SYNOPSIS

Name of Sponsor/Company:	Janssen Pharmaceutica Products, LP
Name of Finished Product:	RISPERDAL® CONSTA®
Name of Active Ingredient(s):	Risperidone (R064766)

Protocol No.: CR002896

Title of Study: An open-label evaluation of the utility of the RISPERDAL® CONSTA® Treatment Guidebook during transition of adult patients with schizophrenia or schizoaffective disorder to RISPERDAL® CONSTA® treatment over three months in the Community Mental Health Center (CMHC) setting

[Coordinating] [Principal] Investigator: multicenter study

Publication (Reference): none

Study Period: 18 Sept 2002 (First patient entered) to 28 Aug 2003 (Database locked)

Phase of development: 3b

Objectives:

Primary

To evaluate the RISPERDAL® CONSTA® Treatment Guidebook in the CMHC setting through clinician assessment of its utility, supported by measures of patient and clinician adherence to treatment guidelines, during three months of RISPERDAL® CONSTA® therapy in patients with schizophrenia or schizoaffective disorder.

Secondary

To evaluate the efficacy of RISPERDAL® CONSTA® as assessed by the Clinical Global Impression (CGI) scale;

To evaluate the safety of RISPERDAL® CONSTA® as assessed by collection of treatment-emergent adverse events (AEs), as well as changes in vital signs, laboratory analyses, and ECG measures;

To evaluate the effect of RISPERDAL® CONSTA® on patient quality of life as measured by the SQLS (Schizophrenia Quality of Life Scale), as well as patient attitude/satisfaction assessments.

Methodology: This was a prospective, open-label, single-arm, flexible-dose, multi-center study to evaluate the RISPERDAL® CONSTA® Treatment Guidebook in the CMHC setting, as measured by clinician assessment of its utility, supported by measures of patient and clinician adherence to treatment guidelines, during three months of RISPERDAL® CONSTA® therapy in patients with schizophrenia or schizoaffective disorder. The proposed study consisted of three phases: Screening, Treatment, and Extension.

During the Screening phase, which lasted up to 14 days, patients continued on a stable dose of oral RISPERDAL® (2 to 6 mg/day). Patients who met all selection criteria were enrolled into the open-label Treatment phase, which consisted of a baseline visit and 6 bi-weekly visits over a period of 12 weeks. During this period, RISPERDAL® CONSTA® was administered every two weeks using a flexible dosing regimen within a pre-assigned dose range (25 to 50 mg).

Each patient's initial dose of RISPERDAL® CONSTA® was based on his or her prescribed dose of oral RISPERDAL® upon entry into the study. Patients on < 4 mg/day received 25 mg, while those on ≥ 4 mg/day received 37.5 mg of RISPERDAL® CONSTA®. All patients continued on their oral RISPERDAL® for the first two weeks of the Treatment phase.

Patients who completed the Treatment phase and were benefiting from RISPERDAL® CONSTA® treatment were eligible to enter the Extension phase, in which they could continue treatment until RISPERDAL® CONSTA® was commercially available. Visits and RISPERDAL® CONSTA® injections were continued at two-week intervals. The results from this Extension phase will not be presented in this report

Number of Subjects (planned and analyzed): 60 patients entered the study and were included in the intent-to-treat population

Diagnosis and Main Criteria for Inclusion: Patients had a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria. They were included in the study if:

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They (or legal representative) had provided written informed consent and agreed to complete all study procedures;

They were 18 to 65 years of age and, if female, were not of child bearing potential or were using adequate contraception;

They were judged to be symptomatically stable, with regard to their psychiatric condition, and medically stable, with no clinically significant or unstable coexistent medical conditions;

They were receiving oral RISPERDAL® monotherapy at a stable dose of 2 to 6 mg/day for the 4 weeks before Baseline.

Test Product, Dose and Mode of Administration, Batch No.:

RISPERDAL® tablets – oral, 2-6 mg/day. Batch numbers: 1 mg – 01C29/F005 (Exp. 4/2004); 2 mg – 01E23/F013 (Exp. 6/2004); 4 mg – 00C29/F12 (Exp. 9/2003).

