symptom at the different time points 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 4-13. Lower scores indicate a better condition. The most frequent of the most troublesome symptoms included aggression, oppositional defiant behaviour, and hyperactivity.

Table 4-13: Visual Analogue Scale: mean (± SE) and mean (± SE) change from open label baseline at Month 12 and at endpoint

	Risperidone (n=319)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
VAS score of the most troublesome symptom					
Month 12	170	26.6±1.4	-49.6±1.8	(-53.2 ; -46.0)	< 0.001
Endpoint	308	33.4±1.4	-40.5±1.6	(-43.7 ; -37.3)	< 0.001

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

The mean change from baseline ranged between -11.5 (Week 1) and -49.6 (Month 12). The improvement at endpoint was -40.5 ± 1.6. The change from baseline was statistically significant at all time points (all $p < 0.001$). Changes were mostly observed during the first 4 weeks of treatment; thereafter, scores remained stable.

4.4.2.3. Subgroup analyses

A subgroup analyses by DSM-IV Axis I (diagnosis group) and Axis II diagnosis (degree of mental retardation) was performed for the primary efficacy parameter (ie, the change versus open label baseline in behaviour at end point as measured on the Conduct Problem subscale of the N-CBRF).

4.4.2.3.1. Subanalysis by diagnosis

Subjects diagnosed with conduct disorder (DSM-IV 312.8) were analyzed separately from those diagnosed with oppositional defiant disorder (DSM-IV 313.81) and subjects with disruptive behaviour 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. Ten subjects had a missing Axis I diagnosis at the time of the interim analysis. The data at endpoint and Month 12 for the 309 subjects with an Axis I diagnosis at baseline are summarized in Table 4-14.

Table 4-14: Conduct Problem subscale score: subanalysis by diagnosis

Time point	Risperidone (n=309)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Subjects diagnosed with conduct disorder					
Month 12	79	14.8±1.2	-18.4 ± 1.1	(-20.7 ; -16.2)	< 0.001
Endpoint	146	17.2±1.0	-15.7 ± 1.0	(-17.6 ; -13.8)	< 0.001
Subjects diagnosed with oppositional defiant disorder					
Month 12	56	17.0±1.4	-16.4 ± 1.8	(-20.0 ; -12.7)	< 0.001
Endpoint	111	17.3±1.0	-16.2 ± 1.3	(-18.8 ; -13.7)	< 0.001
Subjects diagnosed with disruptive behaviour not otherwise specified					
Month 12	27	12.6±1.8	-17.9 ± 2.1	(-22.2 ; -13.6)	< 0.001
Endpoint	52	16.7±1.6	-13.8 ± 1.7	(-17.2 ; -10.4)	< 0.001

SE: standard error
CI: confidence interval
[1] Two-sided p-value for paired T-test on change from open label baseline
Source: Display EFF.STR.DIAG.NCBRF.1B

The mean change from the open label baseline for subjects with conduct disorder ranged between -10.9 at Week 1 and -18.4 at Month 12. The improvement at endpoint was -15.7.

The mean change from the open label baseline for subjects with oppositional defiant disorder ranged between -7.4 at Week 1 and -18.2 at Month 2. The improvement at endpoint was -16.2.

The mean change from the open label baseline for subjects with disruptive behaviour not otherwise specified ranged between -5.8 at Week 1 and -17.9 at Month 12. The improvement at endpoint was -13.8.

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

4.4.2.3.2. Subanalysis by degree of retardation

Subjects diagnosed with borderline intellectual functioning (DSM-IV V62.89) were analyzed separately from subjects diagnosed with mild (DSM-IV 317) or moderate (DSM-IV 318.0) mental retardation. The data 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 subjects. Table 4-15 presents a summary of the data at endpoint and Month 12.

Table 4-15: Conduct Problem subscale score: subanalysis by degree of mental retardation

	Risperidone (n=317)				
			Change from open label baseline		
Time point	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Subjects diagnosed with mild mental retardation					
Month 12	77	16.1 ± 1.3	-16.8 ± 1.3	(-19.5 ; -14.2)	< 0.001
Endpoint	141	16.8 ± 1.0	-16.0 ± 1.0	(-18.1 ; -13.9)	< 0.001
Subjects diagnosed with moderate mental retardation					
Month 12	44	13.6 ± 1.5	-18.0 ± 1.5	(-21.1 ; -15.0)	< 0.001
Endpoint	66	15.4 ± 1.4	-16.3 ± 1.4	(-19.1 ; -13.5)	< 0.001
Subjects diagnosed with borderline mental retardation					
Month 12	47	15.0 ± 1.3	-18.2 ± 1.7	(-21.7 ; -14.7)	< 0.001
Endpoint	110	18.3 ± 1.1	-14.7 ± 1.2	(-17.1 ; -12.3)	< 0.001

SE: standard error
CI: confidence interval
[1] Two-sided p-value for paired T-test on change from open label baseline
Source: Display EFF.STR.MR.NCBRF.1B

The mean change from the open label baseline for subjects with mild mental retardation ranged between -8.4 at Week 1 and -17.5 at Month 2. The improvement at endpoint was -16.0.

The mean change from the open label baseline for subjects with moderate mental retardation ranged between -9.0 (Week 1) and -18.0 (Month 4, 6, 12). The improvement at endpoint was -16.3.

The mean change from the open label baseline for subjects with borderline intellectual functioning ranged between -9.0 at Week 1 and -18.2 at Month 12. The improvement at endpoint was -14.7.

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

4.4.3. PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIPS

Not applicable.

4.4.4. EFFICACY CONCLUSIONS

The interim efficacy results of this one-year multicentre open label trial in 319 children (5 - 14 years of age) with conduct or other disruptive behaviour disorders and borderline intellectual functioning or mild to moderate mental retardation showed that treatment with risperidone (mean mode daily dosage 1.64 ± 0.04 mg or 0.021 ± 0.001 mg/kg) had a statistically significant beneficial effect on the primary efficacy variable (ie, the change from open

label baseline on the Conduct Problem Subscale of the Nisonger Child Behaviour Rating Form (N-CBRF) at endpoint), and on all secondary efficacy parameters (ie, other subscales of the N-CBRF, the Aberrant Behaviour Checklist (ABC), the investigators' Clinical Global Impression (CGI) and the Visual Analogue Scale (VAS) of the most troublesome symptom). The improvement was especially observed during the first 4 weeks of treatment. Scores remained stable thereafter.

A subgroup analysis of the primary efficacy parameter by DSM-IV Axis I diagnosis (conduct disorder, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified) and by DSM-IV Axis II diagnosis (mild or moderate mental retardation, borderline intellectual functioning) did not reveal any differences between subgroups.

4.5. Safety evaluation

All subjects who entered the trial before 31 July 1999 and who received trial medication were included in the safety analysis.

4.5.1. Extent of exposure

Treatment duration is shown in Display SUB.AM.1B. The mean treatment duration was 281.6± 5.9 days (range 7-498 days). The mean treatment duration was 261.0 ± 7.2 days (range 1-498 days) when only days on drug were taken into account.

Out of the 319 subjects, 230 subjects were treated for 6 months or more, and 181 of these 230 subjects were treated for 12 months or more (days on drug only).

4.5.2. Adverse events

4.5.2.1. All adverse events

4.5.2.1.1. Incidence

An overview of all subjects with adverse events by WHO System-organ class and preferred term is presented in Display SAF.AE.1. Table 4-16 presents a summary of all adverse events that were reported by ≥10% of the subjects.

