SYNOPSIS

Trial identification and protocol summary

Company: Johnson & Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica, N.V. **Finished product**: Risperdal® **Active ingredient**: Risperidone (R064766)		
Title: The Safety and Efficacy of Risperidone vs. Placebo vs. Haloperidol as Add-on Therapy to Mood Stabilizers in the Treatment of the Manic Phase of Bipolar Disorder	**Trial No.**: RIS-USA-102 **Clinical phase**: III	
Investigator: Multicenter	**Country**: United States	
Reference: J&JPRD, Clinical Research Report RIS-USA-102, May 2002 (EDMS-PSDB-1833082)		
Trial period: Start: 22 October 1997 End: 29 April 1999	**No. of investigators**: 20 **No. of patients entered**: 180 **No. of patients randomized**: 158 **No. of patients treated:** 156 **No. of patients entered open-label:** 85	
Indication / objectives: Bipolar disorder with acute mania/ 3-week, double-blind assessment of the efficacy and safety of risperidone as an adjunct to known mood stabilizers in the treatment of the manic phase of bipolar disorder and assessment of safety and efficacy data during an open-label risperidone, 10-week, phase.		
Trial design: Double-blind (DB): 3-week, randomized, double-blind, placebo-controlled trial with three parallel treatment groups: placebo (PLA), risperidone (RIS), or haloperidol (HAL) (as internal reference). Open-label (OL): 10-week, open-label treatment with risperidone .		
Patient selection: Inclusion criteria: - Age between 18 and 65 years (extremes included) - Hospitalized for mania with a minimum score, at Baseline, of 20 on the Young Mania Rating Scale (YMRS). Patients with concurrent symptoms of depression could enter the trial; - Diagnosis of Bipolar disorder as defined in the Diagnostic & Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV: 296.4x, 296.6x); - Must be receiving lithium or valproate at the time of randomization; - Medically stable on the basis of a pretrial physical examination, medical history and electrocardiogram; - Inpatients for a minimum of the first four days of double-blind treatment; - Patient signed the informed consent form; or patients' relative, guardian or legal representative signed the informed consent form; in accord with local institutional review board (IRB) requirements; - Patients were randomized within three days after admission to the hospital. Exclusion criteria: - Other Axis I DSM-IV diagnosis, other than nicotine or caffeine dependence; - Use of disallowed concomitant therapy; - History of alcohol or drug abuse or dependence, within four weeks before entry into the trial; - Seizure disorder requiring medication; - Patients with untreated hypothyroidism. Patients with adequately treated thyroid insufficiency could be admitted; - Participation in an investigational drug trial within 30 days prior to the start of the trial; - Known sensitivity to risperidone, haloperidol, lithium, carbamazepine, or valproate; - History of severe drug allergy or hypersensitivity; - History of neuroleptic malignant syndrome; - Use of clozapine within 30 days prior to entry into the trial; - Use of depot neuroleptics within one treatment cycle of entry into the trial; - Patients who were at imminent risk of causing injury to themselves or others, or causing significant damage to property;		

- Laboratory values outside the normal range as defined by Lippert & Lehmann;
- Serious or unstable medical illnesses: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, or metabolic disturbances, (labile hypertension, poorly controlled diabetes mellitus);
- Pregnancy or breast-feeding;
- Women of childbearing potential without adequate contraception (sterilization, abstinence, barrier, intrauterine device, oral contraceptives, intramuscular or subdermal administration of depot-progestagens).

Treatment			
Form - dosing route	matching tablets - oral		
Medication	Placebo tablets	Risperidone 1 mg tablets	Haloperidol 2 mg tablets
Batch number	95I11/F7	97G01/F5 97A24/F5 97D14/F5	96H19/F56
Daily dosage	Double-blind: Days 1 & 2; risperidone 2 mg, haloperidol 4 mg, or placebo 2 tablets Days 3 & 4: risperidone 1-4 mg, haloperidol 2-8 mg, or placebo 2 tablets Days 5-21: risperidone 1-6 mg, haloperidol 2-12 mg, or placebo 1-6 tablets Open-label: risperidone 0-6 mg		
Duration of treatment	Double-blind treatment: three weeks; open-label risperidone: ten weeks		
Duration of trial	13 weeks		
Disallowed medication	Antipsychotics other than the trial medication; Mood stabilizers other than lithium, valproate or carbamazepine Benzodiazepines other than lorazepam, temazepam or flurazepam; After Day 7, no rescue medication for agitation was permitted; Antiparkinson medication was not permitted at baseline (BL) but could be used during double-blind treatment, but only after documentation of the Extrapyramidal Symptom Rating Scale (ESRS).		

