SYNOPSIS

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Name of Sponsor/Company	Janssen-Cilag Medical Affairs EMEA Turnhoutseweg 30 B-2340 Beerse Belgium
Name of Finished Product	Risperdal® Consta®
Name of Active Ingredient(s)	Risperidone long-acting injectable

Protocol No.: RIS-SCH-4043

Title of Study: Is premorbid functioning a predictor of outcome in patients with early onset psychosis treated with Risperdal® Consta®? PROPEL Study

Study Name: PROPEL

EudraCT Number: 2005-004621-25

Coordinating Investigator: NAP

Publication (Reference): Not applicable

Study Period: Date study initiated: 12 Apr 2006 Date study completed: 02 Nov 2007

Phase of Development: IV

Objectives: The primary objective of this study was to test the hypothesis that patients with good premorbid functioning, as assessed using the Premorbid Adjustment Scale (PAS), would respond better to treatment as measured by changes from baseline on the PANSS total score and CGI-S than patients with poor premorbid functioning.

The secondary objectives were:

(a) to assess the effectiveness, safety, tolerability, and functioning of patients in the early phase of psychosis who are treated with of Risperdal® Consta® regarding effectiveness (CGI-S/C, PANSS, retention rate); functioning (SF-36, rehospitalization rates), safety and tolerability (reported adverse event, ESRS and retention rate)

(b) Examine whether greater insight, as measured by the SAI-E and PANSS, was positively associated with better outcomes

Methods: This was 6-month, prospective open-label, multicenter Phase IV study. Approximately 300 patients with recent-onset (≤ 2 years) DSM-IV-TR[2] diagnosis of schizophrenia/schizoaffective disorder had to receive Risperdal® Consta® injections for a period of 6 months. Study assessments were to be conducted at baseline (Visit 1), after 6 weeks (Visit 2), after 12 weeks (Visit 3) and after 26 weeks (Visit 4). In this study, all patients received Risperdal® Consta® in flexible doses, therefore blinding and randomization were not required. The classification of patients to either the good or poor pre-morbid functioning group had to be done at a statistical level, according to pre-defined definition and criteria, thus allowing for single arm design.

Number of Subjects (planned and analyzed): Based on previous data, 300 patients were to be sufficient to expect 192 patients for analysis after accounting for discontinuation with 92% power to find significant differences. 307 subjects were screened, of whom 4 subjects were screening failures and one subject was

excluded from analysis due to incomplete PAS data. AEs for this patient are reported. 302 subjects received study medication at least once and were included in the safety analysis set. 294 subjects received at least one injection, provided post-baseline outcome data and were included in the efficacy analysis set.

Diagnosis and Main Criteria for Inclusion: In-patients or outpatients over 18 years of age who required at least 6 months of antipsychotic treatment.

Further key criteria were: Primary diagnosis of schizophrenia/schizoaffective disorders according to Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV-TR) for less than 2 years following initial diagnosis and treatment, at least 2 previous psychotic episodes, maximum total PANSS score at baseline of ≤ 80.

Test Product, Dose and Mode of Administration, Batch No.: Risperdal® Consta® contains either 25 mg, 37.5 mg or 50 mg risperidone. Risperdal® Consta® is an extended release microspheres formulation of risperidone, composed of risperidone drug substance microencapsulated in polylactide co-glycolide, at a concentration of 381 mg risperidone per gram of microspheres. Treatment had to be initiated in line with local label requirements. The dose of Risperdal® Consta® could be increased by increments of 12.5 mg after a minimum of 6 weeks (3 injections) at the previous dose, to a maximum dose of 50 mg if judged clinically appropriate.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: 6 months.

Criteria for Evaluation: Evaluations to be assessed during the study included:

PANSS, CGI, SF-36, GAF, Insight Measures (SAI-E and PANSS insight item), Premorbid Adjustment Scale (PAS), adverse events, vital signs, body weight, physical examination, ESRS.