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

Table 4-16: Incidence of adverse events reported by 10% or more of all subjects

System Organ Class	Preferred term	Risperidone (n=319) n	(%)
Psychiatric Disorders	Somnolence	90	(28.2)
Respiratory System Disorders	Rhinitis	78	(24.5)
	Pharyngitis	55	(17.2)
	Upper resp tract infect	41	(12.9)
	Coughing	39	(12.2)
Central & Peripheral Nervous System Disorders	Headache	55	(17.2)
Endocrine Disorders	Hyperprolactinaemia	50	(15.7)
Metabolic and Nutritional Disorders	Weight increase	49	(15.4)
Body as a Whole – General Disorders	Fatigue	39	(12.2)
	Fever	39	(12.2)
	Injury	36	(11.3)
Gastrointestinal System Disorders	Vomiting	40	(12.5)
Urinary System Disorders	Urinary incontinence	32	(10.0)
Subjects with any adverse event		288	(90.3)

Source: Display SAF.AE.1

The total number of subjects who reported adverse events during the trial was 288 (90.3%). Somnolence was the most common adverse event, reported by 90 subjects (28.2%). The investigator considered the relationship with the trial medication as possibly, probably or very likely in 63 subjects.

Other frequently reported adverse events were rhinitis (n=78, 24.5%), headache (n=55, 17.2%), pharyngitis (n=55, 17.2%), hyperprolactinaemia (n=50, 15.7%) and weight increase (n=49, 15.4%).

Rhinitis and pharyngitis were only sporadically considered drug-related. Headache was considered drug-related in 13 subjects.

Hyperprolactinaemia was considered drug-related in 26 subjects; the relationship was not assessed in the remaining 24 subjects. Hyperprolactinaemia and other prolactin-related disorders are discussed in section 4.5.3.4.

Weight increase was considered drug-related in the opinion of the investigator in 36 of 49 subjects who reported this adverse event; weight increase was not or doubtfully related in 4 subjects, and the relationship was not assessed in 9 subjects. Body weight is discussed further in section 4.5.4.3.

4.5.2.1.2. Severity

The incidence of adverse events by severity (mild, moderate, severe) is shown in Display SAF.AE.2. A tabulation of all severe adverse events by relationship to the trial medication is given in Display SAF.AE.7. A summary table of all severe adverse events that in the opinion of the

investigator were possibly, probably or very likely related to the trial medication is presented in Table 4-17.

Table 4-17: Incidence of possibly, probably or very likely drug-related severe adverse events

System Organ Class	Preferred term	Risperidone (n=319) n	(%)
Psychiatric Disorders	Somnolence	1	(0.3)
	Anorexia	1	(0.3)
	Anxiety	1	(0.3)
	Apathy	1	(0.3)
	Concentration impaired	1	(0.3)
Body as a Whole—General Disorders	Condition aggravated	2	(0.6)
	Fatigue	1	(0.3)
	Leg pain	1	(0.3)
Central & Peripheral Nervous System Disorders	Headache	1	(0.3)
	Dizziness	1	(0.3)
	Extrapyramidal disorder	1	(0.3)
Metabolic and Nutritional Disorders	Weight increase	3	(0.9)
	Obesity	1	(0.3)
White Cell and RES Disorders	Granulocytopenia	2	(0.6)
	Leukopenia	1	(0.3)
Endocrine Disorders	Hyperprolactinaemia	1	(0.3)
Secondary Terms	Medication error	1	(0.3)
Subjects with one or more severe adverse events that were possibly, probably or very likely drug related		16	(5.0)
Subjects with one or more severe adverse event (related or not)		40	(12.5)

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

The majority of all adverse events was mild. Overall, 40 subjects (12.5%) experienced one or more severe adverse events, and of these subjects, 16 (5.0%) had possibly, probably or very likely treatment-related adverse events. Treatment-related severe adverse events that were reported by more than one subject were weight increase (n=3, 0.9%), granulocytopenia and condition aggravated (n=2 each, 0.6%).

4.5.2.1.3. Drug-relatedness

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

4.5.2.2. Deaths, other serious, and other significant adverse events

4.5.2.2.1. Deaths

None of the subjects included in the interim analysis died during the trial.

4.5.2.2.2. Other serious adverse events

An overview of all subjects with serious adverse events by WHO System-organ class and preferred term is presented in Display SAF.AE.8.

A total of 38 subjects (11.9%) reported serious adverse events while on treatment with risperidone. Serious adverse events (drug-related or not) that were reported by more than one subject were aggressive reaction (n=10, 3.1%), condition aggravated (n=5, 1.6%), and tardive dyskinesia, hypertonia, abdominal pain, pharyngitis, viral infection and surgical intervention (n=2 each, 0.6%).

Serious adverse events that were considered drug-related (ie, possibly, probably or very likely) by the investigator are shown in Display SAF.AE.10, and are summarized in Table 4-18.

Table 4-18: Incidence of possibly, probably or very likely drug-related serious adverse events during risperidone treatment

System Organ Class	Preferred term	Risperidone (n=319) n	(%)
Psychiatric Disorders	Anorexia	1	(0.3)
	Confusion	1	(0.3)
Central & Peripheral Nervous System Disorders	Dyskinesia tardive	1	(0.3)
	Dystonia	1	(0.3)
	Extrapyramidal disorder	1	(0.3)
	Headache	1	(0.3)
	Hypokinesia	1	(0.3)
Body as a Whole—General Disorders	Condition aggravated	1	(0.3)
	Therapeutic response increased	1	(0.3)
Gastrointestinal System Disorders	Saliva increased	1	(0.3)
Secondary Terms	Medication error	1	(0.3)
Skin and Appendages Disorders	Urticaria	1	(0.3)
Red Blood Cell Disorders	Pancytopenia	1	(0.3)
Vision Disorders	Glaucoma	1	(0.3)
White Cell and RES Disorders	Granulocytopenia	1	(0.3)
Subjects with one or more serious adverse events that were possibly, probably, or very likely drug related[1]		10	(3.1)
Subjects with one or more serious adverse event (related or not)[1]		38	(11.9)

[1] One additional subject (A3108) had an aggressive reaction judged serious and possibly drug-related during the placebo run-in phase.
Source: Display SAF.AE.10, Listing SAF.AE.3

Ten subjects (3.1%) reported 15 drug-related serious adverse events during the risperidone treatment phase. One additional subject (A3108) had an aggressive reaction judged possibly drug-related during the run-in placebo phase. The majority of all drug-related serious adverse events were EPS-like adverse events. All EPS-like adverse events (serious or not) are discussed in section 4.5.2.2.4.

All drug-related serious adverse events were reported only once.

4.5.2.2.3. Adverse events leading to treatment discontinuation

An overview of all adverse events that led to permanent stop of the trial medication is given in Display SAF.AE.12, and is summarized in Table 4-19.

Table 4-19: Incidence of adverse events leading to permanent stop

System Organ Class	Preferred term	Risperidone (n=319) n	(%)
Central & Peripheral Nervous System Disorders	Dyskinesia tardive	2	(0.6%)
	Hypertonia	2	(0.6%)
	Convulsions	1	(0.3%)
	Dizziness	1	(0.3%)
	Dyskinesia	1	(0.3%)
	Extrapyramidal disorder	1	(0.3%)
	Headache	1	(0.3%)
	Hypokinesia	1	(0.3%)
Psychiatric Disorders	Anorexia	2	(0.6%)
	Anxiety	2	(0.6%)
	Somnolence	2	(0.6%)
	Appetite increased	1	(0.3%)
	Depression	1	(0.3%)
	Hallucination	1	(0.3%)
Body as a Whole—General Disorders	Fatigue	1	(0.3%)
	Injury	1	(0.3%)
	Leg pain	1	(0.3%)
Gastrointestinal System Disorders	Diarrhoea	1	(0.3%)
	Gastroenteritis	1	(0.3%)
	Nausea	1	(0.3%)
	Vomiting	1	(0.3%)
Metabolic and Nutritional Disorders	Weight increase	2	(0.6%)
	Obesity	1	(0.3%)
Urinary System Disorders	Face oedema	1	(0.3%)
	Urinary incontinence	1	(0.3%)
Endocrine Disorders	Gynaecomastia	1	(0.3%)
Resistance Mechanism Disorders	Sepsis	1	(0.3%)
Respiratory System Disorders	Dyspnoea	1	(0.3%)
White Cell and RES Disorders	Granulocytopenia	1	(0.3%)
Subjects with one or more adverse events leading to discontinuation		22	(6.9)

Note that a subject can have more than one adverse event that led to discontinuation
Source: Display SAF.AE.12, Listing SAF.AE.5

Twenty-two subjects (22, 6.9%) had adverse events that resulted in permanent discontinuation of the trial medication. EPS-like adverse events that led to permanent discontinuation were reported by 5 subjects (see section 4.5.2.2.4).

