SYNOPSIS

Trial identification:

Company: Johnson & Johnson Pharmaceutical Research and Development, L.L.C **Finished product**: RISPERDAL® tablet **Active ingredient**: Risperidone (R064766)		
Title: The Efficacy and Safety of Flexible Dose Ranges of Risperidone vs. Placebo or Divalproex Sodium in the Treatment of Manic or Mixed Episodes Associated With Bipolar I Disorder	**Trial No**.: RIS-USA-240 **Clinical phase**: III	
Investigator: Multicenter	**Country**: USA	
Reference: J&JPRD, Clinical Study Report RIS-USA-240 (EDMS-PSDB-1881045)		
Trial period: Start: 23 April 2001 Last patient out: 14 September 2001 Trial termination date: 16 August 2001 Trial terminated for business reasons	**No. of investigators**: 19 **No. of patients planned:** 432 **No. of patients entered**:68 **No. of patients randomized**: 39	

Protocol summary

Indication / objectives:Manic or mixed episodes associated with Bipolar I disorder / To assess the anti-manic efficacy of risperidone relative to placebo during 3 weeks of treatment in patients with Bipolar 1 disorder who are suffering a manic or mixed episode. The third treatment group, divalproex sodium, is used only as an active control for assay sensitivity.
Trial design: randomized, double-blind, parallel group, multicenter
Main inclusion criteria: Patients must be 18 years of age or older. Female patients had to be 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 an acceptable method). Female patients had a negative urine pregnancy test at screening and baseline. Patients or their legal representative provided informed consent and signed the informed consent form. Patients met the diagnosis of Bipolar I disorder according to the DSM-IV criteria, Most Recent Episode Manic (296.4x), or Most Recent Episode Mixed (296.6x). Other Axis I and II disorders except those listed below were acceptable. Patients were hospitalized voluntarily at the time of enrollment. The primary diagnosis prompting the hospital admission had to be the current manic or mixed episode. Patients had to have at least one prior documented manic or mixed episode that required treatment prior to screening. Such manic and mixed 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 Young Mania Rating Scale (YMRS) score of at least 20 at screening and baseline. • Patients must not have had other serious, unstable illnesses and were otherwise physically healthy on the basis of a physical examination, medical history, electrocardiogram and the results of blood biochemistry, hematology tests and a urinalysis.
Main exclusion criteria: Patients met DSM-IV criteria for schizoaffective disorder. Patients met DSM-IV criteria for rapid cycling. Patients had a known or suspected borderline or antisocial personality disorder. Patients had a known or suspected history of alcohol or drug abuse or dependence, (excluding nicotine and caffeine) according to DSM-IV criteria within 3 months prior to screening. Patients,who as judged by the investigator, to be at significant risk for suicidal or violent behavior during the trial. Female patients were pregnant or breast-feeding.

Patients had a known or suspected seizure disorder.
If ALT or AST test results were more than twice the upper limit of the central laboratory reference range. If results of any other biochemistry, hematology or urinalysis tests were not within the central laboratory's reference ranges, the patient can be enrolled if the investigator judges the deviations are not clinically significant.
Patients with hypo- or hyperthyroidism, unless stabilized on appropriate medication for at least 3 months prior to screening (a normal TSH was required prior to randomization);
Patients whose Young Mania Rating Scale total score at baseline was ≥ 25% lower than their screening score;
Patients received an antidepressant medication or electroconvulsive therapy within the 4 weeks prior to screening;
Patients had a history of neuroleptic malignant syndrome (NMS) or similar encephalopathic syndrome;
Patients had received any prohibited concomitant therapy of psychotropic medication within 3 days prior to baseline. Such patients could be enrolled (no sooner than the following day and with the concurrence of the sponsor) if the investigator determines that their symptoms were much worse relative to screening;
Patients received antiparkinsonian drugs or beta-adrenergic blockers at baseline;
Patients had 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 done at screening (Patients could not be enrolled sooner than the following day and with the concurrence of the sponsor) if the investigator determines that their symptoms are much worse relative to screening;
Patients were intoxicated with alcohol within 3 days prior to baseline, as evidenced by history or as suggested by a blood alcohol level of ≥ 100 mg/dL at screening. (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 had received clozapine within 1 month prior to screening;
Patients had received a depot neuroleptics within one treatment cycle prior to screening;
Patients had a known or suspected history of hypersensitivity or intolerance to risperidone;
Patients had a history of a poor anti-manic response to an antipsychotic drug which was used as the sole anti-manic agent;
Patients had a known or suspected history of hypersensitivity or intolerance to divalproex sodium;
Patients had a known or suspected history of severe drug allergy or hypersensitivity (i.e., Stevens-Johnson syndrome);
Patients had previously participated in this trial;
Patients had participated in any investigational drug trial within 3 months prior to screening;
Patients had an anticipated life expectancy of 6 months or less.

Treatment			
Form – dosing route	Matching tablets – oral		
Medication	Placebo tablets	Risperidone tablets 1 mg	Divalproex sodium 250 mg capsules
Batch number	00F26/F07 00F27/F07 00C13/F07 00K06/F125	00B18/F05	00K13/F242
Daily Dosage	DB Day 1: risperidone 3 mg/day; divalproex 750 mg/day; and placebo DB Day 2: risperidone 2-4mg/day; divalproex: 750 mg/day; and placebo DB Day 3: risperidone 1-5 mg/day; divalproex 1000 mg/day; and placebo DB Day 4-21: risperidone 1-6 mg/day; divalproex 250 to 2500 mg/day; and placebo		
Duration of treatment	Wash-out 1-3 days, double-blind treatment: 3 weeks; and a 2-week taper down period following the double-blind treatment		
Duration of trial	Same as above		

Disallowed medication	Anti-convulsants; anti-depressants/ 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, other possible psychotropics used by the patient for a psychotropic effect (e.g., gingko biloba, kava kava.)