Statistical Methods: The primary hypothesis, that patients with "Stable-good" premorbid functioning would have better outcomes than those with "Stable-poor" premorbid functioning was to be examined by dividing patients into "Stable-good" and "Stable-poor" premorbid functioning groups based on their total scores on the PAS. The combined change measure had to be constructed by computing residualized change scores, controlling for baseline, for both the CGI-S and the PANSS total scores. The division into "Stable-good", "Stable-poor" and "deteriorating" (i.e., a decline from childhood to each subsequent life phase before illness onset) premorbid functioning groups had to be based on the Haas and Sweeney classification[a].

Other secondary analyses: The association of insight and outcomes had to be examined using data from the SAI-E as well as the insight item from the PANSS (item G 12).

[a] Haas GL, Sweeney JA. Premorbid and onset features of first-episode schizophrenia. Schizophr Bull 1992; 18(3): 373-86.

RESULTS:

Subjects were divided into "Stable-good", "Stable-poor" and "Deteriorating" based on their scores on the Premorbid Adjustment Scale (PAS).

Study Completion/Withdrawal Information
(Study RIS-SCH-4043: Efficacy Analysis Set)

	Risperidone long-acting injectable 25, 37.5 and 50 mg			
	Stable-good (N=142)	Stable-poor (N=116)	Deteriorating (N=36)	Total (N=294)
Entered, n (%)	142 (100.0%)	116 (100.0%)	36 (100.0%)	294 (100.0%)
Completed, n (%)	127 (89.4%)	96 (82.8%)	30 (83.3%)	253 (86.1%)
Withdrawn, n (%)	15 (10.6%)	20 (17.2%)	6 (16.7%)	41 (13.9%)
Death*		1 (0.9%)		1 (0.3%)
Adverse event(s)	1 (0.7%)	4 (3.4%)	2 (5.6%)	7 (2.4%)
Withdrawn consent**	4 (2.8%)	9 (7.8%)	3 (8.3%)	16 (5.4%)
Insufficient response	4 (2.8%)	3 (2.6%)		7 (2.4%)
Lost to follow-up	1 (0.7%)			1 (0.3%)
Subject non-compliant	1 (0.7%)	2 (1.7%)		3 (1.0%)
Ineligible	1 (0.7%)	1 (0.9%)		2 (0.7%)
Administrative reason	1 (0.7%)			1 (0.3%)
Other***	2 (1.4%)		1 (2.8%)	3 (1.0%)

* A second subject (Subject 10154) died after study termination. She died after last study visit on 01 Jun 2007 due to SAE gastric cancer with onset during the study (14 May 2007).
** Includes subjects refusing injections or seeing no need to continue therapy, ***Other reason includes: moving to other country

Demographic baseline values showed only minor group differences (see table below). No statistically significant differences in demographic data (race, sex, age, height, weight, BMI and DSM-IV diagnosis) as well as vital parameters (pulse rate, blood pressure) were observed between the subgroups.

Demographic and Baseline Characteristics
(Study RIS-SCH-4043: Efficacy Analysis Set)

