SYNOPSIS

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Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, LLC
Name of Finished Product	RISPERDAL® CONSTA®
Name of Active Ingredient	Risperidone

Protocol No.: CR005035

Title of Study: The SOURCE Study: Schizophrenia Outcomes-Utilization, Relapse, and Clinical Evaluation

Coordinating Investigator: Not applicable for this multicenter observational study

Publication (Reference): None

Study Period: 23 September 2004 – 24 October 2007

Phase of Development: 4

Objectives: This was a large-scale observational study of patients with schizophrenia. The objective of the study was to obtain long-term real world outcomes data for patients initiated with RISPERDAL® CONSTA®. Outcomes were: patient disease severity (Clinical Global Impression [CGI] scale); patient functioning (Global Assessment of Function [GAF], Personal and Social Performance Scale [PSP] and Strauss-Carpenter Level of Functioning [LOF]); healthcare resource utilization; relapse rates; patient-reported health status (Medical Outcomes Survey-Short Form-36 [SF-36]); medication compliance with antipsychotic (AP) medication; and patient satisfaction with AP medication.

Methods: This was a nonrandomized, multicenter, open-label study. There was no study mandated intervention with regard to physician treatment choice or management of patient condition once the patient was enrolled in the study. Therefore, any treatment for schizophrenia could have been stopped, started or changed as deemed appropriate by the physician. There was no blinding or randomization. Use of concomitant psychiatric medications was allowed in accordance with clinical practice.

Outcome measures were collected at the following times: baseline (month 0) and at months 3, 6, 9, 12, 15, 18, 21, and 24. In addition, adverse event (AE) and concomitant medication use were collected throughout the study.

Number of Subjects (planned and analyzed): Planned: approximately 600 patients. Analyzed: 532 patients were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: Adult patients, aged ≥18 years, who had schizophrenia (Disorganized, Catatonic, Paranoid, Residual, or Undifferentiated) that met disease diagnostic criteria as defined in the Diagnostic and Statistical Manual of Mental Disorders IV ([DSM-IV] 295.10, 295.20, 295.30, 295.60, or 295.90) and who required treatment initiation with RISPERDAL® CONSTA®, deemed medically necessary by the Investigator independent of the study.

Test Product, Dose and Mode of Administration, Batch No.: Not applicable

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

Duration of Treatment: Duration of any treatment for schizophrenia was not fixed in this study. After initiation with RISPERDAL® CONSTA®, any treatment for schizophrenia might be stopped, started, or changed as deemed appropriate by the caregiver.

Criteria for Evaluation: Effectiveness endpoints included incidence and frequency of relapse, disease severity (as measured by CGI-S and CGI-C), functionality (as measured by GAF, PSP, LOF), quality of life (as measured by SF-36), patient satisfaction, and healthcare resource utilization (including hospitalization, emergency room (ER) visits, and unscheduled physician/therapy visits), and medication compliance. Safety was assessed by incidence and nature of AEs.

Statistical Methods: Sample sizes are not traditionally calculated for registry studies. However, for this study, to ensure an adequate sample size, the number of patients needed for detecting meaningful changes in a number of the outcome measures was estimated. A 5-point change on an individual SF-36 domain is considered clinically and socially relevant. To detect a 5-point change on the most variable individual SF-36 domain score (role-physical), with 80% power and 0.05 tolerance of type I error, 293 evaluable patients were required. This was based on a two sided paired t-test, assuming within-subject test re-test correlation of 0.60, and SD of 34 (data for the US normal subjects). This sample size also provided approximately 80% power for detection of 0.165 standardized change (effect size) in average number of hospitalizations per year. In terms of precision of event rate estimation (relapse rate, etc.), 293 patients provided a rate estimate with a standard error of $\pm$ 3%. It was expected that approximately 50% patients would drop out of the study within 1 year. To obtain 293 patients with 1-year follow-up, planned enrollment was for 600 patients to be recruited into the study.