4.5.2.2.4. Other significant adverse events

The incidence of EPS-like adverse events is presented in Display SAF.AE.11, and is summarized in Table 4-20. An individual subject listing is given in Listing SAF.AE.4.

Table 4-20: Incidence of EPS-like adverse events

System Organ Class	Preferred term	Risperidone (n=319) n	(%)
Central & Peripheral Nervous System Disorders	Extrapyramidal disorder	25	(7.8)
	Hypertonia	14	(4.4)
	Tremor	13	(4.1)
	Bradykinesia	11	(3.4)
	Hypokinesia	10	(3.1)
	Hyperkinesia	9	(2.8)
	Dyskinesia	10	(3.1)
	Gait abnormal	6	(1.9)
	Dyskinesia tardive	2	(0.6)
	Dystonia	5	(1.6)
	Oculogyric crisis	2	(0.6)
Subjects with one or more EPS-like adverse event		71	(22.3)

Source: Display SAF.AE.11

Seven (2.2%) subjects had EPS-like adverse events that were reported as serious: 2 subjects had hypertonia (1 mild, 1 moderate), 2 subjects had tardive dyskinesia (1 severe, 1 moderate, see below), and 1 subject each with extrapyramidal disorder (severe), hypokinesia (moderate) and dystonia (moderate).

Five (1.6%) subjects permanently discontinued treatment due to EPS-like adverse events, and 2 subjects discontinued temporarily.

Overall, the majority of EPS-like adverse events was mild and possibly, probably or very likely related to risperidone treatment.

Two subjects reported reversible tardive dyskinesia.

A 9-year-old female subject (#3233, 0.6 mg/day risperidone) had an unremarkable medical history. At the final visit, the subject 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 prior to the examination. The mother stated that she noticed that the head and truncal movemements 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 subject'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 subject (#3278, 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 subject presented with marked labial movements, diagnosed as moderate tardive dyskinesia, and medication was stopped. The subject recovered without treatment 2 weeks later. The relationship with the trial medication was judged as very likely. This adverse event was reported as serious.

4.5.2.2.5. Analysis and discussion of deaths, other serious adverse events and other significant adverse events

Individual case reports on deaths, other serious adverse events and adverse events leading to withdrawal are given in Annex 6. These narratives are based on the information that was available in the interim database, and will be updated in the Final Clinical Report.

4.5.3. CLINICAL LABORATORY EVALUATION

4.5.3.1. Laboratory values over time

Clinical laboratory data were available for all subjects. Of the 319 subjects with data, 305 (96%) had paired laboratory data, ie, both at baseline (screening) and at least once during or at the end of treatment. Display SAF.LAB.1B describes the descriptive statistics and the distribution of changes from open label baseline at the different time points for haematology and biochemistry. Shift tables for each parameter are given in Display SAF.LAB.2B. The results of the urinalysis are presented in Display SAF.LAB.5.

Overall, there were no consistent or clinically relevant changes in blood chemistry or haematology, with the exception of prolactin (see section 4.5.3.4). There were no relevant changes in urinalysis.

4.5.3.2. Individual changes

The numbers of subjects with low, normal, or high values, with respect to laboratory normal ranges at screening and at the different time points are given in Display SAF.LAB.2B.

4.5.3.3. Individual clinically significant abnormalities

A total of 152 (50%) subjects showed important abnormalities at some time during the trial. Of these 152 subjects, 61 subjects (20%) had a 'code-4' important abnormality, ie, non-pathological laboratory values before treatment but at least 2 values - or the last one - during the observation period were pathological (Display SAF.LAB.4B).

Individual data on 'code-4' important abnormalities are given in Listing SAF.LAB.2B. The number of subjects with a 'code-4' important abnormality are summarized in Table 4-21.

Table 4-21: Number of subjects with 'code-4' important abnormalities

Laboratory test	Risperidone (n=319)		
	↑	↓	total
Clinical chemistry			
Chloride	1	-	1
Potassium	3	-	3
Total protein	2	1	3
Urea	2	2	4
γ-GT	1	-	1
AST	2	-	2
ALT	4	-	4
Bicarbonate	2	34	35[1]
Haematology			
Haemoglobin	-	6	6
Haematocrit	-	5	5
RBC	-	1	1
WBC	1	1	2
Platelet count	3	2	5

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

There were 34 subjects with pathologically low bicarbonate levels during the trial, but this was considered not clinically relevant.

Three subjects (A03517, A03944, and A03908) had code-4 ALT increases, 1 subject (A03918) had code-4 AST increases, and 1 subject (A03963) had code-4 ALT and AST increases. These 5 subjects are described below.

Subject A03517, a 13-year-old Caucasian girl, had normal ALT values (laboratory limit 30 U/L) at screening through week 4. At Month 3, the subject's ALT (39 U/L) was above the limit, and at Month 6 (61 U/L) exceeded the pathological limit of 60 U/L. (Because this subject was ongoing at the time of the interim analysis, there were no laboratory data

beyond Month 6.) Although not included as a code-4 abnormality, the subject's AST was above the laboratory limit at Month 6 (52 U/L). These laboratory abnormalities were reported as adverse events; their relationship to treatment with risperidone was judged doubtful. Other adverse events, all of which were considered at least possibly, probably, or very likely related to risperidone treatment, were appetite increase, weight increase, and EPS. Also reported were skin striae (its relationship to treatment was judged doubtful). Other laboratory abnormalities included elevated prolactin levels at every evaluation, as well as decreased bicarbonate or urea levels, increased or decreased neutrophil and lymphocyte counts, and increased eosinophil counts sporadically at one or more evaluations between Screening and Month 6 (see Listing SAF.LAB.3 for further details).

Subject A03944, an 8-year-old black boy, had ALT values of 56 and 52 U/L at screening and week 4, respectively, ie, above the laboratory limit of 39 U/L. At Months 3 and 6, this subject's ALT values were 94 and 148 U/L, respectively, which exceeded the pathological limit of 78 U/L. (Because this subject was ongoing at the time of the interim analysis, there were no laboratory data beyond Month 6.) Although not included as code-4 abnormalities, the subject's AST values were above the laboratory limit at Months 3 and 6 (56 and 75 U/L, respectively). Alkaline phosphatase was elevated at Screening (491 U/L), Month 3 (496 U/L), and Month 6 (497 U/L, normal range 70-470 U/L). GGT was elevated at Week 4 (53 U/L), Month 3 (87 U/L), and Month 6 (92 U/L). At Screening and at each evaluation, the following laboratory parameters were below the normal range: uric acid (2.7-3 mg/dL), haemoglobin (11.9-12.3 g/dL), and RBC (3.97-4.2 x $10^6/mm^3$). Laboratory abnormalities that appeared sporadically included elevated prolactin levels, decreased bicarbonate, chloride, and sodium levels, decreased WBC, and increased eosinophil count. The subject experienced anorexia, headache, and nervousness; the relationship of these events to treatment with risperidone was judged doubtful. The subject also had pharyngitis, which was unrelated to treatment, and somnolence on two occasions, which were judged possibly and probably related to treatment.

Subject A03908, a 6-year-old Caucasian boy, had ALT values of 16-36 U/L at double-blind baseline through Month 9, which were within normal laboratory limits (laboratory limits were 45 U/L at double-blind baseline and screening and 39 U/L at Week 4-Month 12). At Month 12, the subject's ALT (97 U/L) exceeded the pathological limit of 78 U/L. The subject's haemoglobin level was decreased at Week 4 through Month 12 (12-13 g/dL). Laboratory abnormalities that appeared sporadically were decreased uric acid, bicarbonate, RBC, WBC, neutrophils, and lymphocytes, and increased eosinophils (Screening only). The subject's adverse events included hyperkinesia, viral infection, injury, otitis media, and upper respiratory tract infection, none of which had any relationship to risperidone treatment. The

subject also experienced somnolence, because of which treatment was temporarily stopped.