RISPERDAL® CONSTA® suspension – intramuscular (gluteal) injection, 25, 37.5, or 50 mg every 2 weeks. Batch numbers: 25 mg – 164-0611AA/107001 (Exp. 3/2004); 37.5 mg – 164-0751AB/107001(Exp.3/2004); 50 mg – 164-1071BB/107001 (Exp. 3/2004).

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

Duration of Treatment:

RISPERDAL® tablets – 2 weeks (Weeks 0 to 2)

RISPERDAL® CONSTA® – 12 weeks (Weeks 0 to 12)

Criteria for Evaluation:

Efficacy: The primary parameter assessed in this study was the utility of the RISPERDAL® CONSTA® Treatment Guidebook, as measured by the following: clinician utility summary; patient adherence with RISPERDAL® CONSTA® therapy; and clinician adherence with RISPERDAL® CONSTA® therapy guidelines. The secondary efficacy rating instruments used in the study were the Clinical Global Impression (CGI) and the Schizophrenia Quality of Life Scale (SQLS).

Safety: Assessments included the regular monitoring and recording of all of treatment-emergent adverse events (AEs) and serious adverse events (SAEs); the monitoring of laboratory tests, including hematology, biochemistry and urinalysis; the regular monitoring of vital signs; and the performance of physical and neurological examinations and ECGs.

Statistical Methods: Sample size: The sample size of 60 patients was based on an expected dropout rate of 20% and the assumption that 300 patient-clinician interactions would be necessary to evaluate the usefulness of the Treatment Guidebook.

Populations: Two populations were used for the efficacy analyses, the intent-to-treat (ITT) population, consisting of patients who had at least one dose of RISPERDAL® CONSTA® and one post-baseline efficacy evaluation, and the 'evaluable' population, consisting of patients without any significant post-baseline protocol violations. The safety population comprised all patients who received at least one dose of RISPERDAL® CONSTA®.

Efficacy analysis: The primary efficacy analysis comprised summary statistics on the Guidebook-utility evaluations, including the Clinician Utility Summary, and the patient and clinician adherence to the treatment and Guidebook. A paired t-test was performed for comparison of baseline and endpoint for the secondary efficacy variables, the CGI and SQLS.

Safety analysis: Assessment of safety was based on the frequency of adverse events (AEs) and on the number of laboratory values that fall outside of pre-determined ranges. Data from other tests (e.g., vital signs, ECG) were listed, notable values were flagged, and any other information collected was listed, as appropriate.

SUMMARY - CONCLUSIONS

Sixty patients of mean age 44.1 (± 11.4) years entered the study (41M/19F). All patients were taking concomitant medication and all received oral RISPERDAL® as per the protocol. No substantial changes were noted in the pattern of concomitant medication use over the course of the study.

EFFICACY RESULTS:

Primary Variable: The primary efficacy parameter in this study was the evaluation of the utility of the RISPERDAL®

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CONSTA® Treatment Guidebook. The results from the Clinician utility summary, which was performed by physicians and other staff involved in patient care, indicate that approximately 90% of the Clinicians found the Guidebook to be 'quite a bit' or 'extremely useful' in administering RISPERDAL® CONSTA® therapy. This was reflected in the Clinician adherence to treatment guidelines. The incidence of various types of non-adherence to the dosing guidelines by Clinicians was generally very low, ranging from no incidents of early dose increases, to the most frequent error, failure to alternate injection site between right and left buttocks, which occurred at only 11% of visits. Patient adherence to the injection schedule was also good, with 87% of patients receiving all of their injections within the specified interval

Secondary Variables: The initial expectation of the majority of patients was that RISPERDAL® CONSTA® would be more convenient or have fewer side effects than their current medication. For those patients who continued treatment at Visit 8, almost 60% felt that the medication was more convenient or easier to use. In addition, patients' concerns about pain from the injection also diminished over time, and, at Endpoint, approximately 70% of patients felt that taking a long-acting injectable medication was 'better' or 'much better' than taking an oral antipsychotic. Regarding RISPERDAL® CONSTA® specifically, 86% of the patients reported that they were 'somewhat' to 'extremely satisfied' with the medication at their Endpoint evaluation.

