SYNOPSIS

Trial identification

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Risperidone depot microspheres **Active ingredient**: risperidone (R064766)		
Title: Risperidone depot (microspheres) vs. placebo in the treatment of patients with schizophrenia	**Trial No**.: RIS-USA-121 **Clinical phase**: III	
Investigator: Multicenter (47 sites)	**Country**: USA	
Reference: JRF, Clinical Research Report RIS-USA-121, 17 May 2001 (EDMS-USTI-2714267)		
Trial period: Start: 21 October 1999 End: 15 December 2000	**No. of investigators: 47** **No. of patients entered: 641** (554 schizophrenia/67 schizoaffective disorder) **No. of patients randomized: 439** (400 schizophrenia/39 schizoaffective disorder)	

Protocol summary

Indication / objectives: Schizophrenia / Primary objective: To compare the efficacy of risperidone depot microspheres 25 mg, 50 mg, or 75 mg with placebo depot on the symptoms of schizophrenia over a 12-week period. The study was powered to demonstrate a statistically significant difference from placebo depot for at least one dose of risperidone depot microspheres on change from baseline to endpoint in total PANSS. Secondary objectives: To document the safety and effects on quality of life of risperidone depot in patients with schizophrenia treated for up to 12 weeks and to assess steady-state plasma concentrations.

Trial design: Multicenter, randomized, double-blind, parallel-group study

Main inclusion criteria:

- Age between 18 and 55, inclusive;
- Diagnosis of schizophrenia according to the DSM IV criteria (295.10, 295.20, 295.30, 295.60, 295.90); (amendment on 25 February 2000 after trial start date excluded patients with schizoaffective disorder)
- Baseline Positive and Negative Syndrome Scale (PANSS) score of ≥60 and ≤120 (1-7 scoring);
- Patient and, when appointed, patient's guardian or legal representative, had signed the informed consent form;
- Patient was otherwise healthy on the basis of a pre-trial physical examination, medical history, electrocardiogram and the results of blood biochemistry, hematology tests and a urinalysis performed within a week of the start of the open risperidone run-in period. If the results of the biochemistry or hematology tests or the urinalysis testing were not within the laboratory's reference ranges, the patient could have been included only on condition that the investigator judged that the deviations were not clinically significant. This was clearly recorded in the source documents and in the CRF as a pre-existing condition. A negative urine pregnancy test, if the patient was a female of childbearing potential, prior to the run in phase.

Main exclusion criteria:

- Patients currently receiving treatment with a depot antipsychotic (last injection within 120 days of screening);
- A DSM IV Axis I diagnosis other than schizophrenia;
- DSM IV diagnosis of substance dependence within 3 months prior to the screening visit (Visit 1) was exclusionary, but nicotine and caffeine dependencies were not exclusionary;
- Tardive dyskinesia, if present, was associated with more than mild symptomatology in the opinion of the investigator.
- History of neuroleptic malignant syndrome;
- Documented organic disease of the central nervous system including, but not limited to stroke, tumor, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, history of brain trauma resulting in significant impairment, chronic infection, neurosyphilis;

- Acute, unstable and/or significant and untreated medical illness (e.g., infection, unstable diabetes, uncontrolled hypertension, unstable angina);
- Current seizure disorder requiring medication;
- A clinically significant ECG abnormality in the opinion of the investigator;
- Pregnant or breast-feeding female;
- Female patient of childbearing potential without adequate contraception. Adequate contraception included: abstinence, oral contraceptives, intrauterine devices, barrier method (diaphragm or condom) plus spermicide, Norplant™ or Depo Provera™;
- Use of disallowed concomitant therapy;
- Patients who had received new antidepressant drug treatment for depression or who had received different dosages of their current antidepressant drug treatment in the three months preceding the run-in period;
- Participation in an investigational drug trial in the 30 days prior to the run-in period;
- Known sensitivity or intolerance to risperidone;
- Patients known to be unresponsive to risperidone;
- Patients known to be refractory to typical neuroleptics;
- History of severe drug allergy or hypersensitivity;
- Patients at risk for violent behavior against other individuals;
- Patients with current suicidal ideation.

