SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RISPERDAL® NAME OF ACTIVE INGREDIENT(S): Risperidone (R064766)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No: CR003274 **Title of Study:** An Open-Label, Long-Term Trial of Risperidone Long-Acting Microspheres in the Treatment of Subjects Diagnosed with Schizophrenia		
Coordinating Investigator: Ronald Brenner, M.D. - Neurobehavior Research Inc., 371 Central Avenue, Lawrence, NY 11559 USA		
Publication (Reference): None		
Study Initiation/Completion Dates: 14 November 2001 to 6 February 2004		**Phase of development:** 3
Objectives: The primary objective was to document the long-term safety of 25, 37.5 and 50 mg risperidone long acting injectable (LAI) given every 2 weeks to subjects diagnosed with schizophrenia who completed CR002761, a 3-month open-label study of risperidone LAI in subjects previously treated with oral neuroleptics other than risperidone. Efficacy in these subjects was evaluated as measured by Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI).		
Methodology: This was an open label, multicenter study of risperidone LAI (depot microsphere) treatment of subjects diagnosed with schizophrenia (DSM-IV) who completed CR002761. For inclusion in CR003274, a subject must have completed CR002761 within ≤7 days of enrollment in this extension study. Visit assessments occurred every 3 months. The end point/last visit of CR002761 served as the first visit of CR003274. The first dose of risperidone LAI administered at Visit 1 was the same as the last dose administered at completion of CR002761 (25, 37.5, or 50 mg). The maximum risperidone LAI dose was 50 mg. Risperidone LAI was administered every 2 weeks by intramuscular injection. After the first injection of CR003274, the dose of risperidone LAI could be increased or decreased by 12.5 mg increments, as determined by the investigator. Throughout the study, oral risperidone could be administered as supplementation to risperidone LAI if the investigator determined that it was needed.		
Number of Subjects (planned and analyzed): No formal sample size calculation was performed for this open-label, long-term safety extension study. Any subject who completed CR002761 was eligible to enter CR003274. It was anticipated that approximately 120 subjects would enter this study. One hundred subjects were enrolled at 23 sites in the United States.		
Diagnosis and Main Criteria for Inclusion: A DSM-IV diagnosis of schizophrenia and completion of CR002761 within ≤7 days of the end of study visit, and signing the CR003274 informed consent form. Inclusion criteria for CR002761 must have been met at entry to CR002761.		
Test Product, Dose and Mode of Administration, Batch No.: Subjects received 25 mg, 37.5 mg or 50 mg of risperidone LAI every 2 weeks. Oral risperidone supplementation could be given based upon investigator assessment. Vials containing 25, 37.5, and 50 mg risperidone LAI (Lot numbers 164-2081BA/107002, 164-0751AB/114004, 164-0751AB/107002, 164-0611AA/114005, 1640611BA2/107002) and prefilled syringes containing reconstitution vehicle (Lot numbers 164-0751AB/107002, 1640611BA/107002, 164-1071BA/107002) for intramuscular injection. Tablets containing 1 mg risperidone (Lot numbers 01C28/F005 and 01L04/F005.		
Reference Therapy, Dose and Mode of Administration, Batch No.: None		

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Duration of Treatment: This study was planned to continue for a period of at least 12 months but not more than 24 months and would end whenever risperidone LAI was commercially available in the U.S. The protocol was amended to allow subjects to continue for more than 24 months, when it seemed unlikely that commercial availability would occur in the first 24 months of the study.		
Criteria for Evaluation: Pharmacokinetics: Not applicable Efficacy: Efficacy was measured by the Positive and Negative Syndrome Scale (PANSS) and by Clinical Global Impression (CGI) - severity. Safety: Safety parameters included adverse events, clinical laboratory tests, vital signs, ECG, physical examinations, and height and body weight. Pharmacokinetic/Pharmacodynamic Relationships: Not applicable		

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Statistical Methods: Descriptive statistics summarized demographic and baseline (previous and extension) data and extent of exposure information.

Efficacy: The intent-to-treat analysis set was used in all efficacy analyses based on all subjects who received 1 dose of study medication. For the PANSS and the CGI-severity, the means and the mean changes from both the previous baseline (CR002761) and the extension baseline (CR003274) were provided at each time point and the extension end point. The results are provided for the observed case data and using the last-observation-carried-forward (LOCF) approach.

Safety: Safety analyses were performed for all subjects who received at least 1 dose of study treatment. The number and percent of subjects with treatment-emergent adverse events including serious adverse events, discontinuations due to adverse event, EPS-related, glucose-related, potentially prolactin-related, injection site-related and cerebrovascular-related adverse events were summarized. Change from baseline (previous) and (extension) in vital signs, laboratory tests and electrocardiograms were summarized with descriptive statistics.