Subject A03918, an 11-year-old Caucasian boy, had an AST value of 74 U/L at screening, which exceeded the laboratory limit of 39 U/L. AST at Week 4 (38 U/L) was normal, but exceeded the laboratory limit at Month 3 (67 U/L). At Month 6, the subject's AST (83 U/L) exceeded the pathological limit of 78 U/L. (Because this subject was ongoing at the time of the interim analysis, there were no laboratory data beyond Month 6.) The subject's ALT values were elevated at screening and throughout treatment, ranging from 87 to 202 U/L. GGT values were elevated at Month 3 (50 U/L) and Month 6 (66 U/L, normal 10-49 U/L). Lactate dehydrogenase was elevated at Screening (310 U/L), Month 3 (320 U/L), and Month 6 (334 U/L, normal 77-296 U/L) because of dyspnoea, somnolence, and weight increase (See Annex 6). At Screening through Month 6, the subject's bicarbonate levels were decreased (20-21 mEq/L) and monocyte counts were increased (11-14%). Laboratory abnormalities that appeared at Screening and/or at one or more visits during the trial included decreased urea, neutrophil count, and lymphocyte count, and increased eosinophil count.

Subject A03963, an 11-year-old Caucasian boy, had ALT and AST values within normal laboratory limits (ie, 39 and 42 U/L for ALT and AST, respectively) at the double-blind baseline and screening. At Week 4, ALT and AST were 231 and 157 U/L, which were above the pathological limit (78 U/L for both). When determined 1 week later, ALT and AST remained elevated at 291 and 170 U/L, respectively. Transaminases had returned to normal at Month 3 (21 and 28 U/L, respectively) and remained normal at Month 6 (15 and 24 U/L, respectively). Lactate dehydrogenase was elevated at Week 4 (368 U/L) and remained elevated 1 week later (376 U/L), but were normal at Month 3 (242 U/L) and Month 6 (229 U/L). These abnormalities were reported as an adverse event; their relationship to treatment with the study medication was considered doubtful. Additional events also considered to have no relationship or doubtful relationship to treatment were coughing, injury, and pharyngitis. Other laboratory abnormalities included elevated growth hormone and prolactin levels at Months 3 and 6, decreased haemoglobin at Weeks 4 through Month 6 (12.1-13 g/dL), decreased RBC at Screening through Month 6 (3.8-4.1 x 10^6/mm^3), and decreased neutrophil counts at Week 4 through Month 6 (26-44%). Laboratory abnormalities that appeared sporadically included increased bicarbonate, decreased bicarbonate, and increased lymphocyte count.

4.5.3.4. Prolactin levels

Descriptive statistics and distribution of changes from the open label screening at the different time points are presented by sex in Display SAF.LAB.3B. Shift tables are shown in Display SAF.LAB.5B. The data at

endpoint and at Month 12 are summarized in Table 4-22. A graphical display of prolactin levels versus time is shown in Figure 4-3.

Table 4-22: Mean (± SE) prolactin levels (ng/ml) by sex

	Risperidone (n=319)				
		Open label baseline		Re-assessment time	
Time point	N	Mean ± SE	Median	Mean ± SE	Median
Males					
Month 12	112	8.4±0.8	5.3	16.5±1.0	14.7
Endpoint	229	8.3±0.5	5.5	18.2±0.8	16.0
Females					
Month 12	14	8.1±1.5	5.2	33.4±10.5	18.5
Endpoint	42	9.6±1.4	6.3	26.5±4.2	18.7

SE: standard error
Source: Display SAF.LAB.3B

Figure 4-3: Prolactin levels (mean ± SE) versus time
a. Male subjects

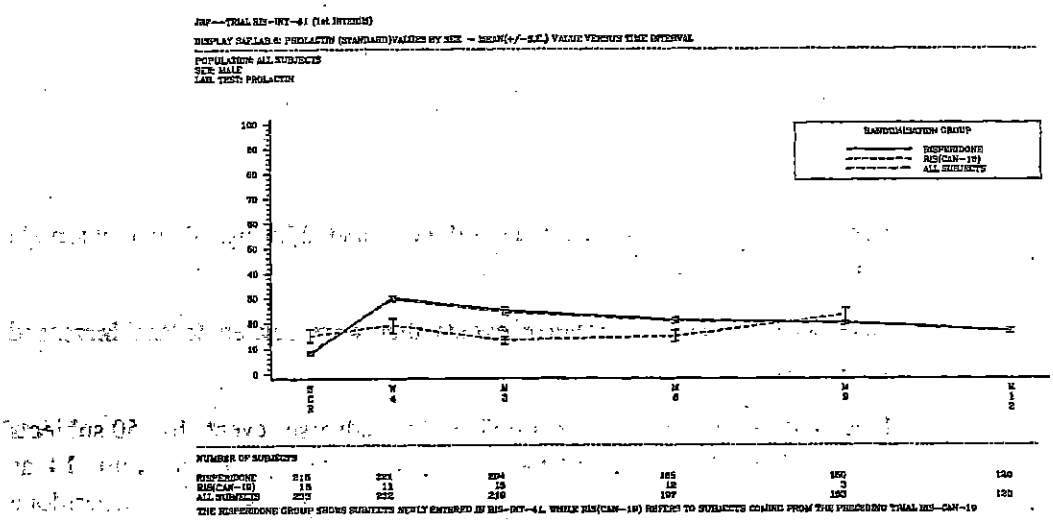
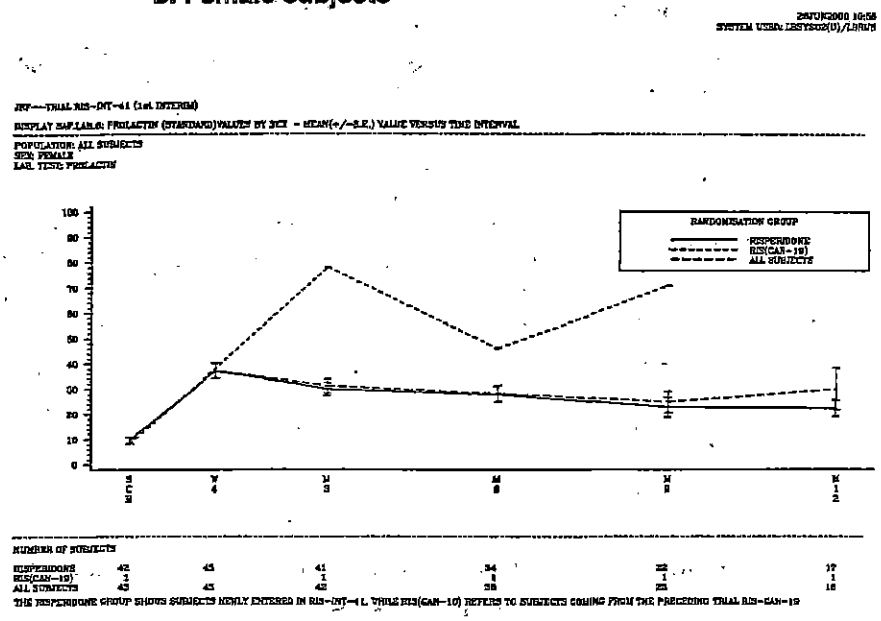


Figure 4-3: Prolactin levels (mean ± SE) versus time
b. Female subjects



There was an increase in mean prolactin levels from screening to Week 4 in both sexes. Mean levels of male subjects increased from 8.3 ng/ml to 29.0 ng/ml, and levels of female subjects increased from 9.3 ng/ml to 37.0 ng/ml. Thereafter, the mean levels decreased, but they were still elevated at endpoint: 18.2 ng/ml in the male subjects, and 27.6 ng/ml in the female subjects.