Assessments **Double-blind Day**	Screen -3 to -1	Baseline 1	 3	Week 1 7	 8	Week 2 14	Week 3 21
Plasma concentration of risperidone				X			X
Serum conc. Divalproex sodium			X		X		
Efficacy							
Primary variable: YMRS	X	X	X	X		X	X
Secondary variables:							
- CGI-Severity		X	X	X	X	X	X
- GAS		X	X	X		X	X
- MADRS		X	X	X		X	X
- PANSS		X		X		X	X
Safety							
Adverse events, ESRS		X	X	X	X	X	
Clinical laboratory	X	X					X
Physical exam	X			X			X
SCID (screening)	X						
ECG		X		X			X
Vital signs	X	X	X	X		X	X
Weight		X		X		X	X

YMRS: Young Mania Rating Scale, CGI-Severity: Clinical Global Impression of Illness item, GAS: Global Assessment Scale, MADRS: Montgomery Asberg Depression Rating Scale, PANSS: Positivie and Negative Syndrome Scale, ECG: electrocardiogram, ESRS: Extrapyramidal Symptom Rating Scale, SCID: Structured Clinical Interview

Statistical methods	Intent-to-treat analysis, paired t-test, Wilcoxon matched-pairs signed-ranks test; no formal between treatment group comparisons were made.

Main features of the subject sample and summary of the results

Baseline characteristics – subject disposition	Placebo N=15	Risperidone N=14	Divalproex sodium N=10
Number of subjects randomized (M/F)	15 (6/9)	14 (7/7)	10 (4/6)
Age: mean (± SE), yrs	40.1(2.12)	40.6 (3.18)	35.5 (3.65)
Age: median (min-max), yrs	39.0(22;53)	41.5 (19;58)	36.5 (18;51)
Discontination of treatment – reason	6 (40.0%)	8 (57.1%)	4 (40.0%)
Adverse event	2 (13.3%)	4 (28.6%)	0
Insufficient response	3 (20.0%)	1 (7.1%)	2 (20.0%)
Other	0	0	1 (10.0%)
Subject non-compliant	1 (6.7%)	0	1 (10.0%)
Subject withdrew consent	0	3 (21.4%)	1 (10.0%)

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 (min-max) after last drug intake (h)**	**Mean ± SD**	**Median (min – max)**
Active moiety				
Week 1 predose	8	13.58 (11.50 – 14.17)	37.0 ± 22.2	27.5 (17.2 – 78.6)
Week 1 postdose	11	1.08 (0.58 – 3.17)	38.5 ± 19.6	30.7 (16.0 – 73.4)
Week 3 predose	3	30.67 (23.83 – 47.78)	13.5 ± 8.5	9.76 (7.52 – 23.3)
Risperidone				
Week 1 predose	8	13.58 (11.50 – 14.17)	2.80 ± 3.81	0.96 (NQ – 11.2)
Week 1 postdose	11	1.08 (0.58 – 3.17)	2.20 ± 2.88	1.12 (NQ – 9.98)
Week 3 predose	3	30.67 (23.83 – 47.78)	0.41 ± 0.62	0.11 (NQ – 1.12)
9-hydroxy-risperidone				
Week 1 predose	8	13.58 (11.50 – 14.17)	34.2 ± 18.7	26.5 (16.7 – 67.4)
Week 1 postdose	11	1.08 (0.58 – 3.17)	36.3 ± 17.4	29.6 (15.7 – 63.4)
Week 3 predose	3	30.67 (23.83 – 47.78)	13.1 ± 7.9	9.76 (7.41 – 22.2)

NQ: not quantifiable by the LC-MS/MS-method (<0.10 ng/mL)

Efficacy	Placebo (N=15)	Risperidone (N=14)	Divalproex sodium (N=10)
Primary variable Change in total YMRS score from baseline; mean (SE)	-6.6 (2.86)	-10.4 (3.35)	-13.6 (3.31)
Secondary variable Change in CGI-severity from baseline; mean (SE)	-0.9 (0.42)	-1.0 (0.47)	-1.4 (0.43)

Safety	Placebo (n=15)	Risperidone (n=14)	Divalproex sodium (n=10)
Adverse events (AE) Most frequently reported AE's in 3 or more patients in any treatment group:			
Headache	6 (40.0%)	3 (21.4%)	3 (30.0%)
Nausea	4 (26.7%)	2 (14.3%)	1 (10.0%)
Anxiety	2 (13.3%)	3 (21.4%)	1 (10.0%)
Insomnia	3 (20.0%)	2 (14.3%)	2 (20.0%)
Somnolence	3 (20.0%)	2 (14.3%)	1 (10.0%)
No. (%) with one or more AE	11 (73.3%)	11 (78.6%)	7 (70.0%)
No. (%) of deaths	0	1 (7.1%)	0
No. (%) with one or more serious AE	1 (6.7%)	3 (21.4%)	0
No. (%) treatment stopped due to AE	2 (13.3%)	4 (28.6%)	0
No. (%) with EPS-related adverse event	2 (13.3)	5 (35.7)	3 (30.0)
No. (%) with glucose-related adverse event	0	0	0
No. (%) with potentially prolactin-related adverse event	0	0	0
Clinical laboratory parameters	No between group differences or clinically important changes were observed		
Vital signs and physical findings	No between group differences or clinically important changes were observed		
Electrocardiogram	No between group differences or clinically important changes were observed		
ESRS	No between group differences or clinically important changes were observed		

ESRS = Extrapyramidal Symptom Rating Scale

Conclusions

Given that the trial was terminated for business reasons and less than 10% of the number of planned patients were enrolled, no meaningful conclusions could be made.