Treatment		
Form – dosing route	Run-in period: oral risperidone Double-blind period: oral risperidone, risperidone depot microspheres, placebo tablets, and placebo depot	
Medication	Batch number	Expiration Date
Placebo tablets	98J12/F07, 00B16/F07	Oct-01, Feb-05
Risperidone 2 mg	98D22/F13, 99J05/F13	April-03, Oct-04
Risperidone 4 mg	99E18/F12	May-01
Risperidone 6 mg	99E19/F11	May-01
For IM administration		
Placebo depot	165-2738BA/F110, 165-0950AA	Oct-00, Apr-02
Placebo solvent	00DS096	Apr-02
Diluent	99ES044/F101	June-01
Risperidone depot 25 mg	164-2438BB/F109, 164-0100AB	Aug-00, Jan-02
Risperidone depot 50 mg	164-2298AB/F109, 164-0100AA	Aug-00, Jan-02
Risperidone depot 75 mg	164-2438BA/F109, 164-0240CB	Aug-00, Jan-02
Dosage	• Run-in Phase: Titration to 4 mg/day oral risperidone • Double-blind Phase: Placebo depot, risperidone depot microspheres 25, 50, or 75 mg every 2 weeks, supplemented for the first 3 weeks of double-blind treatment with oral placebo, 2, 4, or 6 mg oral risperidone daily, respectively.	
Duration of treatment	• Screening: 1 week • Run-in Phase: 1 week • Double-blind Phase: 12 weeks	
Duration of trial	• 14 weeks	
Disallowed concomitant therapy	• Antipsychotic medications other than risperidone; • Mood stabilizers (lithium, valproate, carbamazepine, lamotrigene, gabapentin, topiramate); • Psychostimulants (methylphenidate, dexedrine, pemoline); and • Antidepressants (unless the dose was stable for 3 months prior to screening and was kept constant during the trial).	

Assessments	Visits could be conducted within 3 days (±) of the scheduled assessment day. Visit 1=screening, Visit 2= start of run-in, and Visit 3= start of double-blind period.
Physical examination	Visits 1 and 17
Medical history	Visit 1
Psychiatric history	Visit 1
PK Samples	Visits 3, 4, 5, 6, 7, 8, 10, 12, 13, 15, and 17 (Samples were drawn immediately before depot injection.)
Efficacy	
• Primary variable	
- PANSS	Visits 1, 3, 5, 7, 10, 12, 15, and 17
• Secondary variables	
- CGI	Visits 3, 5, 6, 7, 9, 10, 11, 12, 14, 15, 16, and 17
- CGI-C	Visits 5, 6, 7, 9, 10, 11, 12, 14, 15, 16, and 17
Quality of Life	
• SF-36	Visits 3 and 17 (administered prior to any procedures)
Safety	
• Adverse events	Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, and 17
• Clinical laboratory	Visits 1 and 17
• Vital signs	Visits 1, 3, 4, 5, 6, 7, 8, 10, 12, 13, 15, and 17
• ECG	Visits 1, 3, 4, 6, 8, 13, and 17
• ESRS	Visits 1, 3, 5, 7, 10, 12, 15, and 17
• Injection site evaluation	
- Patient (VAS)	Visits 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 15, 16, and 17
- Investigator	Visits 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 15, 16, and 17