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

Hyperprolactinaemia was reported as an adverse event by 50 subjects (15.7%). Out of the 57 adverse events, 42 were reported as mild, 14 as moderate, and 1 adverse event was severe. The relationship with risperidone treatment was considered possible (n=6), probable (n=6) or very likely (n=18), and was not assessed in 27 cases. Hyperprolactinaemia was considered a laboratory finding that had no clinical relevance.

In most subjects, hyperprolactinaemia was a laboratory finding that had no clinical symptoms.

In total there were 16 subjects with symptoms that could be related to increased prolactin levels. There were 13 reports of gynaecomastia by 11 subjects. In 7 subjects, gynaecomastia was transient, and the subjects recovered. In 10 cases, the adverse event was mild, and in 3 cases it was

considered moderate. The relationship with risperidone treatment was considered possible (n=5), probable (n=3) or very likely (n=4). One case of local oedema in the left breast was considered unrelated. The dosage was adjusted in 1 subject, and another subject permanently discontinued treatment.

There was 1 case of moderate transient galactorrhoea that was considered doubtful related to treatment with risperidone and resolved without intervention. Other adverse events related to the female reproductive system that were reported by 1 subject each during the trial were mild amenorrhoea (very likely related, recovered after treatment with Normensal®), mild menorrhagia (relationship not assessed; resolved without intervention), mild dysmenorrhoea (not related, subject recovered after treatment with Anacin®) and mild vaginal bleeding (not related, treatment was temporarily discontinued and the subject recovered without treatment).

All subjects with prolactin-related adverse events are identified in Table 4-23.

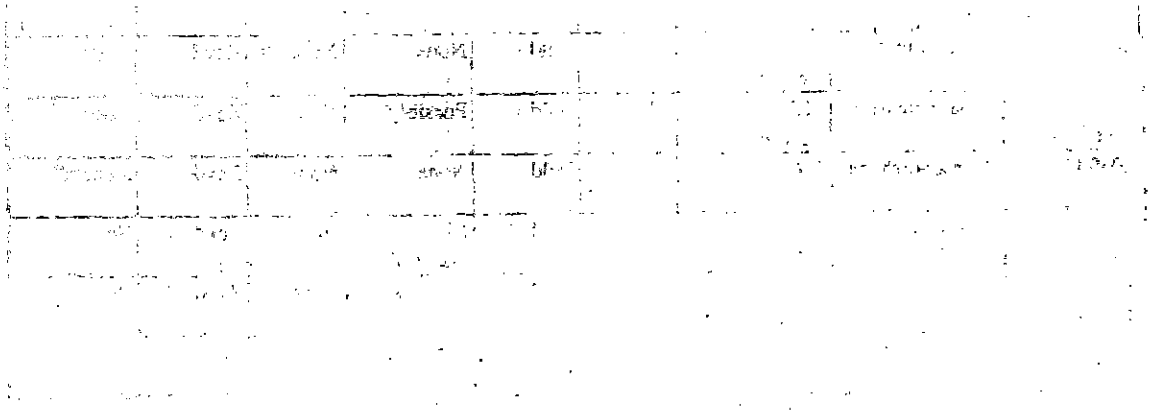


Table 4-23: Subjects with prolactin-related adverse events

Subject 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	Gynaecomastia	207/ 1.2 mg	178	Moderate	Probably	None	Not Rcvd	None
A03374 C/F/8 yr	Gynaecomastia	3/ 0.2 mg	27	Moderate	Very likely	Perm. Stop	Rcvd	None
A03483 C/M/13 yr	Gynaecomastia	260/ 1.4 mg	53	Mild	Possible	None	Rcvd	None
		313/ 1.4 mg	32	Mild	Possible	None	Rcvd	None
A03489 C/M/11 yr	Gynaecomastia	63/ 2.1 mg	105	Mild	Very likely	None	Rcvd	None
A03299 C/M/14 yr	Gynaecomastia	50/ 2.8 mg	>44	Mild	Probably	Dose adjusted	Not Rcvd	None
A03303 C/F/14 yr	Amenorrhoea	18/ 2 mg	254	Mild	Very likely	None	Rcvd	Normensal®
A03344 C/F/13 yr	Nonpuerperal lactation (galactorrhoea)	92/ 3.1 mg	197	Moderate	Doubtful	None	Rcvd	None
A03352 C/M/14 yr	Gynaecomastia	84/ 4 mg	>1	Moderate	Possibly	None	Not Rcvd	None
A03044 C/M/12 yr	Gynaecomastia	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 haemorrhage (bleeding)	144/ 0 mg	4	Mild	None	Temp stop	Rcvd	None
A03190 C/M/7 yr	Gynaecomastia	134/ 1.8 mg	>1	Mild	None	None	Rcvd	None
A03922 B/M/13 yr	Gynaecomastia	113/ 2.5 mg	>1	Mild	Possibly	None	Rcvd	None
A03933 C/F/13 yr	Dysmenorrhoea	33/ 2 mg	1	Mild	None	None	Rcvd	Anacin®
A03237 C/F/12 yr	Menorrhagia	48/ 1.3 mg	13	Mild	Not assessed	None	Rcvd	No
A03703 B/M/9 yr	Gynaecomastia	24/ 2 mg	34	Mild	Very likely	None	Rcvd	No
A03907 C/M/12 yr	Gynaecomastia	76/ 1.5 mg	92	Mild	Probably	None	Rcvd	No

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

4.5.4. OTHER SAFETY OBSERVATIONS

4.5.4.1. 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, systolic and diastolic blood pressure (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 4-24.

Table 4-24: Summary of vital signs: mean (± SE) and mean change (± SE) from open label baseline at Month 12 and at endpoint

	Risperidone (n=319)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Body temperature (degree Celsius)					
Month 12	159	36.3±0.04	-0.08±0.04	(-0.2 ; -0.0)	0.061
Endpoint	299	36.4±0.03	-0.04±0.04	(-0.1 ; -0.0)	0.232
Systolic blood pressure (mmHg)					
Month 12	172	105.8±1.0	3.0±0.9	(1.1 ; 4.8)	0.002
Endpoint	319	105.0±0.7	2.1±0.7	(0.7 ; 3.4)	0.003
Diastolic blood pressure (mmHg)					
Month 12	172	67.9±0.9	2.9±0.9	(1.2 ; 4.7)	0.001
Endpoint	319	67.8±0.6	1.8±0.6	(0.6 ; 3.0)	0.005
Pulse rate (bpm)					
Month 12	172	80.5±0.9	-1.4±1.1	(-3.5 ; 0.7)	0.198
Endpoint	319	81.9±0.6	0.1±0.8	(-1.4 ; 1.7)	0.883
Respiration rate (1/min)					
Month 12	171	20.8±0.3	-0.1±0.4	(-1.0 ; 0.8)	0.827
Endpoint	319	20.9±0.2	-0.2±0.4	(-0.9 ; 0.5)	0.567

SE: standard error
CI: confidence interval
[1] 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 which were not clinically relevant.

Blood pressure and pulse rate were classified as normal or abnormal according to the criteria in Table 3-2. The classification of the shift versus open label baseline is given in Display SAF.VS.2B and is summarized in Table 4-25.

Table 4-25: Classification of vital signs: frequency distribution of shift versus open label baseline at Month 12 and at endpoint

	Risperidone (n=319)			
	Month 12 (n=167)		Endpoint (n=310)	
Vital signs	n	(%)	n	(%)
Systolic blood pressure (mmHg)				
Normal	165	(98.8)	305	(98.4)
Abnormal below	2	(1.2)	5	(1.6)
Diastolic blood pressure (mmHg)				
Normal	163	(97.6)	304	(98.1)
Abnormal below	4	(2.4)	6	(1.9)
Pulse rate (bpm)				
Normal	167	(100.0)	309	(99.7)
Abnormal above	0	(0.0)	1	(0.3)

Source: Display SAF.VS.2B

Only very few subjects had abnormal low (blood pressure) or high (pulse rate) values. Individual values for these subjects can be found in Listing SAF.VS.