Assessments **Double-blind phase**	**Screen** **-3 to -1**	**Baseline** **Day 1**	**Day 3**	**Week 1** **Day 8**	**Week 2** **Day 15**	**Week 3** **Day 22**
Serum concentration of mood stabilizers	X	X	X	X	X	X
Efficacy						
– Primary variable: YMRS	X	X		X	X	X
–Secondary variables: CGI-C[1], BPRS[2], HAM-D[3]		X		X	X	X
Safety						
– Adverse events			X	X	X	X
– Clinical laboratory	X					X
– Physical examination	X					X
– Vital signs	X	X		X	X	X
– Electrocardiogram	X					X
– ESRS		X		X	X	X

[1] CGI-C: Clinical Global Impression of Change.
[2] BPRS: Brief Psychiatric Rating Scale.
[3] HAM-D: Hamilton Depression Rating Scale.

Assessments[a] **Open-label phase**	**Week 1** **Day 7**	**Week 2** **Day 14**	**Week 4** **Day 28**	**Week 6** **Day 42**	**Week 8** **Day 56**	**Week 10** **Day 70**
Serum concentration of mood stabilizers						X
Efficacy –YMRS, CGI-C, BPRS, HAM-D	X	X		X		X
Safety – Adverse events	X	X	X	X	X	X
– Clinical laboratory						X
– Physical examination						X
– Vital signs	X	X		X		X
– Electrocardiogram						X
– ESRS	X	X		X		X
a: The protocol-defined numbering of weeks and days for the open-label phase was changed to more accurately reflect the timing of assessments, since patients could enter the open-label phase after only seven days of double-blind treatment.						
Statistical Methods	Intent-to-treat analysis (ITT), analysis of covariance (ANCOVA), Van Elteren test, generalized Wilcoxon test, paired t-test, Wilcoxon matched-pairs signed-ranks test, Cochran-Mantel-Haenszel test (CMH)					

Main features of the subject sample and summary of the results

Baseline characteristics - subject disposition	Placebo N=51	Risperidone N=52	Haloperidol N=53
Number of patients randomized (M/F)	24/27	26/26	30/23
Age: median (min, max), yrs	43 (18, 64)	41 (18, 61)	44 (20, 66)
Discontinuation[a] (during entire trial): n (%)	31 (60.8)	32 (61.5)	37 (69.8)
Patient withdrew consent	11 (21.6)	12 (23.1)	17 (32.1)
Insufficient response	7 (13.7)	5 (9.6)	3 (5.7)
Adverse event	2 (3.9)	5 (9.6)	5 (9.4)
Patient lost to follow-up	3 (5.9)	3 (5.8)	6 (11.3)
Patient noncompliant	4 (7.8)	3 (5.8)	3 (5.7)
Patient ineligible to continue trial	2 (3.9)	2 (3.8)	3 (5.7)
Other	2 (3.9)	2 (3.8)	0

a: Does not include patients who stopped treatment but continued having trial assessments

Serum concentrations of mood stabilizers	Placebo		Risperidone		Haloperidol	
Mood stabilizer assigned as a randomization strata	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Lithium (mEq/L)						
Double-blind baseline	12	0.6 (0.09)	14	0.7 (0.11)	16	0.5 (0.06)
DB Week 3	6	0.8 (0.13)	11	0.7 (0.08)	8	0.7 (0.07)
OL Week 10	3	0.7 (0.20)	6	0.6 (0.11)	1	0.2 (N/A[a])
Valproate (µg/mL)						
Double-blind baseline	35	52.9 (4.97)	37	53.4 (4.92)	36	50.1 (5.67)
DB Week 3	18	77.3 (6.43	26	65.4 (5.31	24	76.2 (5.22)
OL Week 10	11	66.6 (8.92)	10	52.8 (9.24)	11	70.3 (11.51)