Parameter	**Statistical methods**
Efficacy	
Change from baseline in total PANSS and subscales at endpoint	ANCOVA with treatment group, investigator, baseline value as main effects. Pairwise comparisons of RIS groups to placebo using Dunnett's test. Within-group comparisons by paired t-test.
20% improvement in total PANSS, time to first 20% improvement	CMH general association test controlling for investigator, baseline PANSS stratification; Kaplan-Meier product limit method, generalized Wilcoxon test.
CGI	Continuous: ANCOVA with treatment group, investigator, baseline value, PANSS stratification as main effects. Pairwise comparisons of RIS groups to placebo using Dunnett's test. Within-group comparisons by paired t-test. Categorical: CMH mean scores test with modified ridit scores (Van Elteren's test) controlling for investigator, baseline PANSS stratification
Time to discontinuation due to insufficient response	Kaplan-Meier product limit method, generalized Wilcoxon test.
Safety	
Adverse events	Number and % of patients with adverse event by treatment group
Change from baseline in vital signs, body weight, ECG, laboratory safety parameters, ESRS	ANCOVA with treatment group, investigator, baseline value, PANSS stratification as main effects (and baseline ESRS stratification for EPS-related parameters) . Pairwise comparisons of RIS groups to placebo using Fisher's LSD test. Within-group comparisons by paired t-test. % patients exceeding pre-defined limits.
Pharmacokinetics	Descriptive statistics and graphical display of the concentration of the active moiety, unchanged RIS, and 9-OH RIS at each time point by treatment group. Box and whisker plots of active moiety levels versus pooled visits at steady state (predose versus one week after injection).
Pharmacokinetics/ pharmacodynamics	Visual assessment of the potential relationships between PANSS, ESRS, and ECG parameters with active moiety plasma conentrations

Main features of the patient sample and summary of the results are presented in the synopsis for patients with schizophrenia

Baseline characteristics - patient disposition: All randomized with injection and with schizophrenia	Placebo depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg
Number of patients randomized (M/F)	80/18	68/31	84/19	68/32
Age, years, Mean (SE)	37.7 (0.95)	38.9 (0.99)	36.2 (0.93)	38.1 (1.06)
Range	18 – 54	18 – 55	19 - 55	18 - 55
Race, n (%)				
Black	37 (37.8%)	41 (41.4%)	40 (38.8%)	49 (49.0%)
Caucasian	45 (45.9%)	37 (37.4%)	45 (43.7%)	39 (39.0%)
Hispanic	12 (12.2%)	13 (13.1%)	11 (10.7%)	9 (9.0%)
Oriental	1 (1.0%)	5 (5.1%)	4 (3.9%)	1 (1.0%)
Other	3 (3.1%)	3 (3.0%)	3 (2.9%)	2 (2.0%)
Body Mass Index (kg/m^2)	n=94	n=99	n=102	n=100
Mean (SE)	27.8 (0.62)	30.2 (0.79)	28.5 (0.63)	29.6 (0.76)
Range	18 – 49	17 – 59	18 - 48	19 – 61
Weight (kg)	n=95	n=99	n=102	n=100
Mean (SE)	83.6 (1.72)	88.4 (2.04)	87.4 (2.17)	88.2 (2.25)
Range	56 –138	54 –159	49 -159	49 – 153
Schizophrenia type, n (%)				
Catatonic (295.2)	0	0	1 (1.0%)	0
Disorganized (295.1)	2 (2.0%)	2 (2.0%)	6 (5.8%)	3 (3.0%)
Paranoid (295.3)	78 (79.6%)	76 (76.8%)	74 (71.8%)	74 (74.0%)
Undifferentiated (295.9)	18 (18.4%)	21 (21.2%)	22 (21.4%)	23 (23.0%)
Age at onset,	n=91	n=97	n=100	n=97
Mean (SE);	22 (0.66)	22.8 (0.76)	21.4 (0.7)	20.3 (0.63)
Range	(9-42)	(8-44)	(7-42)	(9-43)
Age at first hospitalization,	n=89	n=91	n=94	n=94
Mean (SE);	24.4 (0.8)	25.1 (0.93)	23.3 (0.79)	23.2 (0.91)
Range	(14-47)	(0-47)	(8-45)	(0-50)
Number of previous hospitalizations	n=89	n=96	n=101	n=94
Median (range)	4 (0-28)	3.5 (0-99)	4 (0-50)	4 (0-63)
Discontinuation of treatment	(N = 98)	(N = 99)	(N = 103)	(N = 100)
Discontinued for any reason	67 (68.4%)	51 (51.5%)	53 (51.5%)	52 (52.0%)
Adverse event	12 (12.2%)	11 (11.1%)	12 (11.7%)	14 (14.0%)
Death	1 (1.0%)	0	0	0
Insufficient response	29 (29.6%)	22 (22.2%)	15 (14.6%)	12 (12.0%)
Other	5 (5.1%)	6 (6.1%)	4 (3.9%)	4 (4.0%)
Ineligible to continue the trial	0	3 (3.0%)	3 (2.9%)	2 (2.0%)
Lost to follow-up	6 (6.1%)	2 (2.0%)	3 (2.9%)	6 (6.0%)
Non-compliant	4 (4.1%)	0	3 (2.9%)	3 (3.0%)
Withdrew consent	10 (10.2%)	7 (7.1%)	13 (12.6%)	11 (11.0%)