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.

4.5.4.2. 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 subjects from the 2 Hungarian centres Szeged and Baja.

Mean changes from the OL baseline in ECG results (axis, heart rate, JT interval, JTCB interval, PR interval, QRS complex, QT interval, and RR interval, as well as QTc intervals using Bazett's formula (QTcB) and Fridericia's formula (QTcF) are presented in Display SAF.ECG.1B and summarized in Table 4-26.

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

Relative to the OL baseline, there were statistically significant mean decreases in axis (-1.97 degrees, p=0.039) and heart rate (-3.7 beats/minute, p<0.001) and statistically significant mean increases in JT interval (+6.17 ms, p<0.001), and QT interval (+6.88 ms, p<0.001). These mean changes had no clinical relevance.

Because of the physiologically higher heart rates in children and the increased heart rate associated with risperidone treatment, Fridericia's correction formula was considered more appropriate for the correction of QTc intervals in this paediatric population than is Bazett's formula.[25] Fridericia's formula (QT/cube root RR) has been demonstrated to be appropriate in other populations as well (adult schizophrenics and elderly demented patients).[26] QTc intervals corrected using the different correction formulas are presented in Display SAF.ECG.1B. No changes from baseline were observed.

Table 4-26: Summary of heart rate and QTcF results at week 12 and endpoint

	Risperidone (n=319)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Heart rate (beats/minute)					
Month 12	145	77.0±1.3	-5.6±1.3	(-8.1;-3.0)	< 0.001
Endpoint	269	79.0±1.0	-3.7±1.0	(-5.7;-1.7)	< 0.001
QTcF interval (ms)					
Month 12	145	387.9±1.5	+2.2±1.5	(-0.8;5.2)	0.151
Endpoint	269	386.6±1.1	+1.7±1.2	(-0.6;4.0)	0.152

SE: standard error
CI: confidence interval
[1]Two-sided p-value for paired T-test on change from open 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[27] 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 intervals is summarized in Table 4-27.

Table 4-27: Distribution of borderline and prolonged QTcF intervals

	Risperidone (N=319)						
		Normal		Borderline		Prolonged	
	N	n	(%)	n	(%)	N	(%)
QTcF							
Screening	297	295	(99.3)	1	(0.3)	1	(0.3)
Month 6	245	243	(99.2)	1	(0.4)	1	(0.4)
Month 12	145	145	(100)	0	(0)	0	(0)
Endpoint	269	268	(99.6)	1	(0.4)	0	(0)

Source: Display SAF.ECG.2

Two subjects had prolonged QTcF: one at screening and one during the trial. One male subject (A03284) had a QTcF interval that was prolonged (500 ms) at screening but not during treatment. One male subject (A03001) had a QTcF interval that was prolonged (490 ms) at Month 6 but normal at screening and at Month 12. No subject 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:

Unlikely to raise concern: <30 ms
Concern about potential risk: 30-60 ms
Clear concern about potential risk: >60 ms

The distribution of increases in QTcF values is summarized in.Table 4-28.

Table 4-28: Distribution of increases from open-label baseline in QTcF values

		Risperidone (N=319)					
		< 30 ms		30-60 ms		> 60 ms	
	N	N	(%)	n	(%)	N	(%)
Month 6	231	207	(89.6)	22	(9.5)	2	(0.9)
Month 12	137	127	(92.7)	10	(7.3)	0	(0)
Endpoint	253	234	(92.5)	19	(7.5)	0	(0)

Source: Display SAF.ECG.4B

At endpoint, 19 subjects (7.5%) had QTcF increases of 30 to 60 ms relative to the OL baseline. Two subjects (0.9%) had increases in QTcF values of >60 ms at Month 6 only.

Subject A03001 an 8-year-old boy, had a QTcF increase of +100 ms to a prolonged value of 490 ms. QTcF for this subject was normal at screening and Month 12 (390 ms). For subject A03217, a 10-year-old girl, QTcF increased from 330 ms at screening to 400 ms (+70 ms increase from screening or an increase of clear concern) at Month 6; at Month 12, QTcF was 390 ms (+60 ms increase, or an increase of concern). Despite these

increases, however, this subject's QTcF remained within the normal range throughout the study.

4.5.4.3. Body weight

Subjects were weighed at baseline and at Visits 7, 9 and 12 and at the end of the trial.

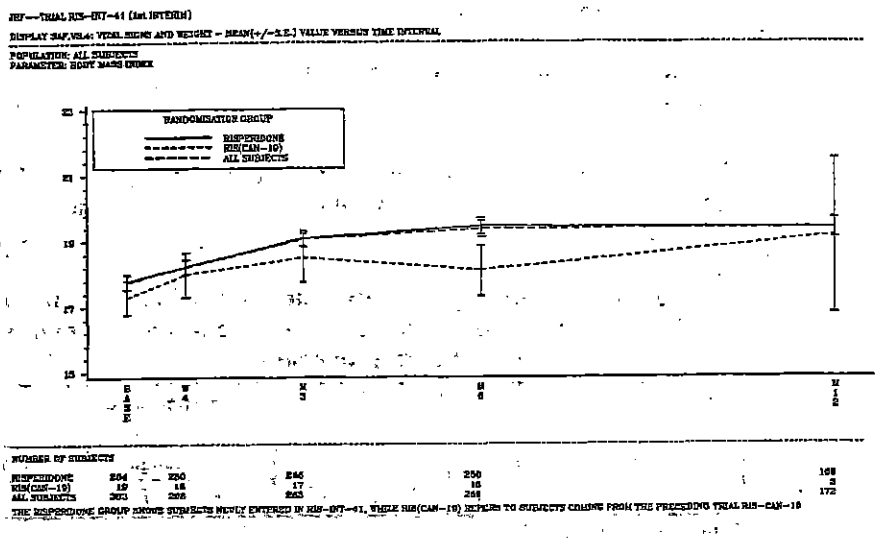
The descriptive statistics for body weight, height and the BMI are given in Display SAF.VS.3B. The data at endpoint and at Month 12 are summarized in Table 4-29. BMI versus time is graphically displayed in Figure 4-4.

Table 4-29: 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=319)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Body weight (kg)					
Month 12	172	42.8±1.1	7.3±0.3	(6.6 ; 8.0)	< 0.001
Endpoint	314	42.1±0.9	6.3±0.3	(5.9 ; 6.8)	< 0.001
Body height (cm)					
Month 12	172	146.7±1.2	7.0±0.2	(6.6 ; 7.5)	< 0.001
Endpoint	314	144.7±0.9	5.2±0.2	(4.8 ; 5.6)	< 0.001
Body mass index (kg/m^2)					
Month 12	172	19.4±0.3	1.7±0.1	(1.5 ; 2.0)	< 0.001
Endpoint	314	19.5±0.2	1.7±0.1	(1.5; 1.9)	< 0.001

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

Figure 4-4: Body Mass Index (mean ± SE) versus time



Body weight increased by an average 6.3 kg (± 0.3) from baseline to endpoint. This increase was statistically significant ($p < 0.001$). Since the subjects were children from 5 to 14 years of age, the effect of risperidone on body weight was confounded by growth. The height of the subjects increased by 5.2 cm (± 0.2) on average from baseline to endpoint. The typical child in the trial was a 10-year-old boy with a baseline weight of 35.99 kg and a height of 140.16 cm. According to the National Centre for Health Statistics (NCHS) percentiles,[28] the 75th percentile weight at age 10 years is 35.61 kg, similar to the average weight in the present study. As the 75th percentile weight at age 11 years is 40.38 kg, the average natural weight gain expected over a 1-year period would be 4.77 kg. This implies that of the 6.3-kg weight gain during the trial, 4.77 kg might be attributed to natural weight gain and 1.53 kg to treatment with risperidone.