A statistically significant ($p = 0.012$) decrease was noted in the mean rating of CGI-Severity at Visit 8 (-0.27 ± 0.75), with a trend ($p = 0.086$) for improvement being observed at Endpoint (-0.18 ± 0.81), compared to the baseline rating.

Results on the psychosocial, motivation/energy and symptoms/ side effects subscales of the SQLS did not indicate any statistically significant change from baseline in patients' quality of life, although a trend ($p= 0.085$) for improvement in the psychosocial subscale (mean score ± SD = -4.41 ± 18.84) was noted at Endpoint.

SAFETY RESULTS:

Fifty patients (83.3%) experienced one or more AEs and 7 patients (11.7%) experienced one or more serious AEs. Three patients (5.0%) discontinued treatment because of an AE. There were no deaths in the study. The most frequently reported AEs are summarized in the following table.

Adverse events reported in ≥5% of patients

Adverse event	Number of patients (%)
Insomnia	13 (21.7)
Psychotic disorder NOS	12 (20.0)
Headache	10 (16.7)
Akathisia	4 (6.7)
Pain in extremity	4 (6.7)
Upper respiratory tract infection NOS	4 (6.7)
Amxiety	3 (5.0)
Back pain	3 (5.0)
Nasopharyngitis	3 (5.0)

Vital signs: No statistically significant change was note in any of the vital sign parameters at any time point in the study. However, at EP, 4 (6.7%) were above and 2 (3.3%) of patients were below the normal range for body weight.

ECG: No statistically significant change from baseline was noted in any ECG parameter at Visit 8 or EP. With regard to clinically notable values, one patient each experienced elevated heart rate, low heart rate, and elevated QT interval (≥500 msec). The evaluation of QTc intervals indicated that no patient had an increase of >60 msec, while one male patient had a prolonged QTc (>450 msec) at EP.

There were no clinically relevant concerns in any of the physical examination findings, laboratory test results, or vital sign parameters.

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CONCLUSIONS:

The results of the present trial confirm the following:

The utility of the RISPERDAL® CONSTA® Treatment Guidebook was established in a 'real-world' setting, the CMHC. This is supported by excellent adherence to treatment, by both physicians and patients, with a novel medication and delivery system. Overall, 90% of Clinicians found the Guidebook to be 'quite a bit' or 'extremely' useful in treating their patients with RISPERDAL® CONSTA®. There was a high rate of adherence by clinicians to the treatment guidelines, with a low frequency of errors due to improper dosing of oral RISPERDAL®, or injections outside the specified window, and no cases of premature dose increases being observed. Failure to alternate injection site from right to left buttock, occurring at only 11% of visits, was the most common type of non-adherence to the guidelines.

The results of the CGI-Severity rating indicated a significant improvement at the final visit in this stable patient population. This overall improvement was also reflected in the mean score for the CGI-Change from baseline rating.

Treatment with RISPERDAL® CONSTA® was well-accepted by patients, with 86% of patients reporting that they were 'somewhat' to 'extremely' satisfied with the medication. This is also supported by the high rates of preference over previous oral therapy and low/declining concern regarding injection pain over the course of the trial

Although no significant changes in quality-of-life were measured using the SQLS, this is considered to be due to the short study duration and the stability of the patient population. A trend for improvement in the Psychosocial subscale was noted at EP.

In this trial, RISPERDAL® CONSTA® was shown to be safe and well tolerated, with the incidence of treatment emergent adverse events being low. Adverse events were mostly of mild to moderate severity and were typical of what would be expected in this patient population. In addition, only 5% of patients discontinued treatment due to adverse events, and only 7 patients experienced SAEs, 6 of which were due to hospitalization for psychiatric disorders.

No clinically important changes were observed in laboratory parameters, vital signs, physical findings, or ECGs, except for a clinically notable increase in body weight at EP, compared to baseline, which was observed in four patients.

Although 10 patients with normal prolactin levels at baseline had high prolactin at EP, for the population as a whole, the mean prolactin levels decreased over the course of therapy.

Date of the report: 08/05/05

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