Janssen Research & Development

Clinical Study Report Synopsis
RIS-USA-93

R064766 (risperidone)

Redaction and Removal of Information in This Document

- 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-USA-93 **Clinical phase**: III	
Principal Investigator: Multicentre	**Country**: USA	
Reference: JRF, Clinical Research Report RIS-USA-93 November 2, 2000 EDMS-USTI-2331953		
Trial period: Start: 20 May 1997 End: 06 October 1998	**No. of investigators**: 11 **No. of subjects entered**: 119 **No. of subjects randomized**: 119	

Indication / objectives: Conduct and other disruptive behaviour disorders in children 5 to 12 years of age 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 (for complete details see Section 3.2)

- 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

Treatment						
Form – dosing route	Matching solutions – oral					
Medication	Placebo			Risperidone 0.02-0.06 mg/kg/day		
Batch numbers	95C13/F71	97A29/F71	96J01/F71	95C10/300	96I24/321	97F25/919
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, and 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
- Behaviour 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 (GH) 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 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=63	Risperidone N=56
Number of subjects randomized (M/F)	50/13	47/9
Age: median, min-max, (years)	8 (5-12)	9 (5-12)
Dropouts – reason*	19 (30.2%)	12 (21.8%)
• Adverse event	0 (0)	2 (3.6%)
• Insufficient response	15 (23.8%)	4 (7.3%)
• Lost to follow-up	3 (4.8%)	1 (1.8%)
• Non-compliant	0 (0)	3 (5.5%)
• Withdrew consent	1 (1.6%)	1 (1.8%)
• Other	0 (0)	1 (1.8%)

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

Drug concentrations

- The average treatment duration of the double-blind period in the placebo group was 35.6 ± 1.29 days (range 11-62 days), and in the risperidone group was 36.1 ± 1.69 days (range 1-49 days).
- The mean daily dose of risperidone was 1.16 ± 0.08 mg or 0.034 ± 0.002 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-normalised to 0.04 mg/kg/day) for samples taken from 20 to 27 hours post-dose:

	N	Mean ± SD	Median (min-max)
Active moiety	21	8.17 ± 7.32	5.58 (NQ – 26.8)
Risperidone	21	2.38 ± 4.32	0.24 (NQ – 15.7)
9-hydroxy-risperidone	21	5.78 ± 5.03	4.83 (NQ – 19.4)

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

SD: Standard deviation

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

Efficacy	Placebo		Risperidone	
	Mean baseline score	Mean ± SE change from BL at endpoint[1]	Mean baseline score	Mean ± SE change from BL at endpoint[1]
Primary variable:				
• Conduct problem subscale of N-CBRF[2]	34.5 ± 0.88	-6.2 ± 1.41	32.9 ± 1.08	-15.2 ± 1.48***
Secondary variables:				
• N-CBRF subscales[2]				
Compliant/calm	4.6 ± 0.35	0.7 ± 0.39	4.9 ± 0.37	2.7 ± 0.49***
Adaptive/social	3.6 ± 0.25	0.1 ± 0.27	3.7 ± 0.27	1.6 ± 0.34***
Insecure/anxious	16.9 ± 1.10	-3.0 ± 0.99	18.4 ± 1.19	-8.4 ± 0.92***
Hyperactive	18.7 ± 0.70	-2.7 ± 0.66	19.3 ± 0.73	-6.3 ± 0.77***
Self-injury/stereotyped	3.1 ± 0.55	-1.0 ± 0.43	3.0 ± 0.53	-2.1 ± 0.51*
Self-isolated/ritualistic	5.8 ± 0.62	-1.6 ± 0.45	6.2 ± 0.64	-3.2 ± 0.52*
Overly sensitive	7.7 ± 0.43	-1.2 ± 0.39	8.9 ± 0.43	-3.5 ± 0.57**
• ABC total score[2]	78.0 ± 3.78	-13.1 ± 3.63	78.5 ± 3.53	-32.6 ± 3.82***
• BPI total score[2]	29.4 ± 2.58	-6.3 ± 2.05	32.6 ± 3.07	-12.0 ± 2.35
• VAS most troublesome symptom	82.8 ± 2.20	-16.4 ± 4.04	83.6 ± 2.62	-38.3 ± 4.02***
• Effect of somnolence	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 without somnolence, indicating that somnolence had no effect on the efficacy of RIS.			
• CGI-C	At endpoint, 5 subjects (7.9%) in the placebo group had a CGI-C rating of very much improved or much improved, while 28 subjects (53.9%) in the risperidone group had that rating. 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 1 ($p=0.027$); differences continued to be statistically significant throughout the study ($p<0.001$ from week 2 through endpoint).			