The increase in BMI was 1.68 ± 0.1 kg/m^2 at endpoint. This effect was statistically significant ($p<0.001$). The increase in BMI was especially observed during the first 3 months of treatment. The BMI remained stable thereafter. The average BMI at baseline in the present study (17.7 kg/m^2) was close to the 50th percentile for BMI at age 10 years (17.2 kg/m^2).[29] 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 1.68 kg/m^2 increase during the trial, 0.6 kg/m^2 might be attributed to a natural increase and 1.08 kg/m^2 to treatment with risperidone.

Appetite increased was reported 36 times by 32 subjects (10.0%). The adverse event was mild (n=17) or moderate (n=18). One event was considered severe. The relationship with risperidone was judged as possible (n=8), probable (n=14) or very likely (n=10). One adverse event was considered unrelated, and for 3 events the relationship was not assessed.

Weight increase was reported 51 times by 49 subjects (15.4%). The adverse events were mostly mild (n=29) or moderate (n=18). Four subjects reported a severe weight increase. The drug-relationship was mostly assessed as possible (n=5), probable (n=20) or very likely (n=10). For 4 events, the relationship was doubtful, and 2 events were unrelated. The relationship of the remaining 10 events was not assessed.

Moderate obesitas was reported by 2 subjects, and 1 subject reported severe obesitas. The relationship was risperidone treatment was judged as possible, probable or very likely (n=1 each).

Twelve subjects reported appetite increase along with weight increase, and 1 subject reported obesitas together with weight increase. None of these adverse events was reported as serious.

For the adverse events weight increase and/or appetite increase and/or obesitas, the dose was adjusted in 3 subjects. In 4 other subjects, the adverse events led to a permanent discontinuation of the treatment.

4.5.4.4. Extrapyramidal Symptom Rating Scale (ESRS)

The presence and severity of extrapyramidal symptoms 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 time points and the mean and median maximum score are summarized in Table 4-30.

Table 4-30: Total ESRS score: mean (± SE), median (min, max) and mean (± SE) change from open label baseline at the different time points

	Risperidone (n=319)				
				Change from open label baseline	
Time point	N	Mean ± SE	Median (min; max)	Mean ± SE	p-value[1]
Baseline	310	1.2 ± 0.2	0.0 (0.0 ; 35.0)		
Week 1	311	1.0 ± 0.2	0.0 (0.0 ; 25.0)	-0.2 ± 0.1	< 0.001
Week 2	307	1.1 ± 0.2	0.0 (0.0 ; 25.0)	-0.1 ± 0.1	0.434
Week 3	307	0.8 ± 0.1	0.0 (0.0 ; 14.0)	-0.3 ± 0.1	0.014
Week 4	308	0.9 ± 0.1	0.0 (0.0 ; 14.0)	-0.3 ± 0.2	0.029
Month 2	289	0.8 ± 0.1	0.0 (0.0 ; 12.0)	-0.4 ± 0.2	0.031
Month 3	291	0.8 ± 0.1	0.0 (0.0 ; 14.0)	-0.4 ± 0.2	0.008
Month 4	275	0.7 ± 0.1	0.0 (0.0 ; 14.0)	-0.5 ± 0.2	0.001
Month 5	274	0.8 ± 0.1	0.0 (0.0 ; 14.0)	-0.5 ± 0.2	0.008
Month 6	273	0.7 ± 0.1	0.0 (0.0 ; 14.0)	-0.5 ± 0.2	0.013
Month 9	201	0.8 ± 0.1	0.0 (0.0 ; 11.0)	-0.6 ± 0.3	0.017
Month 12	172	0.7 ± 0.1	0.0 (0.0 ; 12.0)	-0.7 ± 0.3	0.003
Endpoint	319	0.7 ± 0.1	0.0 (0.0 ; 12.0)	-0.5 ± 0.2	0.006
Maximum	319	2.2 ± 0.2	1.0 (0.0 ; 25.0)	1.1 ± 0.1	< 0.001

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

The overall level of extrapyramidal symptoms was very low. The median score was always 0.0: the majority of subjects did not show any ESRS scores different from zero at any time point during the trial. The mean score at the open label baseline was 1.2. The mean ESRS score decreased during risperidone treatment and was 0.7 at endpoint. The mean decrease ranged from -0.1 at Week 2 to -0.7 at Month 12. The mean decrease at endpoint was -0.5. The decrease was statistically significant at all time points except at Week 2.

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 2.2, which was statistically significantly higher than the score at baseline.

4.5.4.5. 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 4-31.

Table 4-31: Frequency distribution of the change in subjects' Tanner staging condition at Month 12 and at endpoint

	Risperidone (n=319)					
	Open label baseline (n=310)		Month 12 (n=171)		Endpoint (n=292)	
Tanner staging	n	(%)	N	(%)	n	(%)
0[a)]	27	(8.7)	13	(7.6)	24	(8.2)
1	186	(60.0)	78	(45.6)	148	(50.7)
2	52	(16.8)	32	(18.7)	46	(15.8)
3	22	(7.1)	23	(13.5)	33	(11.3)
4	18	(5.8)	18	(10.5)	30	(10.3)
5	5	(1.6)	7	(4.1)	11	(3.8)

a) The Tanner staging scale does not contain a '0' rating. It is highly likely that investigators erroneously coded '0' instead of a rating of '1'. A review of individual subjects with a rating of '0' at any time indicates that subjects with a rating of '0' were young, ie, <10 years of age.

Source: Display SAF.TAN.1

Sexual maturation progressed during the trial. At entry, there were 213 (68.7%) children with a Tanner score of 0 or 1. At endpoint, the number decreased to 172 (58.9%), while the number of subjects in a higher Tanner stage increased.

The subjects grew during the trial. Mean height at endpoint had increased by 5.2 ± 0.2 cm, from 140.3 ± 0.96 cm at the open-label baseline to 145.2 ± 0.94 cm at endpoint ($p<0.001$). A growth rate of 5.3 cm/year might be expected in children of the same age (according to NCHS percentiles[28]).

4.5.4.6. Changes in cognitive function

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

4.5.4.6.1. 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 4-32.

Table 4-32: Modified verbal learning test: mean (± SE) and mean (± SE) change from open label baseline at Month 12 and at endpoint

Cognitive test	Risperidone (n=319)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Modified verbal learning test					
Total long delay free recall					
Month 12	166	6.6±0.2	0.9±0.2	(0.5 ; 1.2)	< 0.001
Endpoint	285	6.5±0.1	0.6±0.1	(0.4 ; 0.9)	< 0.001
Total short delay free recall					
Month 12	166	31.4±0.7	2.2±0.7	(0.8 ; 3.6)	0.002
Endpoint	285	31.6±0.5	2.1±0.5	(1.1 ; 3.1)	< 0.001
Total correct					
Month 12	166	17.5±0.3	1.0±0.3	(0.3 ; 1.6)	0.005
Endpoint	285	17.5±0.3	0.6±0.3	(0.1 ; 1.1)	0.014

SE: standard error
CI: confidence interval
[1] 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 time points (all $p < 0.001$). The effect for the short delay free recall test was statistically significant at endpoint and at Month 12, but not at Month 6 ($p = 0.202$).

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 endpoint and at Month 12, and borderline significant at Month 6 ($p = 0.05$).

4.5.4.6.2. Continuous performance task

The results of the continuous performance task are shown in Display EFF.CT.2B, and are summarized in Table 4-33. Only the total scores are summarized, the scores for the first and second half can be found in Display EFF.CT.2B.

