SYNOPSIS

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

Protocol No.: CR002830

Title of Study: An Open-Label Study of the Efficacy and Safety of RISPERDAL® Long-Acting Microspheres (RISPERDAL® CONSTA®) administered once monthly in Adults with Schizophrenia or Schizoaffective Disorder

Coordinating Investigator: Multicenter Study

Publication (Reference): None

Study Period: 16 May 2002 to 19 December 2003	**Phase of development:** 3b

Objectives: The primary objective of this pilot study was to explore the efficacy of 50 mg RISPERDAL® CONSTA® given once monthly, as measured by relapse incidence over 12 months in subjects with schizophrenia or schizoaffective disorder. Secondary objectives were a pilot exploration of the efficacy of RISPERDAL® CONSTA® given once monthly as assessed by the Clinical Global Impression (CGI) scale, the Positive and Negative Syndrome Scale (PANSS) total score, as well as PANSS positive, negative, and general psychopathology subscales; to explore the safety of RISPERDAL® CONSTA® given once monthly as assessed by collection of treatment-emergent adverse events (AEs), the Extrapyramidal Symptom Rating Scale (ESRS), the Abnormal Involuntary Movement Scale (AIMS), and the Dickson-Glazer Sexual Functioning Inventory (DGSF), as well as changes in vital signs, laboratory parameters, and ECG measures; to explore the effect of RISPERDAL® CONSTA® given once monthly on cognition, functional outcomes, and subject quality of life as measured by a computerized cognitive test battery, the Strauss-Carpenter Level of Functioning Scale (LOF), the Personal and Social Performance Scale (PSP), and the Schizophrenia Quality of Life Scale (SQLS), respectively; to examine the PK profile of RISPERDAL® CONSTA® when given once monthly; to investigate dopamine D2 receptor occupancy in striatal brain regions -using Positron Emission Tomography (PET); and to investigate the relationship between D_2 receptor occupancy and plasma levels of risperidone and 9-OH-risperidone.

Methodology: This prospective, open-label, single-arm, multicenter study consisted of two phases: Pre-treatment and Treatment. In -the Pre-treatment phase -subjects continued on a stable dose of oral RISPERDAL® (2-6 mg/d) for up to 14 days. Prior to the Screening period, subjects were to have been clinically stable on oral RISPERDAL® (2-6 mg/d) for at least six weeks.

The open-label Treatment phase, which consisted of two periods, RISPERDAL® CONSTA® Lead-In and RISPERDAL® CONSTA® Monthly over a total of 52 weeks -The RISPERDAL® CONSTA® Lead-In period consisted of four weeks (two visits) of treatment during which 50 mg RISPERDAL® CONSTA® was administered every two weeks. Two weeks of oral RISPERDAL® supplementation (2-6 mg/d, taken as a single dose) followed the first injection of RISPERDAL® CONSTA® only. The RISPERDAL® CONSTA® Monthly period consisted of 48 weeks of treatment during which treatment with 50 mg RISPERDAL® CONSTA® was administered once monthly. Oral RISPERDAL® was not permitted during -this phase. At the three-week point of each treatment cycle (i.e., 21±3 days post injection), a telephone assessment occurred to assess inter-visit stability.

If criteria for relapse were met during the study, the clinician and subject decided on: (1) the subject was discontinued from the study, or (2) the subject continued in the trial on a higher dose (75 mg) of RISPERDAL® CONSTA® administered once monthly

During the Extension phase, RISPERDAL® CONSTA® was administered using a flexible dosing regimen of pre-assigned doses (25, 37.5, 50 or 75 mg) administered every 2 or 4 weeks until 1 months of commercialization or the decision on noncommercialization.

A very small subset of subjects participated in a Positron Emission Tomography (PET) examination study.

Number of Subjects (planned and analyzed): 80 subjects were planned, 87 subjects entered the study, 67 were analyzed for efficacy in the Intent-to-Treat (ITT) population and 64 in the ITT-2 population, and 87 were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Subjects were 18 to 65 years of age; had a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria; were judged to be symptomatically stable(for psychiatric symptoms)-, and medically stable; were on AP monotherapy with oral RISPERDAL® at a stable dose between 2 and 6

SYNOPSIS (CONTINUED)

mg/day for eight weeks prior to Baseline; were not pregnant or breast-feeding; and were not hospitalized or required acute crisis intervention for symptom exacerbation in the eight weeks prior to Baseline, nor were likely to require hospitalization during the study.

