SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product:** Risperdal® **Active ingredient:** risperidone (R064766)		
Title: A comparison of risperidone and haloperidol for prevention of relapse in subjects with schizophrenia and schizoaffective disorder	**Trial No.:** CR006013. **Clinical phase:** III	
Investigator: Multicenter	**Country:** USA	
Reference: JRF, Clinical Research Report CR006013, February 2000 (N 147502)		
Trial period: Start: 21 May 1996 End: 17 September 1998	**No. of investigators:** 44 **No. of subjects entered:** 397 **No. of subjects randomized:** 395	
Study objectives: The primary objective of this trial was to compare the time to and incidence of relapse in patients who received risperidone or haloperidol and to compare the long-term efficacy and safety of risperidone to that of haloperidol in subjects with schizophrenia and schizoaffective disorder.		
Trial design: This was a long-term, randomized, double-blind, parallel-group, controlled study in subjects with schizophrenia and schizoaffective disorder.		
Main inclusion criteria: Male or female subjects between 18 and 65 years of age; diagnosis of schizophrenia or schizoaffective disorder (DSM-IV) criteria, with a documented 1-year history of schizophrenia or schizoaffective disorder; discharged from an inpatient psychiatric unit, had a partial hospitalization, completed crisis management intervention, or stayed in a psychiatric hospital emergency room holding area for at least 12 hours within the past 24 months; received a stable dosage of antipsychotic medication for the 30 days prior to trial entry. **Methodology:** The study was composed of two phases: a 1-week baseline period and a double-blind treatment period. During the baseline period, the doses of risperidone and haloperidol were gradually increased to 4milligrams (mg)/day for risperidone and 10mg/day for haloperidol. During the first 4 weeks of the study, dosage adjustments (risperidone 2-8mg/day; haloperidol 5-20mg/day) could be made based on clinical evaluations of the patient. The double-blind treatment continued until the last patient entering the study completed 1 year of treatment or for a maximum of 112 weeks. **Number of subjects (planned and analyzed):** The planned sample size was 414 subjects, and 395 were randomized and treated and included in the safety analyses. For efficacy, 365 subjects were included in the analyses. **Criteria for Evaluation:** Efficacy: The primary efficacy assessment was based on the time to relapse, which was defined by six criteria that indicated the subject's illness was no longer under control (e.g., psychiatric hospitalization). Safety: Safety was evaluated on the basis of treatment-emergent adverse events (AEs), clinical laboratory tests, measurements of vital signs and body weight, physical examination and electrocardiogram (ECG) findings, and the Extrapyramidal Symptoms Rating Scale (ESRS).		

Trial identification and protocol summary (continued)

Treatment						
Form - dosing route	matching tablets - oral					
Medication	RIS 1 mg	RIS	2 mg	HAL 2 mg	HAL	5 mg
Batch number	95E05/F5	96A09/F13	96J16/F13	95A19/F56	95L12/F63	96J17/F63
Expiration date	May 1998	Jan. 1999	Oct. 1998	Jan. 2000	Dec. 1998	Oct. 1999
Dosage	2 to 8 mg/day risperidone, 5 to 20 mg/day haloperidol					
Duration of treatment	maximum 2 years					

Statistical methods: Descriptive statistics were performed for the demographic data and Baseline characteristics. For continuous and ordinal data (ie, age, height, weight, etc.), the 2-way analysis of variance (ANOVA) with factors for treatment, investigator and sex were applied. The Van Elteren test controlling for investigator and sex was to be applied if the data were not normal. For nominal categorical data (sex, race, domiciliary status, DSM IV axis I), the Cochran-Mantel-Haenszel test for general association controlling for investigator and sex was performed. For the primary efficacy parameter, stratified logrank test controlling for investigator and sex were performed. For relapse rate, CMH test was used. For continuous variables, treatment effects were examined by means of analysis of covariance (ANCOVA) with factors of treatment, sex, investigator, and Baseline values as covariate. A paired t-test was performed for within-group comparison.