	Risperidone long-acting injectable 25, 37.5 and 50 mg			
	Stable good (N=142)	Stable poor (N=116)	Deteriorating (N=36)	Total (N=294)
Age *(years)*				
Mean (SD)	31.6 (10.2)	30.0 (8.5)	28.6 (9.8)	30.6 (9.5)
Median	29.0	28.0	26.0	28.0
Range	18-62	18-57	18-58	18-62
Sex, n (%)				
Male	77 (54.2%)	76 (65.5%)	25 (69.4%)	178 (60.5%)
Female	65 (45.8%)	40 (34.5%)	11 (30.6%)	116 (39.5%)
Race, n (%)				
Caucasian	141 (99.3%)	113 (97.4%)	34 (94.4%)	288 (98.0%)
Hispanic		1 (0.9%)		1, (0.3%)
Oriental		2 (1.7%)	1 (2.8%)	3 (1.0%)
Other	1 (0.7%)		1 (2.8%)	2 (0.7%)
Weight *(kg)*				
Mean (SD)	73.5 (14.1)	74.9 (13.9)	76.3 (14.7)	74.4 (14.1)
Median	72.4	73.1	75.0	73.0
Range	38-125	46-115	49-111	38-125
Height *(cm)*				
Mean (SD)	170.7 (9.4)	170.9 (9.0)	174.4 (9.6)	171.2 (9.3)
Median	171.0	171.0	175.0	171.0
Range	150-192	150-195	153-193	150-195
BMI *(kg/m²)*				
Mean (SD)	25.12 (3.78)	25.64 (4.33)	25.09 (4.67)	25.32 (4.11)
Median	24.7	25.3	24.0	25.0
Range	16.7-37.3	18.0-37.5	17.3-41.4	16.7-41.4
DSM-IV diagnosis				
Schizophrenia	96 (67.6%)	86 (74.1%)	24 (66.7%)	206 (70.1%)
Schizoaffective disorder	46 (32.4%)	30 (25.9%)	12 (33.3%)	88 (29.9%)
PANSS – Total				
Mean (SD)	67.9 (9.9)	71.8 (11.2)	70.5 (6.4)	69.8 (10.3)
Median	70.0	74.0	71.0	71.0
Range	39-88	36-145	51-80	36-145
CGI – Severity				
Mean (SD)	3.8 (0.7)	3.9 (0.7)	4.0 (0.8)	3.9 (0.7)
Median	4.0	4.0	4.0	4.0
Range	3-6	2-6	2-5	2-6
GAF – Score				
Mean (SD)	61.4 (12.8)	56.2 (11.9)	58.7 (11.1)	59.0 (12.5)
Median	62.0	56.0	60.0	60.0
Range	25-85	25-90	33-80	25-90
SF-36				
Physical component summary	47.54 (8.89)	44.42 (10.33)	47.85 (10.52)	46.38 (9.77)
Mental component summary	35.27 (10.48)	34.80 (11.24)	34.65 (10.62)	35.01 (10.76)

EFFICACY RESULTS: The primary statistical test, an ANCOVA of the combined CGI-S and PANSS residualized change from baseline to endpoint score, showed a significant difference between the premorbid groups (p=0.02). Individual ANCOVAS for each of the two change from baseline to endpoint measures showed significantly more improvement in the Stable-good as compared to the Stable-poor group on the CGI-S (p=0.03) and a non-statistically significant difference on the PANSS total (p=0.14) (see table below).

Primary objective analysis: ANCOVAs comparing premorbid groups on baseline to LOCF endpoint change on efficacy and quality of life measures (ANCOVA estimated marginal mean and 95% CI*) (Study RIS-SCH-4043: Efficacy Analysis Set)