Test Product, Dose and Mode of Administration, Batch No.: RISPERDAL® CONSTA® suspension was administered by intramuscular (gluteal) injection in 50 mg (batch numbers 164-1071BB/115006 and 164-2081BA/115006) or 75 mg (batch number 164-0751AA/115006) doses. -RISPERDAL® was administered orally in 1 mg (batch numbers 01B09/F005 and 01C28/F005), 2 mg (batch number 01L05/F013), or 4 mg (batch number 00C29/F12) tablets.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: RISPERDAL® tablets were administered for 2 weeks (Weeks 0 to 2); RISPERDAL® CONSTA® was administered for 52 weeks (Weeks 0 to 52). - -Those subjects who received RISPERDAL® CONSTA® 75 mg continued treatment for least 6 months-

Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters of active moiety, risperidone and 9-hydroxy-risperidone were determined: -($C_{min,ss}$), --($C_{max,ss}$), -($t_{max,ss}$), -(AUC_{4w}), --($C_{avg,ss}$), and the fluctuation index (FI), -calculated as 100*[(C_{max}-C_{min})/$C_{avg,ss}$]. Peak to trough ratios (C_{max}/C_{min}) were also calculated.

Efficacy: The primary parameter assessed in this trial was relapse, defined by any one of the following: psychiatric hospitalization due to worsening symptomatology -, an increase in the level of psychiatric care required by the subject -and an increase of 25% from Baseline in the PANSS total score, occurring within two weeks of one another; substantial clinical deterioration, as indicated by a score of 6 (“much worse”) or 7 (“very much worse”) on the CGI-C scale; or deliberate self-injury, suicidal or homicidal ideation that is clinically significant as determined by the Investigator, or violent behavior resulting in clinically significant injury to another person or property damage.

The secondary efficacy rating instruments used in the study were the PANSS, the Clinical Global Impression of Severity (CGI-S) scale, the Clinical Global Impression of Change (CGI-C) scale, the LOF scale, the PSP scale, the SQLS, a computerized cognitive test battery; and subject satisfaction and attitude summaries.

Safety: Safety was assessed based on the emergence of treatement-emergent adverse events, physical examination, vital sign and ECG measurements, laboratory evaluations, AIMS, and DGSF scores.

Statistical Methods:

The primary efficacy analysis of time-to-relapse was summarized using Kaplan-Meier methodology using Week 0 (Visit 2) as Baseline. One-year incidence of relapse was the primary endpoint. The secondary efficacy analyses comprised summary statistics on changes from baseline and observed values for the secondary efficacy variables, the PANSS, CGI-C, CGI-S, LOF, PSP, SQLS, and Cognitive measures, at each time of evaluation and at each subject's last efficacy evaluation (Endpoint). A paired t-test for the difference between Baseline and Endpoint was an optional analysis for those secondary parameters over all subjects. Subject preference and attitudes regarding the study medication were measured by a Likert-type scale and summarized using mean, standard deviation, median, minimum, and maximum, or frequencies and percents, as appropriate. Comparison of the stratification subgroups was done using Pearson's chi-square statistic or Wilcoxon rank-sum statistic, as appropriate.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS:

During the 1-month lead-in period with RISPERDAL® CONSTA® every 2 weeks and oral risperidone once daily from Weeks 0-2, average plasma concentrations of active moiety, risperidone, and 9-hydroxy-risperidone at Visits 2-4 were stable and comparable to those in the RISPERDAL® CONSTA® Monthly period. Plasma concentrations of active moiety, risperidone, and 9-hydroxy-risperidone at Visits 5-16 also remained stable throughout the study. Between Week 24 and Week 28, the mean C_{max}/C_{min} ratio of active moiety, risperidone, and 9-hydroxy-risperidone after once monthly injections of 50 mg RISPERDAL® CONSTA® was 7.36 for active moiety, 10.3 for risperidone, and 6.82 for 9-hydroxy-risperidone. The once-monthly injection of 50 mg RISPERDAL® CONSTA® resulted in a “fluctuation index” of 199%, 219% and 192% for active moiety, risperidone, and 9-hydroxy-risperidone, respectively.

EFFICACY RESULTS:

Treatment with RISPERDAL® CONSTA® 50 mg was associated with relapse in 17.9% of subjects (12 of 67) over a 52-week period. Of the 12 subjects who relapsed during the trial, 8 received treatment with 75 mg RISPERDAL® CONSTA® dosed every 4 weeks; none of these 8 subjects relapsed.

SYNOPSIS (CONTINUED)

Improvements from baseline were noted on the PANSS (positive symptoms, negative symptoms, and general psychopathology), CGI-S, and CGI-C in response to 50 mg RISPERDAL® CONSTA® given every 4 weeks (OC analyses). Although subjects who completed the study did well, no statistically significant improvements were seen at the Endpoint evaluation, most likely because (LOCF) analysis included the data from the final efficacy assessments for those subjects who relapsed. As there was no placebo control in this study, a more relevant measure of the efficacy of RISPERDAL® CONSTA® given every 4 weeks is the rate of relapse and the average time to relapse. RISPERDAL® CONSTA® 50 mg led to improvement or maintenance of the baseline "stable" state in approximately 80% of the subjects at endpoint, as judged by the CGI-C.
The majority of subjects rated treatment with RISPERDAL® CONSTA® better than treatment with oral antipsychotics, including oral risperidone, as assessed by the subject's attitude and satisfaction scale. Subjects also had little concern regarding the pain of injection, and overall, were very satisfied with RISPERDAL® CONSTA® as their current treatment.

