Janssen Research & Development

Clinical Study Report Synopsis RIS-USA-93

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.

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SYNOPSIS

Trial identification and protocol summary

Finished product: Risperidone (R064766) Trial No.: RIS-USA-93 Clinical phase: III 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 subjects entered: 119 No. of subjects entered: 119 No. of subjects entered: 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 behaviour (e.g. 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-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 to totherwise specified (312.9) and a total rating of 224 on the N-CBRF Conduct Problem Subscale (Parent version). Subjects also having Attention Deficit/Hyperactivity Disorder (314.9) were eligible. DSM-IV, Axis I diagnosis of Mild Mental Retardation (317.0). Moderate Mental Retardation (318.0) or Borderline Intellectual Functioning (V62.89). These diagnoses represent intelligence quotients (IQs) ranging from ≤84 to ≥35. Vincland Adaptive Beha	Company: JANSSEN	PHARMACEUTICA N.V.				
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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	Form – dosing route	Matching solutions – oral				
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Duration of treatment 1-week placebo run-in; 6 weeks double-blind medication	Dosage	$\frac{13/111}{9/1723/9} = \frac{33000}{1000} = \frac{30000}{1000} =$				
Duration of trial	Duration of treatment	1_week placebo m	n-in: 6 weeks double-blind medication			
	Duration of trial		7 weeks			
Disallowed modication Other antinevolution antidepresents lithium conhemographics velocies acid	Disallowed mediactic	Duration of trial / weeks				
cholinesterase inhibitors clonidine guanfacine and all anticonvulsants	Disanowed medication Unter antipsycholics, antidepressants, lithium, carbamazepine, valproic ac					

Assessments		Placebo		Wk	Wk	Wk	Wk	Wk	Wk
	Screening	run-in	BL	1	2	3	4	5	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	Х		Х		Х		Х		Х
Drug concentration									
- Plasma trough									Х
Efficacy									
Primary variable									
- Nisonger Child									
Behaviour									
Rating Form (N-									
CBRF)	Х		X	X	Х	Х	Х	Х	Х
• Secondary variables									
- Aberrant									
Chaoleliot (ABC)	v		v	v	v	v	v	v	v
Dehaviour	Λ		Λ	Λ	Λ	Λ	Λ	Λ	Λ
- Dellavioui Problems									
Inventory (BPI)	х		x	x	x	x	x	x	x
- Clinical Global									
Impression									
$(CGI)^1$			Х	Х	Х	Х	Х	Х	Х
- Visual Analogue									
Scale (VAS)									
sedation			X	X	Х	Х	Х	Х	Х
- VAS^2			Х	X	X	Х	Х	X	X
Safety									
• Adverse events			Х	Х	Х	Х	Х	Х	Х
• Extrapyramidal									
Symptom Rating			v	v	v	v	v	v	v
Scale (ESKS)			Λ	Λ	А	Λ	Λ	А	Λ
Concomitant therepy			v	v	v	v	v	v	v
Clinical laboratory	v		Λ	Λ	Λ	Λ	Λ	Λ	\mathbf{x}^3
 Clinical laboratory Electrocordiogram 	Λ								Λ
• Electrocardiogram	x								x
 Vital signs 	x		x	x	x		x		x
Cognitive tests			X		**		**		X
¹ overall severity at baselir	ne (BL) and cl	nange from BI	therea	fter					
2 VAS of the most troubles	some symptor	n n							
³ prolactin and growth hor	mone (GH) sa	mples to be ta	ken at t	rial mee	dication	trough	l		
Statistical methods	Descriptive	statistics were	perform	ned for	the den	nograph	nic data	and ba	seline
	characteristi	cs. The compa	rability	of the	demogr	aphic a	nd base	line da	ta
	was assessed	d. For continue	ous and	ordinal	data (a	ge, heig	ght, IQ,	Vinela	nd
	adaptive behaviour scale, etc), the analysis of variance with factors for								
	treatment, investigator and stratum (Conduct Disorder versus Opposition						onal		
	Defiant Disorder or Disruptive Behaviour Disorder not otherwise specific						ified)		
	were applied. The Van Elteren test controlling for investigator and strati						atum,		
	was to be ap	pried if the dat	ia were n Mont	110t nor	inal. FC	or nomi at for co	nal cate	gorical	uata
	controlling f	or investigator	and et	ci-iiael	vere po	st iui ge	10101010	issucial.	1011
	concoming I	or investigator	anu su	atum, \	nure pe		1.		