Efficacy	Placebo			Risperidone			Haloperidol		
	Mean (SE) BL	Mean change (SE) at Week 3	Mean change (SE) at End point DB.)	Mean (SE) at BL	Mean change (SE) Week 3	Mean change (SE) End point DB	Mean (SE) BL	Mean change (SE) at Week 3	Mean change (SE) at End point DB
Primary variable: YMRS total score	n=47 28.1 (0.9)	n=25 -13.4 (1.7)	n=47 -8.2 (1.5)	n=52 28.0 (0.8)	n=38 -16.6^{+} (1.3)	n=51 -14.3* (1.4)	n=52 27.4 (0.9)	n=33 -15.4 (1.6)	n=50 -13.3 * (1.4)
Secondary variables: Change from BL Day 8 on YMRS scale		Wk 1 n=46 -6.1 (1.3)			Wk 1 n=49 -9.7* (1.1)			Wk 1 n=47 -9.4* (1.1)	
Change from BL of double-blind at End point of OL phase			End pt OL n=26 -17.9 (1.4)			End pt OL n=33 -18.2 (1.7)			End pt OL n=24 -19.3 (1.5)
Differences with PLA using ANCOVA statistical model on change from Baseline $^{+}$ p< 0.1, *p < 0.05									
	Placebo			Risperidone			Haloperidol		
	Mean (SE) BL	Mean change (SE) at Week 3	Mean change (SE) at End point DB	Mean (SE) at BL	Mean change (SE) Week 3	Mean change (SE) End point DB	Mean (SE) BL	Mean change (SE) at Week 3	Mean change (SE) at End point DB
	n=47	n=25	n=47	n=52	n=38	n=51	n=52	n=33	n=50
BPRS total score	44.2 (1.6)	-10.3 (2.7)	-7.3 (1.9)	42.5 (1.5)	-9.1 (1.5)	-8.5 (1.5)	41.2 (1.3)	-9.3 (1.5)	-7.6 (1.6)
Anergia cluster	7.0 (0.5)	-1.6 (0.7)	-1.0 (0.5)	6.7 (0.4)	0.1 (0.4)	-0.2 (0.3)	6.5 (0.3)	0.2 (0.5)	0.1 (0.3)
Activity cluster	7.8 (0.4)	-1.0 (0.6)	-0.9 (0.4)	7.7 (0.4)	-2.0 (0.3)	-1.7 (0.3)	7.5 (0.3)	-2.0 (0.4)	-1.8* (0.4)
Anxiety/depression cluster	11.0 (0.6)	-1.8 (0.9)	-1.7 (0.6)	9.8 (0.6)	-0.8 (0.6)	-1.3 (0.5)	10.4 (0.6)	-1.5 (0.6)	-1.0 (0.5)
Hostility cluster	7.5 (0.5)	-2.4 (0.9)	-1.0 (0.7)	7.5 (0.5)	-3.2 (0.6)	-2.5 (0.6)	7.2 (0.4)	-2.4 (0.4)	-1.7* (0.6)
Thought disturbances	10.8 (0.7)	-3.6 (0.8)	-2.7 (0.6)	10.8 (0.5)	-3.2 (0.6)	-2.8 (0.5)	9.6 (0.6)	-3.7 (0.7)	-3.1 (0.6)
*p<0.5 Differences RIS vs. PLA using ANCOVA model on change from Baseline									