A total of 7 subjects (6 male; 1 female) participated in the PET study. Associations of (1) lower plasma levels of the active moiety and lower D2 receptor occupancy and (2) higher plasma levels and greater D_2 receptor occupancy were observed-

SAFETY RESULTS:

Adverse events (AE) Most frequently reported AE (≥5% of subjects):	n (% of subjects)
Schizophrenia NOS aggravated	17 (19.5)
Anxiety	14 (16.1)
Insomnia	14 (16.1)
Headache	10 (11.5)
Agitation	7 (8.0)
Anxiety aggravated	6 (6.9)
Upper respiratory tract infection	6 (6.9)
Nasopharyngitis	5 (5.7)
No. (%) with one or more AE	67 (77)
No. (%) of deaths	0
No. (%) with one or more serious AE	19 (21.8)
No. (%) treatment stopped due to AE	9 (10.3)

Analysis of the safety data collected over a one-year period in 87 subjects indicates that treatment with RISPERDAL® CONSTA® 50 mg (or 75 mg in 8 subjects) using a four-week injection interval is well tolerated and safe. This conclusion is based on the paucity of SAEs (including the absence of deaths) considered causally related to treatment, the infrequent occurrence of AEs rated “severe,” the low rate of discontinuation due to AEs, and the low incidence of notable abnormalities in vital signs, laboratory tests or ECG examinations.

-Ten of the cases of SAEs -were due to worsening of the underlying psychiatric condition. Most of the others SAEs represent concomitant diseases and conditions commonly seen in subjects with schizophrenia. -An interesting finding is the extremely low incidence of injection site pain (2.3%). Overall, very few AEs were rated “severe” (9.5% of all AEs).

The incidence of movement disorders noted as AEs was also low. Tremor was the most frequently reported AE related to movement disorders, with an incidence of 4.5%. On the AIMS, an improvement at endpoint was observed for subjects who received 50 mg of RISPERDAL® CONSTA®, but a slight worsening was seen for those subjects who received 75 mg. A statistically significant improvement was noted at endpoint in the total ESRS score for the subjects receiving 50 mg RISPERDAL® CONSTA®, while those subjects who received the 75 mg dose showed a – numeric improvement.

There were no clinically relevant changes from baseline at endpoint in clinical chemistry, hematology, or urinalysis parameters observed--Five subjects had newly occurring elevations in prolactin levels. - Fourteen(19.4%) subjects had a marked elevation in blood glucose at some time during the trial. However, only 4 subjects with normal glucose levels at baseline had elevated levels at endpoint, while 5 subjects who had high values at baseline which normalized at endpoint. Additionally, no clinically meaningful changes from baseline in any of the vital signs or ECG parameters at endpoint were observed.

Assessment of sexual functioning performed using the DGSF scale indicated improvements in some aspects for both

SYNOPSIS (CONTINUED)

male and female subjects. - Additionally, a number of female subjects reported their periods to be less regular at endpoint, compared to baseline. -

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

There was no apparent relationship between the active moiety, risperidone, and 9-hydroxy-risperidone plasma concentrations and any change in efficacy parameters or movement disorder ratings.

CONCLUSION:

These results represent an initial pilot open-label examination of RISPERDAL® CONSTA® 50 mg administered once monthly. The one-year relapse rate of 19% is similar to historical data from studies evaluating antipsychotic therapies in the long-term treatment of subjects with schizophrenia. The mean time to relapse (SE) was 283 (10.2) days.

Improvements in symptomatology-(PANSS and CGI-C, OC analyses)were seen, despite subjects being clinically stable at baseline.

Safety findings were similar to available data for subjects switched from oral RISPERDAL® to RISPERDAL® CONSTA®, including a mean decrease in movement disorder ratings and serum prolactin concentration, and a mean weight decrease over the course of the year. While population PK analysis found trough plasma concentrations of active moiety to remain stable throughout the study of 50 mg once monthly, intensive PK sampling showed lower C_{min} (trough) values for active moiety (approximately half) in an historical comparison to 25 mg given every two weeks. As well, the percentage fluctuation and the C_{min} to C_{max} ratios were approximately three times higher with monthly injections. The average exposure to active moiety was comparable between the once-monthly injection and historical data with the biweekly injection.

Given the open-label, uncontrolled study design and the rate of relapse observed, which was similar to that of previous studies using biweekly injections, this trial is inconclusive, neither supporting nor refuting the potential value of a 4-week dosing interval. While monthly dosing may ultimately prove to be appropriate for some individual subjects, no predictions can be made from this data regarding individual schizophrenic subjects who would be most likely to benefit from this treatment regimen. The findings of this study do not reject the possible efficacy of a once-monthly injection paradigm, and therefore provide support for - considering a controlled study of an alternative dosing interval. However, the results do not support the use of RISPERDAL® CONSTA® 50 mg given once monthly in clinical practice.

Date of the report: 02 March 2005

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.