Trial identification and protocol summary (continued)

Baseline characteristics - subject disposition	Placebo	Risperidone
	N=63	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%)

Main features of the subject sample and summary of the results

*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-hydroxyrisperidone), 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:

88.			
	Ν	Mean \pm 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

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Efficacy	Pl	acebo	Risperidone		
	Mean	Mean \pm SE	Mean	Mean \pm SE	
	baseline	change from BL	baseline	change from BL	
	score	at endpoint ¹	score	at endpoint ¹	
Primary variable:					
• Conduct problem subscale of					
N-CBRF ²	34.5 ± 0.88	-6.2 ± 1.41	32.9 ± 1.08	$-15.2 \pm 1.48^{***}$	
Secondary variables:					
• N-CBRF subscales ²					
Compliant/calm	4.6 ± 0.35	0.7 ± 0.39	4.9 ± 0.37	$2.7 \pm 0.49^{***}$	
Adaptive/social	3.6 ± 0.25	0.1 ± 0.27	3.7 ± 0.27	$1.6 \pm 0.34 ***$	
Insecure/anxious	16.9 ± 1.10	-3.0 ± 0.99	18.4 ± 1.19	$-8.4 \pm 0.92^{***}$	
Hyperactive	18.7 ± 0.70	-2.7 ± 0.66	19.3 ± 0.73	$-6.3 \pm 0.77 ***$	
Self-injury/stereotyped	3.1 ± 0.55	-1.0 ± 0.43	3.0 ± 0.53	$-2.1 \pm 0.51*$	
Self-isolated/ritualistic	5.8 ± 0.62	-1.6 ± 0.45	6.2 ± 0.64	$-3.2 \pm 0.52*$	
Overly sensitive	7.7 ± 0.43	-1.2 ± 0.39	8.9 ± 0.43	$-3.5 \pm 0.57 **$	
• 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	$-38.3 \pm 4.02^{***}$	
• Effect of somnolence	Significant (p<	<0.001) improveme	nt in the Cond	uct Problem	
	subscale of the	N-CBRF and othe	r N-CBRF sub	scales was	
	observed in su	bgroup analyses of	subjects witho	out somnolence,	
	indicating that	somnolence had no	o effect on the	efficacy of RIS.	
• CGI-C	At endpoint, 5	subjects (7.9%) in	the placebo gr	oup had a CGI-C	
	rating of very	much improved or	much improve	a, while 28	
	subjects (35.9)	mificant difference	between the g	rouns in the CGL	
	C rating show	ing greater improv	ement for the r	isperidone group	
	was seen as ea	rly as week 1 (n=0	.027): differend	ces continued to be	
	statistically sig	gnificant throughou	t the study ($p <$	0.001 from week 2	
	through endpo	oint).	, 1		

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

Asterisks refer to differences with placebo using ANCOVA model on change from baseline (factors: treatment, country baseline score). Levels of significance: $p \le 0.05$; $p \le 0.01$, $p \ge 0.001$. min-max: minimum-maximum

min-max: minimum-maxi

M/F: males/females SE: standard error

¹Endpoint is defined as the last observation (excluding the BL value)

²Nonimputed results

Risperidone-R064766: Clinical Study Report RIS-USA-93

Safety: adverse events (double-blind		Placebo	Risperidone		
phase) (N = number of subjects with data)		N = 63	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 du	e to AE	0 (0)	2 (3.6%)		
Laboratory safety	There were no statistically significant or clinically relevant changes in				
	mean laborat	ory values from baseline to er	ndpoint between the 2		
	treatment gro	oups. An increase in prolactin	levels was observed. There		
	were no prola	actin-related adverse events in	the placebo group. One		
	subject in the	risperidone group reported d	ysmenorrhoea.		
Other safety observations					
Vital signs There were not		o statistically significant or cl	inically relevant differences		
	between grou	ips in the change in vital signs	s and physical findings from		
	baseline to endpoint.				
Weight	Mean change	e at endpoint was $+0.9$ kg in th	e placebo group and		
	+2.2 kg in the	e risperidone group (p<0.001)	. Weight increase was		
	reported as an	n adverse event by 1 subject (1.6%) in the placebo group		
ECC	and in 8 subjects (14.5%) in the risperidone group.				
EUG I here were no clinically relevant differences between the treatment			interval massurements		
	There were no subjects with prolonged OT interval measurements.				
	according to Fridericia's formula (OTaF) in 451 500 ms for malas				
	471 500 ms for females, at week 6 or at and point. There were no				
	subjects with a nathological $OT_{c}F$ value (500 ms) at week 6 or at				
	endpoint. On	he subject (2.2%) in the placebo group and 4 subjects			
	(9.3%) in the	risperidone group had a OTcF increase of 30 to 60 ms.			
	No subject in	either group had a QTcF inci	rease >60 ms.		

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

			Change from		
	Score at	t baseline	baseline at endpoint		
ESRS	Placebo	Risperidone	Placebo	Risperidone	
Total ESRS					
Mean \pm 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				

Main	features	of the su	hiect samı	le and	summary	of the	results (continued	١
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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 \pm
	2.12 mm and that for the risperidone group increased by $5.9 \pm$
	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).