The overall analysis set included all eligible patients entering the study (met entry criteria, completed informed consent, and initiated RISPERDAL® CONSTA®). Unless otherwise specified, this overall analysis set was used for the summary and analysis of all study data (patient characteristics, disposition, patient function, medication effectiveness, treatment exposure and compliance, health resource utilization, patient-reported health status, patient satisfaction with AP medication, concomitant medications, and AEs).

Descriptive statistics included number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous and ordinal variables. Number and percentages of observations in each category were computed for categorical variables. In some cases, an ordinal variable was summarized both as a continuous variable and a categorical variable.

Mixed model methodology was used to analyze longitudinal change from baseline for variables measuring disease severity (CGI-S), patient functioning (GAF, PSP and LOF), and health status (SF-36). The model included the corresponding baseline value as a covariate, a fixed effect for time, and a random effect for study center. Within-subject correlations among the repeated measures were modeled by an unstructured covariance matrix. Inclusion criteria for analysis required patients to have non-missing baseline and at least one postbaseline assessment.

Life table methodology was used to estimate the cumulative probability of relapse during the study. The cumulative relapse rates at each 3-month postbaseline time interval were estimated. Relapse time was censored at the last time interval of known status if one of the following occurred: no relapse by end of follow-up period, withdrawal from study, lost to follow-up, or death. The following measures were presented by the time interval since baseline: the number of patients at risk, the number of patients censored, the number of patients relapsed, the cumulative probability of relapse, and the corresponding 95% confidence intervals (CIs).

Incidence densities for hospitalization and ER visits were calculated. Incidence density is defined as the total number of events for the study population divided by the total length of follow-up in years. To compare the incidence densities between the 1-year period before study entry and the 1-year period after study entry, the bootstrap resampling method was used to obtain a 95% CI.

Frequency of all AEs reported during the study was summarized by the Medical Dictionary for Regulatory Activities (MedDRA, version 7.1) body system and preferred term.

RESULTS:

The study enrolled 532 patients, of whom 305 (57.3%) had at least 12 months follow-up data.

Summary of Patient Disposition

	n (%)
Total patients enrolled	532
Completed the entire study	209 (39.3)[a]
Discontinued	235 (44.2)
Not reported	88 (16.5)
Reason for discontinuation	
Lost to follow-up	73 (13.7)
Other	65 (12.2)
Withdrawal of consent	57 (10.7)
Patient noncompliance	21 (3.9)
Adverse event	7 (1.3)
Insufficient response	6 (1.1)
Death	3 (0.6)
Patient ineligible to continue trial	2 (0.4)
Missing	1 (0.2)
Last Study Visit	
Visit 1 (Month 0)	97 (18.2)
Visit 2 (Month 3)	69 (13.0)
Visit 3 (Month 6)	36 (6.8)
Visit 4 (Month 9)	25 (4.7)
Visit 5 (Month 12)	18 (3.4)
Visit 6 (Month 15)	15 (2.8)
Visit 7 (Month 18)	28 (5.3)
Visit 8 (Month 21)	34 (6.4)
Visit 9 (Month 24)	210 (39.5)[a]

Data Source: Appendix 2.4, Table 1

[a] n = 209 is the number of patients for whom "Patient completed the entire course of the study as specified in the protocol" was checked on the CRF and n = 210 is the number of patients who had at least 1 data point recorded at 24-month visit.

The mean (SD) age was 42.3 (12.8) years and 66.4% of patients were male. The majority of patients were Caucasian (60.3%) or African-American (23.7%). The majority of subjects for whom employment status was known were unemployed (41.0%) or disabled/long-term sick leave (25.2%), and reported an income of less than $20,000 per year (44.9%).

Demographic and Baseline Characteristics	
	N=532
Age (years)[a]	
Mean (SD)	42.3 (12.8)
Median (Min, Max)	43.2 (18, 80)
Gender, (n, %)	
Male	353 (66.4)
Female	179 (33.6)
Ethnicity, (n, %)	
Caucasian	321 (60.3)
African American	126 (23.7)
Hispanic	61 (11.5)
Mixed Race	9 (1.7)
Other	8 (1.5)
Asian	7 (1.3)

Data Source: Appendix 2.4, Table 2

[a]n=528

The majority of patients had a diagnosis of schizophrenia, paranoid type (67.5%). The mean (SD) length of illness was 17.9 (12.3) years.