	Risperidone long-acting injectable 25, 37.5 and 50 mg						
Measures	a. Stable-good (n=142)	b. Stable-poor (n=116)	c. Deteriorating (n=36)	Signifi-cance	Least Significance Difference (p=)		
				Overall	a>b	a>c	b>c
Primary measures ** CGI-severity change	-0.98 (-1.22; -0.73)	-0.73 (-0.96;-0.49)	-0.56 (-0.91;-0.21)	f=3.78, p=0.02	0.03	0.02	0.33
PANSS total-change	-15.0 (-18.4;-11.6)	-12.5 (-15.7;-9.3)	-8.1 (-12.9;-3.3)	f=4.1, p=0.02	0.14	0.005	0.07
PANSS Negative-change	-3.9 (-5.0;-2.9)	-3.4 (-4.4;-2.4)	-2.6 (-4.1;-1.1)	f=1.56, p=0.21	0.33	0.09	0.28
PANSS Positive-change	-3.6 (-4.5;-2.7)	-3.2 (-4.0;-2.3)	-2.1 (-3.4;-0.9)	f=2.6, p=0.07	0.31	0.02	0.11
PANSS General Psychopathology-change	-6.9 (-8.8;-5.1)	-5.9 (-7.7;-4.2)	-3.4 (-6.0;-0.7)	f=3.7, p=0.03	0.28	0.007	0.05
Secondary measures *** GAF	10.8 (8.9;12.8)	6.7 (4.5;8.9)	6.4 (2.7;10.1)	f=4.83, p=0.009	0.005	0.04	0.87
CGI-C change	2.7 (2.3;3.0)	2.8 (2.5;3.1)	3.2 (2.8;3.6)	F=3.3, p=0.04	0.26	0.01	0.07
SF-36 Mental Component summary	7.5 (5.0;10.0)	4.2 (1.7;6.6)	4.9 (1.3;8.5)	f=3.8, p=0.024	0.007	0.16	0.67
Emotional well being	11.6 (7.4;15.9)	8.4 (4.3;12.5)	8.4 (2.3;14.5)	F=1.4, p=0.25	0.12	0.29	0.99
Social functioning	19.5 (13.4;25.6)	8.9 (3.1;14.7)	16.9 (8.2;25.7)	f=6.7, p=0.001	0.0004	0.56	0.07
Role limitations due to emotional problems	28.2 (17.8;38.5)	16.5 (6.7;26.4)	13.4 (-1.5;28.2)	F=3.5, p=0.03	0.02	0.05	0.67
Energy fatigue (Vitality)	10.3 (6.0;14.7)	4.1 (0.0;8.3)	9.3 (3.0;15.5)	F=4.6, p=0.01	0.004	0.733	0.10
Physical Component summary	4.6 (2.9;6.4)	2.5 (0.8;4.1)	3.4 (0.9;5.8)	F=3.1, p=0.05	0.01	0.31	0.48
Physical functioning	14.5 (9.9;19.1)	7.8 (3.4;12.2)	12.0 (5.4;18.6)	F=4.5, p=0.01	0.003	0.45	0.21
Pain	4.9 (0.2;9.7)	1.3 (-3.3;5.8)	4.4 (-2.5;11.2)	F=1.30, p=0.27	0.12	0.87	0.38
General health	8.4 (4.1;12.6)	3.0 (-1.1;7.1)	6.6 (0.5;12.7)	f=3.41, p=0.034	0.01	0.55	0.25
Role limitations due to physical health	32.0 (22.0;42.1)	20.7 (11.1;30.3)	14.8 (0.5;29.2)	F=4.14, p=0.02	0.02	0.018	0.42

* Adjusted for baseline symptom measure score (except for CGI-C), age, sex, center and last dose.
There were no meaningful interactions, thus only main effects were included.
** negative change reflects improvement, *** positive change reflects improvement

Secondary Objective Analysis: Hierarchical linear regression using insight measures to predict change from baseline to endpoint on the PANSS total score was conducted. The first block included PANSS total score at baseline, center, sex, final dose and age. The second block included the SAI-E and the PANSS insight item. The coefficient of interest was the change in R-square after block two was included. The addition of the insight measures did not improve the R-square and the contribution of the insight items were far from being statistically significant ($p<0.80$). Logistic regression was used in a similar fashion as the linear regression to examine the association of insight and clinical improvement (i.e., 20% improvement on the PANSS total). Neither insight measure was significantly associated with clinical improvement ($p<0.44$). Cox regression was conducted to examine the association of insight and time in trial. This analysis found that neither insight measure was a significant predictor of time in trial ($p<0.20$). These results did not support an association of insight and treatment outcomes.

