SYNOPSIS

Trial identification

Company: Johnson & Johnson Pharmaceutical Research and Development, L.L.C. **Finished product**: Risperdal® **Active ingredient**: Risperidone (R64766)		
Title: The Efficacy and Safety of Flexible Dosage Ranges of Risperidone vs Placebo in the Treatment of Manic Episodes Associated With Bipolar I Disorder	**Trial No**.: RIS-USA-239 **Clinical phase**: III	
Investigator: Multicenter	**Country**: USA	
Reference: J&JPRD, Clinical Study Report RIS-USA-239, 9 OCT 2002 (EDMS-PSDB-2059592)		
Trial period: Start: 29 November 2000 End: 23 May 2002	**No. of investigators**: 29 **No. of patients entered**: 337 **No. of patients randomized**: 262	

Protocol summary

Indication / objectives: The primary objective of this trial was to assess the anti-manic efficacy of risperidone relative to placebo during 3 weeks of treatment in patients with Bipolar I disorder who are suffering a manic episode. Secondary trial objectives included: 1) to determine whether risperidone is associated with either improvement or worsening in comorbid depressive symptoms, 2) to estimate the time of onset of maintained anti-manic clinical response to risperidone, 3) to assess the safety and tolerability of risperidone, and 4) to explore pharmacokinetic relationship to efficacy and safety of risperidone.

Trial design: This was a 3-week, randomized, double-blind, parallel-group, multicenter, placebo-controlled Phase 3 trial conducted in (initially) hospitalized patients with Bipolar I disorder who were experiencing a manic episode (according to DSM-IV).

Main selection criteria:

Inclusion criteria:

- Patients must have been 18 years of age or older.
- Female patients were either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (oral or parenteral hormonal contraceptives; intrauterine device; barrier and spermicide. Abstinence was not considered an acceptable method, except while the patient was hospitalized in a sex-segregated unit.
- Female patients must have had a negative urine pregnancy test at screening and at baseline.
- Patients or their legal representatives provided informed consent and signed an informed consent document prior to screening.
- Patients must have met DSM-IV criteria for Bipolar I Disorder, Most Recent Episode Manic (296.4x). Other Axis I and II disorders except those listed below were allowable.
- Patients were voluntarily hospitalized at the time of enrollment. The primary diagnosis prompting the hospital admission must have been the current manic episode.
- Patients had a history of at least one documented manic or mixed episode that required treatment prior to screening. Such manic episodes must not have been “manic-like” episodes in that they must not have been caused by somatic antidepressant treatment.
- Patients must have received a total score of at least 20 on the Young Mania Rating Scale (YMRS) at screening and at baseline.
- Patients had less than or equal to 20 on the Montgomery Asberg Depression Rating Scale (MADRS) at baseline.

Exclusion criteria:

- Patients who met DSM-IV criteria for Schizoaffective Disorder.
- Patients who met DSM-IV criteria for rapid cycling.
- Patients who had a known or suspected borderline or antisocial personality disorder.
- Patients who had a known or suspected history of substance dependence (excluding nicotine and caffeine) according to DSM-IV criteria within the three months prior to screening.
- Patients who were believed by the investigator to be at significant risk for suicidal or violent behavior during the course of the trial.
- Female patients who were pregnant or nursing.
- Patients who had a known or suspected seizure disorder.
- Patients who had a known or suspected history of other serious, unstable illnesses; patients must have been otherwise healthy on the basis of a physical examination, medical history, electrocardiogram, and the results of blood biochemistry, hematology, and urinalysis tests.
- Patients for whom results of serum ALT or AST tests were greater than twice the upper limit of the central laboratory's reference range. Patients were eligible for enrollment when the results of any other biochemistry, hematology, or urinalysis tests were not within the central laboratory's reference ranges only when the investigator judged the deviations not to be clinically noteworthy.
- Patients who had hypo- or hyper-thyroidism unless stabilized on appropriate medication for at least 3 months prior to screening (a normal TSH was required prior to randomization).
- Patients whose YMRS total score at baseline had decreased by 25% or more from their screening score.
- Patients who had received an antidepressant medication or electroconvulsive therapy within the 4 weeks prior to screening. Antidepressant medications include known antidepressants used for other indications (e.g., anxiety disorders, sleep disturbance, smoking cessation) as well as St. John's Wort.
- Patients who had a history of neuroleptic malignant syndrome (NMS) or similar encephalopathic syndrome.
- Patients who, by history, had received within 3 days prior to baseline, any psychotropic medication prohibited in the Concomitant Therapy section of the protocol. (Such patients could be enrolled no sooner than the following day and with the concurrence of the Sponsor if the investigator determined that their symptoms were much worse relative to screening.)
- Patients who were receiving antiparkinsonian drugs or beta-adrenergic blockers at baseline.
- Patients who received cocaine, phencyclidine, amphetamine, methylphenidate, pemoline, an opioid, or a hallucinogen within 3 days prior to baseline, as evidenced by history or as suggested by a positive urine drug screen (UDS).
- Patients who had been intoxicated with alcohol within 3 days prior to baseline, as evidenced by history or as suggested by a blood alcohol level (BAL) of greater than or equal to 100 mg/dl at screening. (Such patients may have been enrolled no sooner than the following day and with the concurrence of the Sponsor if the investigator determined that their symptoms were much worse relative to screening.)
- Patients who received clozapine within 1 month prior to screening.
- Patients who received a depot antipsychotic within one treatment cycle prior to screening.
- Patients who had a known or suspected history of hypersensitivity or intolerance to risperidone.
- Patients who had a history of a poor anti-manic response to an antipsychotic drug which was used as the sole anti-manic agent.
- Patients who had a known or suspected history of severe drug allergy or hypersensitivity.
- Patients who had previously participated in this trial.
- Patients who had participated in any investigational drug trial within 3 months prior to screening.
- Patients who had an anticipated life expectancy of 6 months or less.