At the baseline visit, before initiating on RISPERDAL® CONSTA®, 67.1% of patients started and stopped previous antipsychotic therapy: 39.1% started and stopped oral antipsychotics (atypical and conventional), 25.0% multiple antipsychotics, and 3% conventional depot treatment.

For 53.8% of patients, the reason for initiating RISPERDAL® CONSTA® was insufficient response to previous therapy and for 48.1%, the reason was lack of compliance to previous therapy (Note: patients could select multiple reasons).

The initial dose of RISPERDAL® CONSTA® was 25 mg for 75.4% of patients.

The average mean (SD) duration between RISPERDAL® CONSTA® injections was 18.1 (18.1) days and the average median duration was 16.8 (18.0) days.

The mean (SD) medication possession ratio calculated from the data for RISPERDAL® CONSTA® was 74.1% (26.7%) and the median was 85.1%. Medication possession ratios were relatively stable over time.

The physician-reported compliance for all antipsychotic medication prescribed since last visit was consistent with patient adherence data.

EFFECTIVENESS RESULTS:

The cumulative probability of relapse was 10.6% (95% CI: 8.2% to 13.6%) by the end of the first 3 months of the study and was 28.5% (95% CI: 24.0% to 33.6%) by 24 months.

For the effectiveness measures CGI-S, GAF, PSP, total LOF, and the mental health summary score of the SF-36, all postbaseline mean values showed improvements over baseline (P<0.0001). No statistically significant change was observed in the physical summary score from the SF-36 during the 24-month study period.

MEDICAL RESOURCE UTILIZATION RESULTS:

The medical resource utilization analysis included 435 patients who had a baseline visit, at least 1 postbaseline visit and valid hospitalization dates. A significant decrease in hospitalizations (-0.29, 95% CI: -0.39 to -0.18), psychiatric hospitalizations (-0.35, 95% CI: -0.44 to -0.26), and ER visits (-0.26, 95% CI: -0.44 to -0.10) per person-year was observed after initiation with RISPERDAL® CONSTA® compared to before RISPERDAL® CONSTA® initiation.

SAFETY RESULTS:

Of the 532 patients enrolled in the study, 249 (46.8%) experienced at least 1 AE and 142 (26.7%) experienced at least 1 SAE during the study. Three patients died during the study (Patients 10031, 10441, and 10811) and 1 patient died (Patient 10557) within 30 days of study discontinuation. Three deaths were assessed as not related to medication; for 1 death, relatedness was not reported. Seven subjects discontinued the study because of AEs; for 5 of these subjects, the relationship to medication was assessed as none or doubtful, for 1 possible (AE: agitation) and 1 subject, probable (AEs: psychotic disorder, sexual dysfunction).

The system organ class with the highest incidence of AEs was psychiatric disorders (29.3%), followed by nervous system disorders (13.2%) and gastrointestinal disorders (7.9%). The most commonly reported AEs by preferred term were psychotic disorder (9.4%), anxiety (7.7%), and depression (7.5%).

Regarding severity, 24.5% of AEs were assessed as mild, 39.3% as moderate, 35.7% as severe, and 0.5% were missing a severity attribution. The relationship to medication was assessed as not related or doubtful for 84.7% of the AEs, possible, probable, or very likely for 14.7%, and was missing for 0.6%.

STUDY LIMITATIONS: This was a nonrandomized, longitudinal observational study without a comparator group; therefore, causal attribution to any particular treatment cannot be determined with certainty.

CONCLUSIONS:

Patients with schizophrenia who initiated therapy on RISPERDAL® CONSTA® had statistically significant improvement in disease severity, functionality, and mental health after 3 months of treatment. These improvements were maintained for 24 months.

Significant decreases in rates per person-year were observed for hospitalizations, psychiatric hospitalizations, and ER visits after initiation on RISPERDAL® CONSTA®.

The 2-year estimated relapse rate of 28.5% compares favorably with literature-reported 2-year relapse rates for similar patients treated with oral AP medications.

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