Total PANSS score and PANSS subscales: All three PANSS subscales and five Marder PANSS factors showed a significant improvement between baseline and LOCF. A clinical response was defined as a 20% or greater reduction in PANSS total score from baseline (Visit 1) until Visit 4 (LOCF). A clinical response was obtained by 136/294 subjects (46.3%). This included 70/142 (49.3%) in the "Stable-good" group, 55/116 (47.4%) in the “Stable-poor” group and 11/36 (30.6%) in the "Deteriorating" group. Using the correction factor described in the SAP, the respective response rates were 106/142 (74.6%), 76/116 (65.5%) and 19/36 (52.8%) in the "Stable-good", "Stable-poor" and "Deteriorating" subgroup. Of the 201 patients with clinical response (corrected) only five of them relapsed (Stable-good, n=2, Stable-poor, n=1 and Deteriorating, n=2). Using uncorrected response only 2 relapsed.

The total CGI-S score showed a significant improvement in the total population as well as the subgroups.

The GAF score showed a significant improvement in the total population as well as in subgroups.

All items of the SF-36 questionnaire showed a significant improvement between baseline and LOCF in all subgroups.

SAFETY RESULTS: Including the one pre-treatment AE (acute respiratory infection), a total of 201 AEs were observed in 106/302 subjects (35.1%) (97 AEs in 54/145 (37.2%), 72 AEs in 37/121 (30.6%) and 32 in 15/36 (41.7%) subjects in “Stable-good”, “Stable-poor” and “Deteriorating” subgroup).

Most frequently affected system organ class (SOC) was nervous system disorders (28/145 (19.3%), 16/121 (13.2%) and 6/36 (16.7%) subjects in the “Stable-good”, “Stable-poor” and “Deteriorating” subgroup). The table below summarizes the number of patients with treatment emergent AEs by system organ class (SOC) and preferred term as coded according to MedDRA 9.1. Only terms applying to at least 3 subjects (≥ 1%) in the Safety Analysis Set were considered.

The vital signs heart rate, blood pressure, weight and BMI showed marginal or minor changes. Glucose related AEs (including increased blood glucose or glycosylated hemoglobin) as well as injection site related AEs were not observed.

Extrapyramidal symptoms showed a significant reduction regarding the Parkinson related subscales "Parkinsonism, dystonia, dyskinesia and akathisia", "Parkinsonism", CGI score of dyskinesia and Parkinsonism, "total score" as well as "hyperkinesia" and "hypokinesia" in the exploratory sense. In general, mean baseline scores and changes were most pronounced in the "Stable-poor" subgroup.

Adverse Events in ≥ 1% of Subjects by Preferred Term
(Study RIS-SCH-4043: Safety Analysis Set)

