SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN RESEARCH FOUNDATION **Finished product:** RISPERDAL® **Active ingredient:** risperidone (R64,766)		
Title: The safety and effectiveness of risperidone 8 mg QD and 4 mg QD compared to placebo in the treatment of schizophrenia	**Trial No.:** RIS-USA-72 **Clinical phase:** III	
Investigator: Multicenter	**Country:** U.S.A	
Reference: JRF, Clinical Research Report RIS-USA-72, November 1996		
Trial period: Start: 20 July 1995 End: 15 March 1996	**No. of investigators:** 28 **No. of patients:** 246	
Indication/objectives: Schizophrenia/To evaluate the safety and effectiveness of risperidone 8 mg and risperidone 4 mg given once daily compared to placebo in schizophrenic patients.		
Trial design: Double-blind, parallel-group, multicenter study		
Patient selection • Inclusion criteria: - Male or female patients between the ages of 18 and 65, inclusive, who gave informed consent - Patients meeting DSM-IV criteria for schizophrenia (295.10, 295.20, 295.30, 295.60, or 295.90) - Patients who had a total score between 80 and 120, inclusive, on the PANSS, and a score of ≥ 8 in the sum of two symptoms from the following list: conceptual disorganization (P2), hallucinatory behavior (P3), suspiciousness/persecution (P6), and unusual thought content (G9) at the selection visit (Visit 1) - Patients who were in good health as determined by a complete physical examination, laboratory tests, and 12-lead ECG - Patients who were inpatients at the start of the study - Patients who had not received depot neuroleptics within one usual treatment cycle for that patient at the time of Visit 2		
• Exclusion criteria: - Patients who had an Axis I, DSM-IV psychiatric disorder other than schizophrenia or nicotine dependence - Patients who had clinically significant organic or neurologic disease, including epilepsy - Patients who had a history of neuroleptic malignant syndrome (NMS) - Patients who, in the opinion of the Investigator, had clinically significant abnormal laboratory test results - Patients who had clinically relevant abnormal ECG findings, including, but not limited to, a QTc greater than 450 msec - Patients who had a history of substance dependence (with the exception of 305.10, nicotine dependence), as defined by DSM-IV, within the past 3 months, and patients who had a positive urine drug screen at the screening visit - Patients who had received investigational drugs within 4 weeks prior to study initiation - Female patients who were pregnant or lactating, or female patients of child-bearing age who were not using acceptable methods of birth control (i.e., intrauterine devices, oral contraceptives, barrier plus spermicide, or a levonorgestrel implant) - Patients who had a known hypersensitivity to risperidone - Patients who had, in the past year, presented with their first psychotic episode - Patients who, in the opinion of the investigator, had received adequate trials of risperidone in the past and have not demonstrated significant improvement - Patients who had taken antidepressants, lithium, or anticonvulsants for psychiatric indications within the past seven days of study initiation - Patients who, in the opinion of the investigator, had a history of treatment-refractoriness to conventional antipsychotics, or had been treated with clozapine because of treatment resistance to other antipsychotics - Patients who, in the opinion of the investigator, were at risk for self-harm or violence		

Trial identification and protocol summary, continued

Treatment							
Form - dosing route	matching tablets - oral						
Medication	Ris 8 mg QD		Ris 4 mg QD		Placebo		
Batch numbers	94I26/F13, 95A20/F13, 94E12/F12, 93E25/F11, 93E26/F10				93D29/F7		
Dosage	(titration to) 4 mg, 8 mg, or placebo daily						
Duration	28 days						
Disallowed medication	antidepressants, lithium, anticonvulsants, other psychiatric medications (Note: lorazepam, chloral hydrate, anticholinergics, and beta blockers were allowed)						
Assessments	Visit:	1	2	3	4	5	6
	Day:	-2 to -1	0	8	15	22	28
Informed consent		X					
Demographics		X					
Psychiatric history		X					
Medical history		X					
Physical examination		X					X
Vital signs		X	X	X	X	X	X
ECG		X					X
Laboratory tests[a,b]		X					X
PANSS and ESRS[c]		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Concomitant medications			X	X	X	X	X
Count returned drug						X	X
Dispense randomized medication[d]					X	X	

[a] Pregnancy test was included for women of child-bearing potential (Visit 1 only).
[b] The urine drug screen was performed at Visit 1 only.
[c] The ESRS was done beginning on Day 0.
[d] Dispensing of medication occurred only when the patient had been discharged.

Statistical methods	Cochran-Mantel-Haenszel (CMH) test to identify differences in clinical response; Last-observation-carried-forward (LOCF) evaluation for patients with no Week 4 evaluation; Analysis of variance (ANOVA) to determine possible differences in PANSS.