Table 4-33: Continuous performance task: mean (± SE) and mean (± SE) change from open label baseline at Month 12 and at endpoint

Cognitive test	Risperidone (n=319)				
			Change from open label baseline		
	N	Mean ± SE	Mean ± SE	95% CI	p-value[1]
Continuous performance test, easy					
Total hits					
Month 12	155	35.8±0.6	2.0±0.6	(0.8 ; 3.2)	0.002
Endpoint	271	36.2±0.4	1.8±0.4	(1.0 ; 2.6)	< 0.001
Total false alarm					
Month 12	154	6.0±1.0	-1.9±1.2	(-4.2 ; 0.3)	0.096
Endpoint	271	6.0±0.7	-2.3±0.8	(-3.9 ; -0.8)	0.003
Total misses					
Month 12	155	4.2±0.6	-1.8±0.6	(-3.0 ; -0.6)	0.004
Endpoint	271	3.8±0.4	-1.6±0.4	(-2.4 ; -0.8)	< 0.001
Continuous performance test, hard					
Total hits					
Month 12	133	36.4±0.5	2.2±0.7	(0.8 ; 3.6)	0.002
Endpoint	248	35.8±0.4	1.9±0.5	(1.0 ; 2.9)	< 0.001
Total false alarm					
Month 12	133	19.5±8.9	-2.6±1.1	(-4.8 ; -0.4)	0.023
Endpoint	248	14.1±4.8	-3.3±0.9	(-5.1 ; -1.6)	< 0.001
Total misses					
Month 12	132	4.3±0.9	-1.7±0.9	(-3.5 ; 0.2)	0.073
Endpoint	248	4.5±0.6	-1.7±0.6	(-2.8 ; -0.5)	0.004

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

There was a statistically significant increase in the total number of hits from baseline to the end of the trial, and a statistically significant decrease in the total number of false alarms and misses, both in the easy and in the hard version of the task.

The mean reaction times for hits and false alarms decreased (range –23.0 to -99.8 ms), but the effect was not always statistically significant.

4.5.5. SAFETY CONCLUSIONS

The results from the safety analysis show that long term treatment with 0.02 - 0.06 mg/kg/day risperidone (mean treatment duration 261.0 ± 7.2 days) was safe and well tolerated.

The most commonly reported adverse events were somnolence (28.2% of all subjects), rhinitis (24.5%), headache (17.2%) and pharyngitis (17.2%). The majority of all adverse events was mild. EPS-like adverse events were reported by 22.3% of all subjects. The overall EPS-level was low. The

majority of subjects did not show any ESRS scores different from zero at any time point during the trial.

Mean prolactin levels increased from screening to Week 4. Thereafter, the mean levels decreased, but they were still elevated at endpoint. Females attained higher levels than males. Increased prolactin levels led to clinical manifestations in 16 subjects (5.0%). There were no serious adverse events that were related to the increased prolactin levels.

An increase in body weight was especially observed during the first 3 months of treatment. According to the NCHS percentiles,[2828] 4.77 kg (76% of the weight gain) might be attributed to natural weight gain and 1.53 kg (24% of the weight gain) to treatment with risperidone. The increase in BMI was 1.68 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 adverse event during treatment by 49 subjects (15.4%). Appetite increase was reported by 32 subjects (10.0%).

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.

5. SUMMARY AND DISCUSSION

Conduct and other disruptive behaviour 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 Behaviour Disorder not otherwise specified, has varied from 20% to 64%. Factors that predispose individuals to greater severity and poorer outcome include comorbid conditions, amongst which ADHD and reduced intelligence.

There have been many different approaches to the treatment of conduct and other disruptive behaviour disorders, including drug therapy, behavioural 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. 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 (RIS-USA-93).

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

An interim analysis was carried out in order to provide the regulatory authorities with long term safety and efficacy data in a sufficient number of young subjects. All subjects that entered the study before 31 July 1999 were included in the interim analysis.

Out of the 319 subjects that entered the trial before 31 July 1999, 19 subjects had previously participated in study RIS-CAN-19 and 300 subjects newly entered the trial. Sixty subjects (18.8%) dropped out before trial completion.

The overall mean mode daily dosage was 1.64 ± 0.04 mg/day or 0.021 ± 0.001 mg/kg/day, and the mean treatment duration was 261.0 ± 7.2 days (range 1-498 days). Out of the 319 subjects, 230 subjects were treated for 6 months or more, and 181 of these 230 subjects were treated for 12 months or more.

The overall plasma concentrations of risperidone, the active moiety and 9-hydroxy-risperidone remained fairly constant over the entire trial period. The mean plasma levels of active moiety (dose-normalized to 0.04 mg/kg/day) were 11.8 ng/ml at visit 7, 13.5 ng/ml at visit 12 and 12.4 ng/ml at endpoint.

The primary efficacy parameter was the change in behaviour from open label baseline to endpoint as measured on the Conduct Problem subscale of the N-CBRF. The mean score dropped from 32.7 ($\pm$ 0.4) at baseline to 17.0 ($\pm$ 0.6) at endpoint. The improvement was especially observed during the first 4 weeks of treatment. Scores remained stable thereafter. The mean change at endpoint was -15.6 ($p < 0.001$).

A subgroup analyses for the primary efficacy parameter revealed no differences between subjects with conduct disorder, with oppositional defiant disorder and with disruptive behaviour disorder not otherwise specified. There were also no differences between subjects with different levels of intellectual functioning (mild mental retardation, moderate mental retardation or subjects with borderline intellectual functioning).

The results from the secondary efficacy analysis showed a similar profile as for the primary efficacy parameter. A statistically significant improvement at endpoint was observed on all subscales of the N-CBRF (compliant/ calm +3.2 $\pm$ 0.2; adaptive/ social +2.0 $\pm$ 0.2; insecure/ anxious -5.4 $\pm$ 0.5; hyperactive -7.0 $\pm$ 0.4; self-injury/ stereotyped -1.1 $\pm$ 0.2; self-isolated/ ritualistic -1.6 $\pm$ 0.2; overly sensitive -2.1 $\pm$ 0.2), on the total score of the

Aberrant Behaviour Checklist (-28.2 ± 1.8) and on the Visual Analogue Scale of the most troublesome symptom (-40.5 ± 1.6). The improvements were especially observed during the first 4 weeks of treatment. Scores remained stable thereafter. The ratings of the investigators' Clinical Global Impression showed 16 (5.1%) subjects with severe or extremely severe symptoms at endpoint compared to 110 (36.1%) at baseline.

Risperidone was well tolerated. There were 11 subjects (3.4%) who reported drug-related serious adverse events. The discontinuation rate for adverse events was 6.9% (22 subjects). The most commonly reported adverse events were somnolence (28.2%), rhinitis (24.5%), headache (17.2%), pharyngitis (16.3%), hyperprolactinaemia (15.7%) and weight increase (15.0%). The majority of all adverse events was mild.

EPS-like adverse events were reported by 71 subjects (22.3%). The majority of these events was mild. The overall EPS-level was low. The majority of subjects did not show any ESRS scores different from zero at any time point during the trial. Only 5 subjects 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.[30] There were 2 subjects with reversible tardive dyskinesia (0.6%) in this trial. These results suggest that risperidone has a better safety profile with respect to tardive dyskinesia compared to 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, although the levels never returned to baseline levels during the one-year treatment period. Females attained higher levels than males. The incidence of clinical manifestations in the present trial was low. There were 16 subjects (5.0%) 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 haematology, biochemistry or urinalysis were detected.

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

Body weight increased by an average 6.3 kg (± 0.3) 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 subjects were children and the effect on weight was confounded by growth. According to NCHS percentiles,[2828] 4.77 kg (76% of the weight gain) might be attributed to natural weight gain and 1.53 kg (24% of the weight gain) to treatment with risperidone. The increase in BMI was 1.68 kg/m^2 at endpoint. According to the NCHS percentiles,[29] 0.6 kg/m^2 might be attributed to natural weight gain and 1.08 kg/m^2 to 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 subjects had grown by 5.2 ± 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 tasks showed a small, but statistically significant improvement at endpoint. There is clearly no evidence indicating that risperidone has negative effects on cognitive function.

6. OVERALL CONCLUSIONS

The interim results from this one-year, multicentre, open trial demonstrate that risperidone was effective in the treatment of conduct and other disruptive behaviour disorders in children 5 to 14 years of age with borderline intellectual functioning or mild to moderate mental retardation.

Apart from increases in body weight and prolactin levels, a review of all adverse events, extrapyramidal symptoms, laboratory parameters, vital signs and body weight shows that long-term treatment with risperidone was safe and well tolerated.

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