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

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

Safety: adverse events (double-blind phase) (N = number of subjects with data)	Placebo N = 63	Risperidone N = 55
Most frequently reported AEs (≥10% in any group)		
• Somnolence	6 (9.5%)	28 (50.9%)
• Headache	9 (14.3%)	16 (29.1%)
• Vomiting	4 (6.3%)	11 (20.0%)
• Dyspepsia	4 (6.3%)	8 (14.5%)
• Appetite increased	4 (6.3%)	6 (10.9%)
• Weight increased	1 (1.6%)	8 (14.5%)
• Rhinitis	3 (4.8%)	6 (10.9%)
• Hyperprolactinaemia	1 (1.6%)	7 (12.7%)
No. (%) with 1 or more AE	44 (69.8%)	54 (98.2%)
No. (%) of deaths	0 (0)	0 (0)
No. (%) with 1 or more other serious AE	0 (0)	0 (0)
No. (%) treatment stopped due to AE	0 (0)	2 (3.6%)

Laboratory safety	There were no statistically significant or clinically relevant changes in mean laboratory values from baseline to endpoint between the 2 treatment groups. An increase in prolactin levels was observed. There were no prolactin-related adverse events in the placebo group. One subject in the risperidone group reported dysmenorrhoea.
Other safety observations	
Vital signs	There were no statistically significant or clinically relevant differences between groups in the change in vital signs and physical findings from baseline to endpoint.
Weight	Mean change at endpoint was +0.9 kg in the placebo group and +2.2 kg in the risperidone group ($p<0.001$). Weight increase was reported as an adverse event by 1 subject (1.6%) in the placebo group and in 8 subjects (14.5%) in the risperidone group.
ECG	There were no clinically relevant differences between the treatment groups from baseline to endpoint for ECG interval measurements. There were no subjects with prolonged QT intervals corrected according to Fridericia's formula (QTcF), ie, 451-500 ms for males, 471-500 ms for females, at week 6 or at endpoint. There were no subjects with a pathological QTcF value (>500 ms) at week 6 or at endpoint. One subject (2.2%) in the placebo group and 4 subjects (9.3%) in the risperidone group had a QTcF increase of 30 to 60 ms. No subject in either group had a QTcF increase >60 ms.

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

ESRS	Score at baseline		Change from baseline at endpoint	
	Placebo	Risperidone	Placebo	Risperidone
Total ESRS				
Mean ± SE	1.3 ± 0.42	1.0 ± 0.28	0.0 ± 0.34	-0.6 ± 0.25
Median (min-max)	0.0 (0-19)	0.0 (0-9)	0.0 (-5-15)	0.0 (-7-4)
Bucco-linguo-masticatory factor				
Mean ± SE	0.0 ± 0.00	0.0 ± 0.00	0.1 ± 0.05	0.0 ± 0.00
Median (min-max)	0.0 (0-0)	0.0 (0-0)	0.0 (0-3)	0.0 (0-0)
Parkinsonism/dystonia total				
Mean ± SE	1.3 ± 0.41	1.0 ± 0.25	-0.1 ± 0.27	-0.6 ± 0.23
Median (min-max)	0.0 (0-18)	0.0 (0-6)	0.0 (-5-8)	0.0 (-5-4)
Parkinsonism total score				
Mean ± SE	1.2 ± 0.37	1.0 ± 0.25	-0.1 ± 0.27	-0.6 ± 0.23
Median (min-max)	0.0 (0-15)	0.0 (0-6)	0.0 (-5-8)	0.0 (-5-4)
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-C. Two subjects (3.6%) in the risperidone group and none in the placebo group had extrapyramidal symptoms reported as an adverse event.				
VAS of sedation	Mean values on the 100-mm VAS of sedation were very low at baseline (5.4 mm for both groups). A statistically significant (p=0.008) difference between the groups was observed at endpoint, when the mean value for the placebo group decreased by 2.0 ± 2.12 mm and that for the risperidone group increased by 5.9 ± 2.76 mm.			
Cognitive tests	No significant differences between the placebo and risperidone groups were noted in the results of the cognitive tests, which were performed by 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.			

Conclusions: 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 of age with borderline intellectual functioning and mild to moderate mental retardation, in whom destructive behaviours (eg, aggression, impulsivity, stereotyped, and self-injurious behaviours) are prominent.

- 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 mild to moderate mental retardation.
- Risperidone is well tolerated, and its safety profile is generally similar to that of placebo. Somnolence was the most frequent AE, 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 is observed in both male and female subjects. There were no other changes in laboratory parameters.
- Apart from a 2.2-kg increase in body weight, there were no significant changes in vital signs or ECG data.

Overall, the results of this trial show that, in this subject population, risperidone is well tolerated and effective at 0.02-0.06 mg/kg/day (mean dose 0.034 mg/kg/day).