Efficacy con't	Placebo			Risperidone			Haloperidol		
	Mean (SE) BL	Mean change (SE) at Week 3	Mean change (SE) at End point DB.)	Mean (SE) at BL	Mean change (SE) Week 3	Mean change (SE) End point DB	Mean (SE) BL	Mean change (SE) at Week 3	Mean change (SE) at End point DB
	n=47	n=25	n=47	n=52	n=38	n=51	n=52	n=33	n=50
HAM-D total score (21 item)	16.3 (1.2)	-5.9 (1.5)	-3.0 (1.2)	14.7 (1.3)	-4.4 (1.2)	-4.0 (1.0)	14.8 (1.2)	-3.7 (1.3)	-2.5 (1.1)
Anxiety/ somatization	5.3 (0.5)	-1.8 (0.6)	-0.8 (0.4)	4.3 (0.4)	-0.7 (0.5)	-0.5 (0.4)	4.3 (0.4)	-0.5 (0.5)	-0.1 (0.4)
Weight	0.5 (0.1)	-0.2 (0.2)	-0.3 (0.1)	0.3 (0.1)	–0.3 (0.1)	-0.2 (0.1)	0.3 (0.1)	0.2 (0.2)	0.0 (0.1)
Cognitive disturbance	4.6 (0.4)	-2.0 (0.4)	-1.1 (0.3)	4.2 (0.4)	-2.0 (0.4)	-1.8 (0.3)	4.0 (0.3)	-1.5 (0.5)	-1.2 (0.4)
Diurnal variation	0.6 (0.2)	0.0 (0.3)	0.0 (0.2)	0.6 (0.2)	-0.1 (0.2)	-0.1 (0.2)	0.9 (0.2)	-0.3 (0.2)	-0.2 (0.2)
Retardation	2.9 (0.5)	-0.9 (0.6)	-0.2 (0.5)	2.5 (0.4)	0.1 (0.4)	-0.0 (0.3)	2.7 (0.3)	-0.4 (0.4)	-0.1 (0.4)
Sleep disturbance	2.8 (0.3)	-1.0 (0.4)	-0.6 (0.3)	3.2 (0.3)	-1.6 (0.4)	-1.5 (0.4)	3.1 (0.3)	-1.2 (0.3)	-1.1 (0.3)

p<0.05 RIS vs. PLA at End point DB using ANCOVA model on change from Baseline

Efficacy (continued)	
Clinical Global Impression – Change from Baseline (CGI-C)	The CGI-C ratings in the RIS treatment group at End point DB were significantly better than those of the PLA group (p = 0.002 Van Elteren test controlling for investigator).
Number of patients who discontinued early from DB phase	Twenty-seven patients (52.9%) from the PLA group, 16 patients (30.8%) from the RIS group, and 20 patients (37.7%) from the HAL group discontinued the DB treatment early. Four patients from the PLA group, four patients from the RIS group and one patient from the HAL group discontinued DB treatment prematurely and entered OL risperidone treatment.
Time to premature discontinuation from BL of DB	Twenty-five percent of PLA patients discontinued by Day 9 (of double-blind) while 25% of RIS patients discontinued by Day 15.5. This was a statistically significant difference between risperidone and placebo (p = 0.037). Twenty-five percent of HAL patients discontinued by Day 11.
Number of patients with ≥50% improvement on YMRS	Eighteen patients (38.3%) of the PLA group reached at least 50% improvement on the YMRS at End point DB, compared with 29 patients (56.9%) in the RIS group (p = 0.055, CMH test).
Time to ≥30% improvement on YMRS	The mean number of days to achieve onset of therapeutic response (30% decrease from Baseline YMRS score) was 13.4 days in the PLA group, and 11.3 days in the RIS group (p = 0.247, generalized Wilcoxon test).
% of patients using rescue medication	There was no statistically significant difference in the use of rescue medication between RIS and PLA patients. There was a statistically significant difference between HAL and PLA patients in the use of antiparkinson medications (p<0.001).
% of days on rescue medication	The PLA group used lorazepam 32.4% of the time, compared with 23.7% in the RIS group (p = 0.082, ANOVA). The HAL group used lorazepam 23.8% of the time. Mean percent of antiparkinson medication use was 45.6% ± 16.0 of the time by the PLA group, compared to 43.4% ±8.72 and 41.2% ±6.03 by the RIS and HAL groups, respectively (p = 0.742, ANOVA).