Drug concentrations Active moiety, ng/ml plasma ±SD	Placebo depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg
Visit 3 (Day 1)	25.3±19.3	28.7±21.1	28.6±24.5	27.1±20.7
Visit 4 (Day 8)	2.08±6.46	20.9±14.7	34.1±24.3	49.0±35.1
Visit 5 (Day 15)	1.04±2.82	21.5±20.0	30.3±21.1	55.3±44.6
Visit 6 (Day 22)	0.40±0.98	22.4±18.6	35.2±23.1	63.3±42.0
Visit 7 (Day 29)	0.15±0.30	11.7±7.66	25.3±15.0	34.9±16.9
Visit 8 (Day 33)	0.10±0.19	17.1±8.83	39.8±25.0	56.5±25.8
Visit 10 (Day 43)	1.75±8.19	18.1±11.5	33.5±18.4	48.6±27.1
Visit 12 (Day 57)	0.44±1.95	17.5±8.81	37.0±19.8	46.9±25.1
Visit 13 (Day 61)	0.17±0.56	20.6±11.9	37.9±24.0	56.3±28.3
Visit 15 (Day 71)	0.04±0.14	17.0±8.34	34.0±19.1	47.5±22.7
Visit 17/Endpoint (Day 85)	2.84±8.93	18.7±9.23	35.5±18.7	44.7±20.6

- Of the 102 patients treated with placebo depot who had pharmacokinetic blood samples drawn, only 5 patients exhibited drug plasma levels greater than 1 ng/mL during any one of the depot injection visits (Visit 6-15).
- The steady-state plasma concentrations increased dose-proportionally with depot doses of 25, 50 and 75 mg.
- There was no evidence of early drug release following depot injections.

Efficacy: intent-to-treat patients with schizophrenia[a]	Placebo depot		RIS depot 25 mg		RIS depot 50 mg		RIS depot 75 mg	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Total PANSS								
Baseline	92	82.0 (1.54)	93	81.7 (1.32)	98	82.3 (1.41)	87	80.1 (1.53)
Endpoint	92	84.5 (2.12)	93	75.6 (2.35)	98	73.6 (2.03)	87	74.5 (2.31)
Change from baseline to endpoint:								
Mean	92	2.5 (1.73)	93	-6.1 (2.08)	98	-8.7 (1.55)	87	-5.6 (1.88)
Least squares mean		2.6		-6.2**		-8.5***		-7.4***
Positive symptoms								
Baseline	92	24.5 (0.57)	93	25.2 (0.53)	98	24.9 (0.55)	87	24.5 (0.65)
Endpoint	92	24.8 (0.79)	93	23.0 (0.81)	98	21.6 (0.66)	87	22.5 (0.85)
Change from baseline to endpoint:								
Mean	92	0.3 (0.65)	93	-2.2 (0.67)	98	-3.4 (0.51)	87	-2.0 (0.67)
Least squares mean		-0.2		-2.3*		-3.5***		-3.0**
Negative symptoms								
Baseline	92	20.0 (0.63)	93	20.2 (0.59)	98	20.1 (0.62)	87	19.0 (0.51)
Endpoint	92	20.5 (0.62)	93	17.4 (0.67)	98	18.5 (0.66)	87	17.9 (0.63)
Change from baseline to endpoint:								
Mean	92	0.4 (0.44)	93	-2.8 (0.62)	98	-1.5 (0.56)	87	-1.1 (0.60)
Least squares mean		0.9		-2.4***		-1.2*		-1.2*