SUMMARY - CONCLUSIONS

CR003274 was an open-label study that lasted approximately 2 years for subjects who completed CR002761. Baseline characteristics and psychiatric history were taken from the baseline of CR002761. The majority of subjects who entered the study were Caucasian and male. The mean age at the time of enrollment was 45.4 years, 7 subjects were 65 years or older.

Of 100 subjects treated in CR003274, 30 (30.0%) received risperidone LAI for ≤6 months, 22 subjects (22.0%) for 7 to 12 months, 46 subjects (46.0%) for 13 to 24 months and 2 subjects (2.0%) for >24 months. The mean period of treatment was 347 days (SD 239 days), the median was 344.5 days and the range was 1 to 798 days. The distribution for the mode daily dose was as follows: 16 subjects at risperidone LAI 25 mg every 2 weeks, 28 subjects at 37.5 mg, and 56 subjects at 50 mg. The median mode-dose of risperidone LAI was 50 mg. The mean percentage of time with mode-dose risperidone LAI treatment was 93.12%.

PHARMACOKINETICS: Not applicable

EFFICACY RESULTS: During treatment with risperidone LAI, 36 (37.9%) subjects had a CGI rating at extension end point that indicated the severity of disease had improved from the previous baseline. At extension end point, 35 of 93 (37.6%) subjects demonstrated a clinical improvement (decrease of ≥20%) in their total PANSS score from the previous baseline. The overall incidence of discontinuation due to insufficient response was 11.0%.

Subjects who completed the study demonstrated an improvement in total PANSS and positive symptom subscale, based upon observed case means, versus subjects who discontinued treatment. The LOCF means for the total PANSS and positive symptom subscale remained below the mean scores from the previous baseline. A tendency towards worsening of the LOCF means relative to the extension baseline indicated that subjects who discontinued earlier in the study had worse scores than those who continued in the study.

For the PANSS negative symptoms subscale, the LOCF means steadily increased from extension baseline, and were higher than the previous baseline mean from Month 12 onward.

A slight increase in total PANSS and CGI mean scores by LOCF analysis was not considered of major clinical importance.

The efficacy results for the group who received oral risperidone supplementation during the extension study were similar to those for the group who did not receive oral risperidone. The 2 groups' efficacy was similar at the previous baseline and at the extension end point. At extension baseline, efficacy as demonstrated by PANSS was similar for both groups. The CGI was rated of moderate or marked severity for 13 (24.1%) subjects who did not receive oral risperidone and 17 (38.6%) subjects who received oral risperidone.

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SAFETY RESULTS: No major safety concerns were observed in this long-term extension study that lasted approximately 2 years. A total of 87 of 100 subjects reported treatment-emergent adverse events. Headache was the most frequently occurring treatment-emergent event (25.0%) followed by psychosis (21.0%). The overall incidence of EPS-related adverse events with onset during CR003274 was 22.0%. No adverse event of tardive dyskinesia was reported. Serious adverse events occurred in 25.0% of subjects. Most serious adverse events were of a psychiatric nature and were most likely due to the underlying disease condition.

Ten subjects prematurely discontinued study treatment associated with a treatment-emergent adverse event; 2 of the 10 subjects discontinued treatment due to a treatment-emergent adverse event and a non-treatment-emergent adverse event (weight increase and hyperkinesia). One additional subject discontinued due to an adverse event (hyperprolactinemia) with onset during the prior study. The majority of treatment-emergent adverse events were of mild or moderate intensity as determined by the investigators.

One subject died during treatment with risperidone LAI; the death was due to cardiac arrest and pulmonary arrest secondary to severe COPD, pulmonary hypertension and arteriosclerotic heart disease. The investigator assessed the adverse events leading to death as unrelated to study medication.

Overall, 64.0% of subjects discontinued study treatment. The most frequent reason for discontinuation was withdrawal of consent (21 [21.0%] of 100 subjects) followed by adverse event and insufficient response in 11 (11.0%) subjects each. There was no apparent relationship between the dose of risperidone LAI and withdrawal of consent.

There was no pattern of laboratory findings, ECG data, or vital signs that were of concern in this study. Subjects with abnormally high glucose values had only transient increases that resolved without treatment. Most abnormally high values for liver enzymes (ALT, AST, and GGT) were transient and returned to normal levels by end point.

An increase in mean body weight (1.7 kg) and mean BMI (0.6 kg/m^2) was observed from previous baseline to end point. An increase from extension baseline to end point was seen in mean body weight of 1.3 kg and mean BMI of 0.4 kg/m^2. In this extension study, little or no further increase in weight occurred after the first 12 months.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: not applicable

CONCLUSION: Risperidone LAI (25, 37.5, and 50 mg) intramuscular injection, given every 2 weeks, was safe, well tolerated, and effective in maintenance treatment of subjects with schizophrenia

Date of the report: 4 March 2005

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