Safety (n = number of patients treated)	Placebo (n=51)	Risperidone (n=52)	Haloperidol (n=53)
Adverse events during double-blind treatment			
Most frequently reported (≥10%) adverse events (AEs) **during double-blind** treatment			
Somnolence	6 (11.8)	13 (25.0)	16 (30.2)
Headache	12 (23.5)	11 (21.2)	8 (15.1)
Dyspepsia	9 (17.6)	9 (17.3)	9 (17.0)
Extrapyramidal disorder	2 (3.9)	7 (13.5)	15 (28.3)
Dizziness	1 (2.0)	7 (13.5)	4 (7.5)
Constipation	2 (3.9)	3 (5.8)	6 (11.3)
Tremor	2 (3.9)	2 (3.8)	6 (11.3)
No. (%) with at least one AE **during double-blind**	43 (84.3)	42 (80.8)	48 (90.6)
No. (%) with EPS-like AE **during double-blind**	6 (11.8)	13 (25.0)	28 (52.8)
No. (%) with EPS-like SAE **during double-blind**	0	0	1 (1.9)
No. of deaths **during double-blind**	0	0	0
No. (%) with one or more other serious AEs **during double-blind**	4 (7.8)	2 (3.8)	4 (7.5)
No. (%) treatment stopped due to AE **during double-blind**	2 (3.9)	2 (3.8)	2 (3.8)
No. (%) ECG abnormalities **during double-blind**			
Pathologic QTcB	0	1 (2.9)	0
QTcB change of clear concern	0	1 (3.1)	0
Adverse events during open-label risperidone treatment	Double-blind Placebo n=26	Double-blind Risperidone n=34	Double-blind Haloperidol n=25
Most frequently reported (≥10%) adverse events (AEs) **during open-label** treatment			
Extrapyramidal disorder	6 (23.1)	10 (29.4)	9 (36.0)
Dizziness	3 (11.5)	3 (8.8)	0
Headache	7 (26.9)	3 (8.8)	1 (4.0)
Hyperkinesia	3 (11.5)	3 (8.8)	3 (12.0)
Hypertonia	4 (15.4)	3 (8.8)	4 (16.0)
Tremor	7 (26.9)	3 (8.8)	3 (12.0)
No. (%) with at least one AE **during open-label**	25 (96.2)	32 (94.1)	22 (88.0)
No. (%) with EPS-like AE **during open-label**	17 (65.4)	19 (55.9)	15 (60.0)
No. (%) of deaths **during open-label**	0	1 (2.9)	0
No. (%) with one or more serious AEs **during open-label**	3 (11.5)	6 (17.6)	4 (16.0)
No. (%) treatment stopped due to AE **during open-label**	0	3 (8.8)	4 (16.0)
No. (%) ECG abnormalities **during open-label**			
Pathologic QTcB	0	0	0
QTcB or QTcF change of clear concern	1 (6.3)	1 (5.6)	1 (9.1)
Safety parameters in the overall trial			
ESRS	No consistent changes were noted in ESRS scores or the need for antiparkinson treatment. The average level of EPS was low throughout the trial. The only statistical significance between RIS and PLA ESRS scores at End point DB or at maximum change was seen in Questionnaire at End point and which favoured placebo (p=0.021, Van Elteren test).		

Vital signs	No clinically relevant abnormalities were seen in blood pressure or heart rate throughout the trial (DB and OL).
Body weight	The mean weight change at End point in the RIS group (+2.42 kg at End point DB) was statistically significantly larger than that of the PLA (mean change of 0.51 kg) group ($p<0.001$ paired t-test vs. Baseline). At End point of the OL phase, there was a mean weight increase of +1.44 kg in the PLA group (now receiving RIS), of 1.16 kg in the RIS group, and of +1.34 kg in the HAL group, compared to the weight reached at the End point of the DB phase.
Laboratory safety	There were no consistent changes or clinically relevant abnormalities in the laboratory results throughout the trial.

Conclusion: The efficacy results showed that risperidone was superior to placebo as an adjunctive therapy to mood stabilizers in the treatment of manic episodes associated with Bipolar Disorder. Risperidone was statistically significantly superior to placebo on the primary efficacy parameter, change from the Young Mania Rating Scale score relative to Baseline after three weeks of double-blind treatment ($p = 0.009$). The efficacy shown on the primary variable was supported by the clinical benefit seen in the Clinical Global Impression of Change ratings and the number of patients who showed therapuetic response on the Young Mania Rating Scale.
Analyses of 3-week double-blind as well as 10-week open-label safety data provided no suggestion of a unique safety concern with the use of risperidone in patients with bipolar disorder suffering a manic or mixed episode.