Main features of the trial sample

Baseline characteristics - patient disposition	Ris 4 mg QD	Ris 8 mg QD	Placebo
• Number of patients entered	85	78	83
• Gender			
- Male	67	64	65
- Female	18	14	18
• Age: median (min-max), years	38.0 (19-62)	38.5 (19-65)	37.0 (18-66)
• Race			
- White	50 (59%)	38 (49%)	48 (58%)
- Black	26 (31%)	31 (40%)	27 (33%)
- Oriental	0	0	2 (2%)
- Hispanic	8 (9%)	8 (10%)	6 (7%)
- Indic	1 (1%)	0	0
- Polynesian/East Asia	0	1 (1%)	0
• Diagnosis			
- Disorganized	3 (4%)	1 (1%)	2 (2%)
- Paranoid	53 (62%)	58 (74%)	60 (72%)
- Residual	0	0	1 (1%)
- Undifferentiated	29 (34%)	19 (24%)	20 (24%)
• Number of patients discontinued	27 (32%)	25 (32%)	27 (33%)
- Adverse experiences	6 (7%)	5(6%)	0
- Inadequate response	4 (5%)	4 (5%)	11 (13%)
- Ineligible	0	0	1 (1%)
- Lost to follow-up	1 (1%)	2 (3%)	1 (1%)
- Chose to discontinue	14 (17%)	10 (13%)	10 (12%)
- Poor compliance	2 (2%)	4 (5%)	3 (4%)
- Other reason	0	0	1 (1%)

Summary of the results

Effectiveness (n = number of patients with data)	Risperidone 4 mg (n = 82)	Risperidone 8 mg (n = 75)	Placebo (n = 79)
LOCF analysis			
• Clinical response via PANSS at endpoint			
- Improved	53 (65%)*	57 (76%)***	37 (47%)
- Not improved	29 (35%)	18 (24%)	42 (53%)
• Total PANSS score			
- Baseline	94.70	94.09	94.23
- Endpoint	75.26	72.79*	81.62
• Positive symptom subscale			
- Baseline	24.22	23.81	23.80
- Endpoint	17.71**	16.84**	20.39
• Negative symptom subscale			
- Baseline	24.40	24.39	23.20
- Endpoint	19.32*	19.99	20.59
• General subscale			
- Baseline	46.07	45.89	47.23
- Endpoint	37.73	35.96	40.63
• PANSS-derived BPRS			
- Baseline	53.73	53.44	54.29
- Endpoint	42.07	40.65*	45.94
• Key BPRS items			
- Baseline	16.16	16.27	15.97
- Endpoint	11.30**	11.04**	13.00

Levels of significance: * $p \leq 0.05$; **$p \leq 0.01$, ***$p \leq 0.001$

Summary of the results, continued

Safety (n = number of patients with data)	Risperidone 4 mg (n = 85)	Risperidone 8 mg (n = 78)	Placebo (n = 83)
• Number of patients with an adverse experience (AE)	77 (91%)	72 (92%)	72 (87%)
• Adverse events with a total of incidence of ≥5%			
- Insomnia	35 (41%)	32 (41%)	35 (42%)
- Somnolence	22 (26%)	25 (32%)	9 (11%)
- Agitation	19 (22%)	21 (27%)	24 (29%)
- Anxiety	12 (14%)	13 (17%)	12 (15%)
- Headache	27 (32%)	30 (39%)	33 (40%)
- Dizziness	9 (11%)	15 (19%)	3 (4%)
- Extrapyramidal disorder	8 (9%)	13 (17%)	1 (1%)
- Hyperkinesia	7 (8%)	6 (8%)	2 (2%)
- Dyspepsia	8 (9%)	16 (21%)	9 (11%)
- Nausea	10 (12%)	8 (10%)	6 (7%)
- Constipation	9 (11%)	7 (9%)	11 (13%)
- Mouth dry	7 (8%)	6 (8%)	2 (2%)
- Vomiting	8 (9%)	4 (5%)	10 (12%)
- Pain	4 (5%)	8 (10%)	7 (8%)
- Fatigue	3 (4%)	6 (8%)	0
- Back pain	4 (5%)	5 (6%)	1 (1%)
- Pharyngitis	3 (4%)	4 (5%)	5 (6%)
- Rhinitis	7 (8%)	4 (5%)	9 (11%)
- Vision abnormal	4 (5%)	4 (5%)	1 (1%)
- Toothache	1 (1%)	0	7 (8%)
- Sinusitis	2 (2%)	2 (3%)	6 (7%)
• No. of pts. who had a serious AE	5 (6%)	6 (8%)	7 (8%)
• No. of pts. who discontinued treatment due to AE	6 (7%)	5 (6%)	0
ECG parameters	No clinically significant changes in ECG intervals were noted.		
Laboratory safety tests	No clinically significant abnormalities were reported.		

Conclusions

The results of this study demonstrate that:

- the clinical response (via PANSS) of the risperidone 4 mg and risperidone 8 mg given once day was statistically significantly different compared to placebo (LOCF analysis); and
- the two doses of risperidone were well tolerated.