Summary of the results:

Efficacy (dataset without 1 site)	RIS		HAL	
Primary variable	N=177		N=188	
- Time to relapse (days)	452.23 (SE 17.68)		391.33 (SE 21.83)	
Secondary variables				
- Number of patients with psychotic relapse				
- at 1 year	41 (23.2%) **		65 (34.6%)	
- at Endpoint	45 (25.4%) **		75 (39.9%)	
- PANSS, change from Baseline to Endpoint	BL	mean change	BL	mean change
- Total PANSS score	65.06	-3.15***	67.38	1.79
- Positive symptoms	18.58	-1.56**	19.15	-0.24
- Negative symptoms	16.98	-0.53**	17.80	0.77
- Disorganized thoughts	14.97	-0.79**	15.38	0.17
- Uncontrolled hostility/excitement	6.04	0.29	6.26	0.73
- Anxiety/depression factor	8.45	-0.52**	8.76	0.24
- CGI-C, change from BL to Endpoint				
- Very much improvement	12 (6.9%)***		8 (4.3%)	
- Much improvement	41 (23.7%)		25 (13.4%)	
- Minimum improvement	50 (28.9%)		35 (18.7%)	
- Unchanged	35 (20.2%)		59 (3 1.6%)	

Levels of significance: * p<= -0.05; **p<= -0.01, ***p<= -0.001 positive for RIS

Summary of the results (continued)

Safety (dataset with all sites)	RIS N=192 n	RIS N=192 %	HAL N=203 n	HAL N=203 %
Adverse events (AE)	171	89.1	184	90.6
Serious Adverse Events	49	25.5	62	30.5
Most frequently reported AE				
- insomnia	47	24.5	56	27.6
- psychosis	36	18.8	54	26.6
- somnolence	24	12.5	48	23.6
- agitation	24	12.5	40	19.7
- headache	35	10.4	34	16.7
- dizziness	20	8.3	17	8.4
	RIS N=192		HAL N=203	
Most frequently reported AE (continued)	n	%	n	%
- extrapyramidal symptoms	16	6.3	30	14.8
- hypertonia	12	4.7	23	11.3
- tremor	9	4.2	22	10.8
- hyperkinesia	8	4.2	40	19.7
- injury	21	10.9	19	9.4
- vomiting	15	7.8	22	10.8
- rhinitis	29	15.1	22	10.8
No. of patients with 1 or more AE	171		184	
No. of patient deaths	1		0	
No. of patients with 1 or more other serious AE	49		62	
No. of patients with treatment stopped due to AE	44		71	

	RIS				HAL			
ESRS, change	n	BL	mean change	SE	n	BL	mean change	SE
- Total	187	4.35	-0.71**	0.36	201	4.99	0.45	0.47
- Questionnaire	187	1.69	-0.12**	0.20	202	1.97	0.40	0.24
- Parkinsonism	187	3.07	-0.47***	0.26	201	3.50	0.64	0.35
- Dystonia	187	0.12	-0.01	0.04	202	0.15	-0.04	0.05
- Dyskinesic movements	187	1.15	-0.24	0.13	202	1.33	-0.14	0.19
- Hyperkinesia	187	0.85	-0.17**	0.11	202	1.05	0.13	0.16
- Hypokinesia	187	2.03	-0.29***	0.17	202	2.22	0.46	0.23
Other Safety Parameters	n		mean change	SE	n		mean change	SE
- Body weight (kg) changes BL to Endpoint	166		2.36***	0.60	182		-0.56	0.52
- ECG	No clinically relevant changes from BL to Endpoint or between treatment groups							
- Vital signs	No clinically relevant changes from BL to Endpoint or between treatment groups							
- Clinical laboratory	No clinically relevant changes from BL to Endpoint or between treatment groups							

Levels of significance: * p<= 0.05; **p<= 0.01, ***p<= 0.001

Conclusions

Risperidone was statistically significantly more effective than haloperidol in maintaining clinical improvement during continuing therapy in adult outpatients with schizophrenia or schizoaffective disorder. Treatment with risperidone was well tolerated and associated with less EPS than haloperidol. Except for weight gain, there were no consistent changes or clinically relevant abnormalities in the vital signs, ECG data, or clinical laboratory results with risperidone treatment.

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