Janssen Research & Development

Clinical Study Report Synopsis
RIS-CAN-19

R064766 (risperidone)

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- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product:** Risperdal® **Active ingredient**: risperidone (R064766)		
Title: The safety and efficacy of risperidone versus placebo in conduct disorder in mild, moderate and borderline mentally retarded children aged 5 to 12 years	**Trial No.:** RIS-CAN-19 **Clinical phase:** III	
Principal Investigator: Multicentre	**Country:** Canada, USA, South Africa	
Reference: JRF, Clinical Research Report RIS-CAN-19, November 2, 2000 (EDMS: USTI-2322718)		
Trial period: Start: 18 September 1997 End: 01 July 1999	**No. of investigators:** 16 **No. of subjects entered:** 133 **No. of subjects randomized and treated**: 110	

Indication / objectives: Conduct and other disruptive behaviour disorders in children 5 to 12 years of age (inclusive) with borderline intellectual functioning or mild to moderate mental retardation, in whom destructive behaviours (eg, aggression, impulsivity, stereotyped and self-injurious behaviours) are prominent. The primary objective was to assess the efficacy and safety of 0.02 to 0.06 mg/kg/day of oral risperidone versus placebo.

Trial design: double-blind, placebo-controlled, randomized, parallel-group, multicentre, outpatient trial

Subject selection: The following is a summary of the main inclusion and exclusion criteria

- Inclusion criteria:
  - 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 on the N-CBRF Conduct Problem Subscale (Parent version). Subjects also having Attention Deficit/Hyperactivity Disorder (314.xx, 314.9) were eligible.
  - DSM-IV, Axis II diagnosis of Mild Mental Retardation (317), Moderate Mental Retardation (318.0) or Borderline Intellectual Functioning (V62.89). These diagnoses represent intelligence quotients (IQs) ranging from ≤84 to ≥35.
  - Vineland Adaptive Behaviour Scale ≤84
- Exclusion criteria:
  - DSM-IV diagnosis of Pervasive Development Disorder (299.00, 299.80, 299.10)
  - DSM-IV diagnosis of Schizophrenia and/or Other Psychotic Disorders (295.xx, 297.xx, 298.8, 293.xx)
  - Head injury as a cause of mental impairment
  - Seizure disorder currently requiring medication
  - Serious or progressive illness
  - History of tardive dyskinesia, neuroleptic malignant syndrome or known hypersensitivity to neuroleptics
  - Female subjects of childbearing potential engaging in sexual activity who were not using a validated birth control method

Treatment		
Form – dosing route	Matching solutions – oral	
Medication	Placebo	Risperidone
Lot number	97A24/F71	94D26/164
Dosage	0.02 to 0.06 mg/kg/day, once daily in the morning	
Duration of treatment	1-week placebo run-in; 6 weeks double-blind medication	
Duration of trial	7 weeks	
Disallowed medication	Other antipsychotics, antidepressants, lithium, carbamazepine, valproic acid, cholinesterase inhibitors, clonidine, guanfacine, all anticonvulsants.	

Trial identification and protocol summary (continued)

Assessments	Screening	Placebo run-in	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Day	–10 to –7	–7 to 0	0	7	14	21	28	35	42
Visit	1	2	3	4	5	6	7	8	9
Weight	X		X		X		X		X
Drug concentration plasma trough									X
Efficacy									
• Primary variable									
- Nisonger Child Behaviour Rating Form (N-CBRF)	X		X	X	X	X	X	X	X
• Secondary variables									
- Aberrant Behaviour Checklist (ABC)	X		X	X	X	X	X	X	X
- Behavioural Problems Inventory (BPI)	X		X	X	X	X	X	X	X
- Clinical Global Impression (CGI[1])			X	X	X	X	X	X	X
- Visual Analogue Scale (VAS) sedation			X	X	X	X	X	X	X
- VAS[2]			X	X	X	X	X	X	X
Safety									
• Adverse events			X	X	X	X	X	X	X
• Extrapyramidal Symptom Rating Scale (ESRS)			X	X	X	X	X	X	X
• Concomitant therapy			X	X	X	X	X	X	X
• Clinical laboratory	X								X[3]
• Electrocardiogram (ECG)	X								X
• Vital Signs	X		X	X	X		X		X
• Cognitive tests			X						X

[1]overall severity at baseline (BL) and change from BL thereafter
[2]VAS of the most troublesome symptom
[3]prolactin and growth hormone samples to be taken at trial medication trough

Statistical methods	Descriptive statistics were performed for the demographic data and baseline characteristics. The comparability of the demographic and baseline data was assessed. For continuous and ordinal data (age, height, IQ, Vineland adaptive behaviour scale, etc), the 2-way analysis of variance with factors for treatment, investigator and stratum (Conduct Disorder versus Oppositional Defiant Disorder or Disruptive Behaviour Disorder not otherwise specified) were applied. The Van Elteren test controlling for investigator and stratum was to be applied if the data were not normal. For nominal categorical data (sex, race, etc), the Cochran-Mantel-Haenszel test for general association controlling for investigator and stratum, were performed.