a: All randomized patients with schizophrenia with at least one depot injection and at least one postbaseline PANSS assessment.

Asterisks refer to significant differences with placebo

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

Safety: all randomized patients with injection and schizophrenia	Placebo depot N=98	RIS depot 25 mg N=99	RIS depot 50 mg N=103	RIS depot 75 mg N=100
Adverse events in ≥15% of patients				
Any adverse event	81 (82.7%)	79 (79.8%)	86 (83.5%)	82 (82.0%)
Agitation	24 (24.5%)	15 (15.2%)	11 (10.7%)	20 (20.0%)
Insomnia	14 (14.3%)	16 (16.2%)	13 (12.6%)	16 (16.0%)
Anxiety	15 (15.3%)	7 (7.1%)	6 (5.8%)	14 (14.0%)
Psychosis	23 (23.5%)	15 (15.2%)	10 (9.7%)	12 (12.0%)
Headache	12 (12.2%)	15 (15.2%)	23 (22.3%)	21 (21.0%)
Deaths	1	0	0	0
One or more treatment-emergent serious adverse events	23 (23.5%)	13 (13.1%)	14 (13.6%)	15 (15.0%)
Treatment-emergent adverse events leading to discontinuation	13 (13.3%)	10 (10.1%)	12 (11.7%)	12 (12.0%)
Clinical laboratory parameters	no clinically important findings			
Body weight, mean (SE) change from baseline at endpoint	N=83 -1.4 (0.45)	N=90 0.5 (0.50)	N=87 1.2 (0.40)	N=98 1.9 (0.36)
Vital signs and physical findings	no clinically important findings			
Electrocardiogram	no clinically important findings			
ESRS Total score				
Baseline, median (range)	N=98 3.0 (0- 21)	N=99 4.0 (0- 33)	N=103 2.0 (0- 25)	N=100 2.5 (0- 27)
Change from baseline to endpoint, median (range)	N=93 0.0 (-13- 23)	N=97 -1.0[a] (-19- 8)	N=98 0.0 (-15-11)	N=90 0.0 (-19- 15)
Local tolerability of injections				
Pain rating on 100-point VAS scale				
Injection 1 (Baseline), mean (SE)	N=96 16.7 (2.11)	N=97 12.0 (1.61)	N=102 18.2 (2.38)	N=100 16.7 (2.00)
Injection 6 (Week 10), mean (SE)	N=32 12.6 (3.08)	N=44 9.0 (1.55)	N=43 11.8 (3.23)	N=45 8.5 (2.14)

a: p=0.046
Treatment-emergent events during double-blind phase.
ESRS = Extrapyramidal Symptom Rating Scale. VAS = Visual Analog Scale

Conclusions: Risperidone depot microspheres (25 mg, 50 mg and 75 mg injected intramuscularly every 2 weeks) was more effective than placebo depot in treating in- and outpatients with schizophrenia for up to 12 weeks on the primary and most secondary efficacy measures. There was no apparent added effect with the highest dose of risperidone depot, 75 mg. In addition, treatment with risperidone depot microspheres had a good safety and tolerability profile compared to placebo depot treatment. Steady-state plasma concentrations of the active moiety (sum of risperidone and 9-hydroxy-risperidone) increased proportionally with the dose.