Time and Events Schedule (RIS-USA-239)

Visit	Screening	Double-blind (DB) treatment									
		Baseline						DB Wk 1		DB Wk 2	DB Wk 3[a]
Day	-3 to -1	1	2	3	4	5	6	7	8[b]	14	21
Consent	X										
Psych evaluation/ Medical history	X										
Physical exam[a]	X										X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Body weight		X						X		X	X
ECG		X						X			X
Labs, urinalysis, urine pregnancy test[c]	X[d]	X									X
BAL, UDS, DNA analysis[e]	X										
PK sampling[f]								X			X
SCID	X										
YMRS	X	X		X				X		X	X
PANSS		X						X		X	X
CGI-Severity		X		X				X	X[g]	X	X
GAS		X		X				X		X	X
MADRS		X		X				X		X	X
ESRS[h]		X						X		X	X
Pre-assessment for lorazepam use	X	X		X				X		X	X
Trial drug administration		X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X
Hospital discharge[i]									X		

[a] DB Week 3 assessments and repeat physical exam done if patient prematurely withdrew from trial.
[b] Day 8 assessments conducted on each subsequent day of inpatient hospitalization, except for CGI (see footnote g).
[c] For patients who entered Treatment Period within 48 hours of the collection of screening samples, only a baseline urine pregnancy test (females) was needed and the central lab provided testing kits to the investigational sites.
[d] If serum glucose >250 mg/dL (13.87 mmol/L) at screening, Hb_{A1c} was also measured.
[e] Blood alcohol level (BAL) and urine drug screen (UDS) obtained only at screening; genotype could be obtained once at either screening, baseline or DB Week 3.
[f] All blood for PK samples was to be drawn immediately before the intake of trial medication (pre-dose), except that on Day 7 a second sample was to be drawn post-dose at least 1 hour after the first withdrawal.
[g] The CGI-Severity was to be assessed on the day of discharge. However, a CGI-S performed within 24 hours prior to discharge could be used as the basis of discharge.
[h] Additional ESRS was to be performed immediately prior to initiation of antiparkinsonian medication
[i] If criteria were met.

Treatment		
Form – dosing route	Matching tablets – oral	
Medication	Placebo tablets	Risperidone tablets (1 mg)
Batch numbers	00B16/F07	99J04/F5
Dosage	Day 1: 3 mg; Day 2: 2-4 mg; Day 3: 1-5 mg; Days 4-21: 1-6 mg	
Duration of treatment	3 weeks double-blind placebo or risperidone treatment	
Duration of trial	3 weeks	
Disallowed medication	The following psychotropic drugs were not allowed within 3 days (at a minimum) prior to the baseline visit or during the trial except as indicated below. • Anticonvulsant drugs. • Antidepressant drugs/St. John's Wort (prohibited within 4 weeks of screening). • Anti-manic drugs. • Antipsychotics/neuroleptics, other than trial medication. • Cognition enhancers. • Dopamine-releasing or dopamine agonist drugs. • Lithium. • Sedatives/hypnotics/anxiolytics (lorazepam was permitted except in 8 hours prior to behavioral assessments). • Other drugs or herbal preparations used by the patient for a psychotropic effect (e.g., Gingko Biloba, kava kava).	