Main features of the subject sample and summary of the results

Baseline characteristics – subject disposition	Placebo N=57	Risperidone N=53
Number of subjects randomized (M/F)	42/15	41/12
Age: median, min-max (years)	9 (5-12)	9 (5-12)
Dropouts – reason*		
• Adverse event	0 (0)	0 (0)
• Insufficient response	19 (33.3%)	2 (3.8%)
• Lost to follow-up	0 (0)	1 (1.9%)
• Noncompliant	0 (0)	0 (0)
• Withdrew consent	0 (0)	0 (0)
• Other	0 (0)	3 (5.7%)

*****not including subjects who stopped treatment but continued having trial assessments

Drug concentrations

- The average (mean ± SE) treatment duration of the double-blind period in the placebo group was 36.2 ± 1.35 days (range 12-54 days), and in the risperidone group 39.8 ± 1.02 days (range 13-50 days).
- The mean daily dose of risperidone was 0.98 ± 0.06 mg or 0.033 ± 0.001 mg/kg.
- Plasma concentrations (ng/mL) of the active moiety (=sum of risperidone and 9-hydroxy-risperidone), risperidone and 9-hydroxy-risperidone at the last visit (dose-normalized to 0.04 mg/kg/day) for samples taken from 15 to 41 hours post-dose:

	N	Median (min-max)	Mean ± SD
Active moiety	35	6.26 (0.87-41.8)	9.77 ± 8.62
Risperidone	35	0.27 (NQ-29.3)	2.99 ± 6.75
9-hydroxy-risperidone	35	5.02 (NQ-17.7)	6.83 ± 4.57

SD: standard deviation
NQ: <0.20 ng/mL for active moiety and <0.10 ng/mL for risperidone.

Efficacy	Placebo		Risperidone	
	Mean BL score	Mean ± SE change from BL at endpoint[1]	Mean BL score	Mean ± SE change from BL at endpoint[1]
Primary variable: Conduct problem subscale of N-CBRF[2]	32.6 ± 0.83	-6.8 ± 1.49	33.4 ± 0.86	-15.9 ± 1.48***
Secondary variables: N-CBRF subscales[2]				
Compliant/calm	4.9 ± 0.39	0.8 ± 0.49	5.3 ± 0.45	2.3 ± 0.64*
Adaptive/social	3.9 ± 0.26	0.3 ± 0.35	4.3 ± 0.30	1.6 ± 0.41**
Insecure/anxious	15.9 ± 1.07	-2.9 ± 0.91	19.4 ± 1.09	-9.6 ± 1.05***
Hyperactive	17.2 ± 0.68	-3.7 ± 0.83	19.6 ± 0.74	-7.9 ± 0.93**
Self-injury/stereotyped	2.0 ± 0.40	-0.6 ± 0.39	2.7 ± 0.50	-2.0 ± 0.47*
Self-isolated/ritualistic	5.5 ± 0.54	-1.7 ± 0.51	6.7 ± 0.54	-4.1 ± 0.55**
Overly sensitive	7.6 ± 0.39	-2.3 ± 0.53	8.8 ± 0.50	-3.4 ± 0.51
ABC total score[2]	65.3 ± 3.12	-13.0 ± 3.41	77.4 ± 3.93*	-38.6 ± 4.00***
BPI total score[2]	24.8 ± 2.18	-5.0 ± 1.70	25.5 ± 2.62	-12.0 ± 2.14**
VAS most troublesome symptom	77.7 ± 2.51	-13.2 ± 3.73	79.6 ± 2.97	-29.8 ± 5.07*

Main features of the subject sample and summary of the results (continued)