	Risperidone long-acting injectable 25, 37.5 and 50 mg			
Body System Preferred Term	Stable-good (N=145)	Stable-poor (N=121)	Deteriorating (N=36)	Total (N=302)
Subjects with AEs	54 (37.2%)	37 (30.6%)	15 (41.7%)	106 (35.1%)
NERVOUS SYSTEM DISORDERS	28 (19.3%)	16 (13.2%)	6 (16.7%)	50 (16.6%)
AKATHISIA	7 (4.8%)	6 (5.0%)	1 (2.8%)	14 (4.6%)
EXTRAPYRAMIDAL DISORDER	5 (3.4%)	1 (0.8%)	3 (8.3%)	9 (3.0%)
PARKINSONISM	4 (2.8%)	2 (1.7%)	2 (5.6%)	8 (2.6%)
TREMOR	3 (2.1%)	2 (1.7%)		5 (1.7%)
HEADACHE	3 (2.1%)	2 (1.7%)		5 (1.7%)
DYSKINESIA	3 (2.1%)			3 (1.0%)
SOMNOLENCE	2 (1.4%)		1 (2.8%)	3 (1.0%)
PSYCHIATRIC DISORDERS	17 (11.7%)	16 (13.2%)	6 (16.7%)	39 (12.9%)
ANXIETY	4 (2.8%)	3 (2.5%)		7 (2.3%)
INSOMNIA	3 (2.1%)	2 (1.7%)	2 (5.6%)	7 (2.3%)
DEPRESSION	3 (2.1%)	3 (2.5%)	1 (2.8%)	7 (2.3%)
SCHIZOPHRENIA PARANOID TYPE		3 (2.5%)	1 (2.8%)	4 (1.3%)
AGITATION	1 (0.7%)	3 (2.5%)		4 (1.3%)
HALLUCINATION	1 (0.7%)	2 (1.7%)		3 (1.0%)
PSYCHOTIC DISORDER	1 (0.7%)	1 (0.8%)	1 (2.8%)	3 (1.0%)
SCHIZOPHRENIA	3 (2.1%)			3 (1.0%)
DEPRESSED MOOD	1 (0.7%)	1 (0.8%)	1 (2.8%)	3 (1.0%)
INFECTIONS AND INFESTATIONS	5 (3.4%)	2 (1.7%)	2 (5.6%)	9 (3.0%)
INVESTIGATIONS	6 (4.1%)	3 (2.5%)		9 (3.0%)
WEIGHT INCREASED	6 (4.1%)	3 (2.5%)		9 (3.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4 (2.8%)	3 (2.5%)	2 (5.6%)	9 (3.0%)
GALACTORRHOEA	1 (0.7%)	2 (1.7%)	1 (2.8%)	4 (1.3%)
GASTROINTESTINAL DISORDERS	3 (2.1%)	1 (0.8%)	2 (5.6%)	6 (2.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (2.1%)	2 (1.7%)		5 (1.7%)
ENDOCRINE DISORDERS	3 (2.1%)	1 (0.8%)		4 (1.3%)
HYPERPROLACTINAEMIA	2 (1.4%)	1 (0.8%)		3 (1.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1.4%)	1 (0.8%)	1 (2.8%)	4 (1.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.7%)	1 (0.8%)	1 (2.8%)	3 (1.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.4%)	1 (0.8%)		3 (1.0%)

Multiple entries per patient possible.
All AEs were treatment emergent except for one case of acute respiratory infection in the "Stable-good" subgroup
NOTE: Subjects with multiple occurrences of the same adverse event are counted only once for that particular preferred term or body system.

Including the one pre-treatment AE, a total of 201 AEs were observed in 106/302 subjects (35.1%) during the study. This concerned 21 patients with serious AEs. Two subjects died. Most frequent were AEs of the system organ class nervous system disorders. EPS-related AEs were observed in the following number of subjects: Extrapyramidal disorder (n=9); Parkinsonism (n=8); Akathisia (n=14); Tremor (n=5); Muscle rigidity (n=1); Dystonia (n=1); Dyskinesia (n=3), Bradykinesia (n=1), Joint stiffness (n=1), Psychomotor retardation (n=1).

Second in frequency was the SOC psychiatric disorders where AEs were mostly related to the underlying disease. Weight gain as an AE was reported in 9 subjects. Potentially-prolactin-related AEs were observed in the following number of subjects: Amenorrhea (n=1); Dysmenorrhea (n=1); Galactorrhea (n=4); Loss of libido (n=1); Hyperprolactinemia (n=3); Menses delayed (n=2); Menorrhagia (n=1).

CONCLUSION: The analysis of efficacy parameters reveals a consistent picture of better treatment response associated with good premorbid functioning. The primary hypothesis that patients with good premorbid functioning would have better treatment response was confirmed. Insight was not found to be associated with treatment response. The results also show notable improvement during treatment on efficacy parameters. Overall, the present study demonstrates good antipsychotic efficacy and tolerability of risperidone LAI as indicated by the significant improvement of all major psychiatric assessment scales as well as extrapyramidal symptoms . Though patients appeared to profit most from risperidone LAI therapy in the Stable-good group, significant clinical improvement was observed the other subgroups (i.e. Stable-poor and Deteriorating) as well. Important factors that likely contributed to this result are the improved compliance and pharmacokinetic profile of risperidone LAI. Analysis of the safety parameters demonstrates adequate tolerability and improved EPS-related symptoms during treatment with Risperdal® Consta® in the treatment of patients with schizophrenia and schizoaffective disorders.

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