Variable	**Statistical methods**
Efficacy	
Change from baseline in total YMRS, CGI-S, GAS, total PANSS, MADRS scores at every timepoint	ANCOVA model including treatment group, investigator, and baseline psychosis as factors and baseline value as a covariate. The difference in LSMeans between RIS and placebo groups was used in comparing between treatment groups in efficacy. Within-group comparisons paired t-test.
50% improvement in total YMRS score	CMH test controlling for investigator and psychosis for comparison between risperidone and placebo treatment groups.
Change from baseline in Total YMRS at Day 3, Weeks 1, 2, and 3	Longitudinal analysis using a mixed effects model
Onset of maintained response measured by total YMRS score	CMH test for row mean score difference, controlling for investigator and psychosis
Safety	
Adverse events	Number and % of patients with adverse event by treatment group
Change from baseline in vital signs, body weight, ECG, ESRS, and laboratory safety	Descriptive statistics (N and % of patients exceeding pre-defined limits, mean, and SE) were estimated for each treatment group. Ordered ridit score (Van Elteren) test controlling for investigator and psychotic features used for between-treatment group comparisons. Within-group comparisons made with paired t-test or Wilcoxon signed-rank, as appropriate.
Pharmacokinetics	Descriptive statistics of the concentration of the active moiety, risperidone, and 9-hydroxy-risperidone at each timepoint.

Main features of the patient sample and summary of the results

Baseline characteristics - patient disposition	Placebo N =125	Risperidone N = 134
Number of patients treated (M/F)	76/49	71/63
Age: mean (SE), yrs	39.5 (1.09)	38.1 (1.03)
Age: median (min; max), yrs	39.0 (18; 69)	37.0 (18; 69)
BMI: mean (SE)	29.64 (0.707)	29.38 (0.636)
Discontinuation of treatment – total n (%)	73 (58.4)	59 (44.0)
Adverse event	7 (5.6)	10 (7.5)
Insufficient response	45 (36.0)	19 (14.2)
Other	1 (0.8)	1 (0.7)
Patient lost to follow-up	0	4 (3.0)
Patient non-compliant	1 (0.8)	3 (2.2)
Patient withdrew consent	19 (15.2)	22 (16.4)
Trial medication[a]		
Mean number tablets per day, mean (SE)	4.63 (0.080)	3.98 (0.093)
Mode number tablets per day, mean (SE)	5.0 (0.11)	4.1 (0.12)

BMI: Body mass index
a: risperidone 1 tablet = 1 mg

Pharmacokinetics

Descriptive statistics of the plasma concentrations (ng/mL) of the active moiety, risperidone and 9-hydroxy-risperidone at each visit (normalized to a 4-mg dose)

Visit	**N**	**Median time after last drug intake (min – max) (h)**	**Mean ± SD**	**Median (min – max)**
Active moiety				
Week 1 predose	87	22.00 (13.08 - 31.58)	20.8 ± 10.0	19.4 (0.36 - 60.6)
Week 1 postdose	89	1.00 (0.08 - 2.03)	39.9 ± 20.1	37.1 (0.33 - 103)
Week 3 predose	73	17.58 (7.75 - 25.00)	27.4 ± 15.7	24.3 (0.13 - 66.8)
Risperidone				
Week 1 predose	87	22.00 (13.08 - 31.58)	2.34 ± 5.04	0.37 (NQ[a] - 26.8)
Week 1 postdose	89	1.00 (0.08 - 2.03)	15.7 ± 13.4	12.0 (NQ - 61.1)
Week 3 predose	73	17.58 (7.75 - 25.00)	4.99 ± 8.59	0.87 (NQ - 41.6)
9-hydroxy-risperidone				
Week 1 predose	87	22.00 (13.08 - 31.58)	18.4 ± 8.69	17.2 (0.36 - 51.8)
Week 1 postdose	89	1.00 (0.08 - 2.03)	24.2 ± 10.3	23.2 (0.33 - 65.7)
Week 3 predose	73	17.58 (7.75 - 25.00)	22.4 ± 13.0	19.6 (0.13 - 59.5)

a: not quantifiable by the LC-MS/MS-method

Efficacy

Primary variable	
Change from baseline at Week 3 LOCF/endpoint in total YMRS score	
Placebo (N=119)	**Risperidone (N=127)**
-5 (0.87)	-11.1 (0.90) ***