CGI-C: At endpoint, 6 subjects (10.5%) in the placebo group had a CGI-C rating of very much improved or much improved, while 18 subjects (34.0%) in the risperidone group had that rating (p=0.003). A statistically significant difference between the groups in the CGI-C rating, showing greater improvement for the risperidone group, was seen as early as week 2 (p=0.003); differences continued to be statistically significant throughout the study (p<0.001 at endpoint).
Subgroup and additional analyses: Analyses of the primary efficacy parameter, the Conduct Problem Subscale of the N-CBRF, demonstrated no significant effect of age or IQ (mild-to-moderate mental retardation versus borderline intellectual functioning) on efficacy. Analyses of the primary efficacy parameter as well as of N-CBRF subscales, total ABC and subscales, total BPI and subscales, and VAS of the most troublesome symptom as assessed by the parent or caregiver, indicated that efficacy was unaffected by psychoanaleptic medications. Significant (p<0.001) improvement in the Conduct Problem subscale of the N-CBRF and other N-CBRF subscales was observed in subgroup analyses of subjects who did not have somnolence, indicating that efficacy was not a result of somnolence.

Asterisks refer to differences with placebo using an analysis of covariance (ANCOVA) model on change from baseline (factors: treatment, country, baseline score). Levels of significance: *p≤0.05; **p≤0.01, ***p≤0.001.
M/F: males/females
min-max: minimum-maximum
SE: standard error
[1]Endpoint defined as the last observation (excluding the BL value).
[2]Nonimputed results

Safety: adverse events (double-blind phase) (N = number of subjects with data)	Placebo N=57	Risperidone N=53
Most frequently reported AEs (≥10% in any group)		
• Somnolence	8 (14.0%)	22 (41.5%)
• Headache	4 (7.0%)	9 (17.0%)
• Appetite increased	2 (3.5%)	8 (15.1%)
• Dyspepsia	4 (7.0%)	8 (15.1%)
• Rhinitis	5 (8.8%)	7 (13.2%)
• Urinary incontinence	3 (5.3%)	7 (13.2%)
• Coughing	3 (5.3%)	6 (11.3%)
• Hyperprolactinaemia	0 (0)	6 (11.3%)
• Saliva increased	1 (1.8%)	6 (11.3%)
• Vomiting	4 (7.0%)	6 (11.3%)
• Upper respiratory tract infection	10 (17.5%)	5 (9.4%)
No. (%) with one or more AE	42 (73.7%)	46 (86.8%)
No. (%) of deaths	0 (0)	0 (0)
No. (%) with one or more other serious AE	1 (1.8%)	0 (0)
No. (%) treatment stopped due to AE	0 (0)	0 (0)

Laboratory safety	There were no clinically relevant changes in mean laboratory values from baseline to endpoint between the 2 treatment groups. There were 10 subjects (18%) in the placebo group and 11 subjects (22%) in the risperidone group with "code 4" important laboratory abnormalities, ie, nonpathological laboratory values before treatment but pathological values at the end of treatment. The tests involved included alanine transaminase (ALT, n=1), bicarbonate (n=9), haematocrit (n=9), and platelet count (n=2). There were no differences between risperidone and placebo. An expected increase in the mean prolactin level was observed in risperidone-treated subjects. One subject in the placebo group reported dysmenorrhoea. There were no prolactin-related adverse events in the risperidone group.

Main features of the subject sample and summary of the results (continued)

Other safety observations	
Vital signs	There were no clinically relevant differences between groups in the mean change in vital signs from baseline to endpoint, although a statistically significant (p=0.023) difference from baseline in mean pulse rate was noted. Pulse rate for the risperidone group increased an average of 6.2 beats/minute at endpoint, while that for the placebo group remained essentially unchanged.
Weight	There were significant (p<0.001) differences between the groups at increases from baseline to endpoint in mean weight and body mass index. Mean body weight increased by 0.2 ± 0.23 kg in placebo-treated subjects and by 2.22 ± 0.18 kg in risperidone-treated subjects. The mean increase in body mass index from baseline to endpoint was 0.1 in the placebo group and 1.2 in the risperidone group (p<0.001). Weight gain was reported as an adverse event by no subject in the placebo group and by 4 subjects (7.5%) in the risperidone group.
ECG	There were no clinically relevant differences between the treatment groups from baseline to endpoint for ECG interval measurements. However, there was a statistically significant (p=0.043) difference between the groups in QT interval at week 6, a result of an increase of 14.5 ms from baseline for the placebo group and a decrease of 3.7 ms from baseline for the risperidone group. There were no subjects with pathological QTc increases (>500 ms) when corrected by Bazett's (QTcB) or Fridericia's (QTcF) formulas. Two of 39 male subjects (5.1%) in the placebo group, 1 of 38 male subjects (2.6%) in the risperidone group, and 1 of 12 female subjects (8.3%) in the risperidone group had QTcB interval prolongation (451-500 ms) at endpoint. No subject in either group had QTcF interval increases that were prolonged. Three subjects in the placebo group (5.8%) and 7 subjects in the risperidone group (14.9%) had a QTcB increase from baseline of 30 to <60 ms. One subject in the placebo group (1.9%) and 1 subject in the risperidone group (2.1%) had a QTcB increase ≥60 ms. Two subjects in the placebo group (3.8%) and 3 subjects in the risperidone group (6.4%) had QTcF increases of 30 to <60 ms. One subject in the placebo group (1.9%) and 1 subject in the risperidone group (2.1%) had a QTcF increase ≥ 60 ms.

ESRS	Score at baseline		Change from baseline at endpoint		
	Placebo	Risperidone	Placebo	Risperidone	p-value
Total ESRS					
Mean ± SE	0.4 ± 0.12	0.4 ± 0.17	0.2 ± 0.24	0.1 ± 0.17	
Median (min-max)	0.0 (0-4)	0.0 (0-8)	0.0 (-4-8)	0.0 (-5-6)	0.844
Bucco-linguo-masticatory factor					
Mean ± SE	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	
Median (min-max)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	--
Parkinsonism/dystonia total score					
Mean ± SE	0.3 ± 0.11	0.4 ± 0.16	0.1 ± 0.20	0.1 ± 0.16	
Median (min-max)	0.0 (0-4)	0.0 (0-7)	0.0 (-4-8)	0.0 (-4-6)	0.831
Parkinsonism total score					
Mean ± SE	0.3 ± 0.11	0.4 ± 0.16	0.1 ± 0.20	0.1 ± 0.16	
Median (min-max)	0.0 (0-4)	0.0 (0-7)	0.0 (-4-8)	0.0 (-4-6)	0.831

Main features of the subject sample and summary of the results (continued)

Non-parametric analysis (Van Elteren test controlling for investigator, stratum) showed no statistically significant differences between the placebo and risperidone groups in the change from baseline at endpoint in ESRS symptoms. There were no statistically significant differences between the risperidone group and the placebo group in ESRS scores as rated on the CGI. Three subjects in the placebo group (5.3%) and 7 subjects (13.2%) in the risperidone group had extrapyramidal symptoms reported as an adverse event during the double-blind treatment period.	
VAS of sedation	The baseline of the VAS of sedation was low (indicating less sedation), PLA 8.5 mm, RIS 7.8 mm. A significant (p=0.001) difference in change from baseline to endpoint in VAS was observed between the placebo (-2.9 ± 2.07) and the risperidone groups (+8.0 ± 3.10).
Cognitive tests	Apart from a significant difference between the placebo and risperidone groups noted in one parameter of the CPT, there were no differences between the groups in the results of the cognitive tests, including the CPT and the California Verbal Learning Test-Children's version. The absence of a difference between the groups indicates that risperidone has no negative effect on cognitive function.

Asterisks refer to differences with placebo. Levels of significance: * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

Conclusions: Overall, the results of the present trial demonstrate that risperidone at dosages of 0.02 to 0.06 mg/kg/day orally is safe and effective in the treatment of conduct and other disruptive behaviour disorders in children 5 to 12 years old with borderline intellectual functioning or mild to moderate mental retardation.

- Risperidone is statistically superior to placebo in reducing the behavioural disturbances of conduct and other disruptive behaviour disorders in children with borderline intellectual functioning or mental retardation.
- Risperidone is well tolerated, and its safety profile is generally similar to that of placebo. Somnolence was the most frequent adverse event for the risperidone group in this study, but it was generally mild to moderate in intensity. The EPS profile for risperidone was comparable to that for placebo.
- An increase in prolactin levels was observed in both male and female subjects. Apart from dysmenorrhoea in one subject in the placebo group, there were no clinical manifestations of this increase. There were no other differences between the groups in laboratory parameters.
- Apart from a 2.2-kg increase in body weight and an increase of 1.2 in body mass index, there were no significant changes in vital signs or ECG data.

Overall, results of this trial show that, in this population, risperidone is safe and effective at 0.02-0.06 mg/kg/day (mean dosage 0.033 mg/kg/day).