Secondary variables				
Visit	**Placebo**		**Risperidone**	
Total YMRS score – Change from baseline at Day 3, Week 1, and Week 2				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	118	-4.3 (0.49)	124	-6.9 (0.62) ***
Week 1 LOCF	119	-5.1 (0.71)	127	-10.5 (0.81) ***
Week 2 LOCF	119	-5.4 (0.86)	127	-11.4 (0.84) ***
YMRS response rate (≥50% decrease from baseline)				
	N	**n (%)**	**N**	**n (%)**
Day 3 LOCF	118	7 (6%)	124	16 (13%)
Week 1 LOCF	119	20 (17%)	127	45 (35%) **
Week 2 LOCF	119	26 (22%)	127	52 (41%) **
Week 3 LOCF/Endpoint	119	28 (24%)	127	54 (43%) **
CGI-severity – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	119	-0.2 (0.05)	124	-0.4 (0.07) **
Week 1 LOCF	120	-0.6 (0.08)	127	-1.0 (0.10) ***
Week 2 LOCF	120	-0.5 (0.09)	127	-1.2 (0.11) ***
Week 3 LOCF/Endpoint	120	-0.5 (0.11)	127	-1.2 (0.12) ***
GAS – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	117	3.2 (0.68)	123	4.1 (0.52)
Week 1 LOCF	119	5.8 (0.91)	126	10.0 (1.02) ***
Week 2 LOCF	119	5.9 (1.08)	126	12.3 (1.20) ***
Week 3 LOCF/Endpoint	119	6.1 (1.28)	126	12.9 (1.35) ***
PANSS – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Week 1 LOCF	111	-3.2 (1.41)	122	-8.6 (1.60) **
Week 2 LOCF	111	-2.1 (1.60)	122	-10.1 (1.64) ***
Week 3 LOCF/Endpoint	112	-1.5 (1.71)	122	-10.0 (1.69) ***
MADRS – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	118	-0.8 (0.36)	124	-1.7 (0.33) *
Week 1 LOCF	119	-0.5 (0.49)	127	-2.4 (0.45) **
Week 2 LOCF	119	-0.5 (0.54)	127	-2.1 (0.47) *
Week 3 LOCF/Endpoint	119	-0.1 (0.58)	127	-1.6 (0.56)
Onset of maintained YMRS response – n (%)				
	Placebo (N=119)		**Risperidone (N=127) ***	
Day 3	2 (2%)		8 (6%)	
Week 1	9 (8%)		14 (11%)	
Week 2	8 (7%)		12 (9%)	

LOCF=last observation carried forward.

* p value <0.05, ** p value <0.01, *** p value <0.001 indicates significant difference between placebo and risperidone.

A negative change indicates a decrease from the baseline mean.

For all but GAS, a negative mean change indicates an improvement from baseline.

Risperidone was superior to placebo in the treatment of acute manic episodes associated with Bipolar disorder, as measured by the primary efficacy variable, mean change from baseline to endpoint in the YMRS total score over a 3-week period.

Safety (N = number of patients with data)	**Placebo** **N = 125**	**Risperidone** **N = 134**
Most frequently reported (≥10%) adverse events (preferred term)		
• Hyperkinesia	6 (4.8)	21 (15.7)
• Headache	19 (15.2)	19 (14.2)
• Dizziness	11 (8.8)	15 (11.2)
• Somnolence	9 (7.2)	38 (28.4)
• Dyspepsia	7 (5.6)	15 (11.2)
• Nausea	2 (1.6)	15 (11.2)
No. (%) with one or more adverse event	88 (70.4)	118 (88.1)
No. (%) of deaths	2 (1.6)	0
No. (%) with one or more serious adverse event	10 (8.0)	17 (12.7)
No. (%) treatment stopped due to adverse event	7 (5.6)	10 (7.5)
No. (%) with EPS-related adverse event	21 (16.8)	49 (36.6)
No. (%) with glucose-related adverse event	1 (0.8)	2 (1.5)
No. (%) with prolactin-related adverse event	2 (1.6)	8 (6.0)
Mean (SE) weight change from baseline to endpoint	-0.25 (0.22)	1.63 (0.19)***

ESRS	• There was a statistically significant difference between the treatment groups in ESRS Parkinsonism/Dystonia/Dyskinesia total change from baseline to endpoint. More of the patients who exhibited a worsening were in the risperidone group. The extent of the change for most of those patients was small: 1-5 points, on a scale with a total range of 0-102. This is consistent with EPS-related adverse events being mostly rated as mild in severity
Vital signs	• There were no unexpected findings with regard to vital signs.
ECG	• There were no clinically meaningful differences in ECG parameters between treatment groups. No patients in either treatment group had a QTc >500 ms, regardless of correction used.
Clinical laboratory values	• There were no clinically important changes in mean laboratory values, except for increased prolactin in the risperidone group.

***: $p<0.001$ for comparison with placebo

There were no unexpected adverse events. Of the EPS-related adverse events in the risperidone group, 62.5% were rated as mild and 36.1% were rated as moderate. In the risperidone group there was 1 patient who discontinued due to EPS-related adverse events, which were rated as moderate in severity.

Conclusions

Risperidone with flexible-doses of 1 to 6 mg/day was effective as monotherapy in the treatment of acute manic episodes associated with Bipolar I disorder over a 3-week period without induction of depression. This treatment was safe and generally well-tolerated; there were no unexpected adverse events.