SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Risperidone NAME OF ACTIVE INGREDIENT(S): Risperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR002017

Title of Study: Risperidone depot (microspheres) in the treatment of subjects with schizophrenia or schizoaffective disorder – an open-label follow-up trial of RIS-INT-62 and RIS-INT-85

Principal Investigator: Dr. Wlodzimierz Chrzanowski, Klinika Psychiatrii AMB, Choroszcz, Poland

Publication (Reference): None

Study Initiation/Completion Dates: 22 October 2001 / 01 March 2005 **Phase of development:** 3

Objectives: This was an open-label, long-term follow-up study of at least 1-year duration. Up to 280 subjects with schizophrenia or schizoaffective disorder who had participated in RIS-INT-62 and up to 160 subjects with schizophrenia who participated in RIS-INT-85 were to be included. The objective of the study was to document the long-term safety of 25, 37.5, or 50 mg risperidone LAI (microspheres) given every 2 weeks to subjects with schizophrenia or schizoaffective disorder.

Methodology: This open-label multicenter study conducted in Australia, Austria, Belgium, France, Germany, Great Britain, Greece, Poland, Russia, Spain, Sweden, and the Netherlands was designed to follow, for a period of at least 1 year, subjects from RIS-INT-62 or RIS-INT-85. RIS-INT-62 was a 12-month, multicenter, open-label, randomized, flexible-dose study comparing risperidone LAI with olanzapine in subjects with schizophrenia or schizoaffective disorder. RIS-INT-85 was a 12-week, multicenter, open-label, flexible-dose study exploring a switching regimen from typical depot neuroleptics to risperidone LAI in subjects with schizophrenia. Subjects began RIS-INT-80 within 7 days of their final visit in either RIS-INT-62 or RIS–INT-85. The end point visit of the preceding study served as the first visit of the open-label study. The risperidone LAI (depot microsphere) formulation (25, 37.5, 50, or 75 mg) was given as an intramuscular (IM) injection every 2 weeks. Subjects could start this study on the same dose of the last LAI injection that they received in the previous study or at a dose that was 12.5 mg lower or higher than the previously received dose; the lowest dose allowed in the study was 25 mg for all subjects. Subjects who received 75 mg during RIS-INT-62 could continue on this dose, however, an attempt was made to decrease the dose to 50 mg within 3 months. Efficacy and safety assessments were performed at regular intervals throughout the study. It was the intention of the sponsor to continue this study until the risperidone LAI microsphere formulation was commercially available or until the development of the risperidone LAI microsphere formulation was discontinued.

Number of Subjects (planned and analyzed): A maximum of 280 subjects from RIS-INT-62 and 160 from RIS-INT-85 could be recruited. A total of 315 subjects were included in this study. Investigators at 61 centers in 12 countries participated. No formal sample size calculation was done for this open-label, long-term safety extension study.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were those who either completed RIS-INT-62 or RIS-INT-85 in its entirety or who fulfilled, after being randomized, predefined withdrawal criteria from RIS-INT-62. Subjects had to continue to meet the following inclusion criteria:

- Male or female subject, aged >18 years;
- Diagnosis of schizophrenia (subjects from RIS-INT-62 or RIS-INT-85) or schizoaffective disorder (subjects from RIS-INT-62 only) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (295.10, 295.20, 295.30, 295.60, 295.70, or 295.90);
- Subjects who completed the risperidone microspheres arm of RIS-INT-62 or who completed RIS-INT-85. In addition, subjects in the risperidone microspheres arm of RIS-INT-62 who discontinued due to treatment with 75-mg risperidone LAI were eligible;

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Diagnosis and Main Criteria for Inclusion (Continued):

- No more than 7 days elapsed between subject participation in RIS-INT-62 or RIS-INT-85 and the start of RIS-INT-80 study;
- Subject signed the RIS-INT-80 informed consent form.

Subjects meeting one or more of the following criteria could not be selected:

- A DSM-IV Axis I diagnosis other than schizophrenia or schizoaffective disorder;
- History of neuroleptic malignant syndrome;
- Acute, unstable, and/or significant and untreated medical illness (e.g., infection, unstable diabetes, uncontrolled hypertension, unstable angina);
- A clinically significant electrocardiogram (ECG) abnormality;
- Pregnant or breast-feeding female;
- Female subject of childbearing potential without adequate contraception. Adequate contraception includes: abstinence, oral contraceptives, intrauterine devices, barrier method (diaphragm or condom) plus spermicide, Norplant™, or Depo Provera™;
- Known hypersensitivity to risperidone;
- History of severe drug allergy or hypersensitivity;
- Known to be unresponsive to risperidone;
- Use of disallowed concomitant therapy;
- Serious illnesses: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastro-intestinal (GI), endocrine, neurological, psychiatric, or metabolic disturbances.

Test Product, Dose and Mode of Administration, Batch No.: Subjects received 25, 37.5, 50, or 75 mg of risperidone long-acting injectable (LAI; depot microspheres) injections. Vials containing 25, 37.5, 50, or 75 mg risperidone LAI (batch number F109) and prefilled syringes containing reconstitution vehicle (diluent, batch number F101) for IM injection.

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

Duration of Treatment: Subjects were titrated to a best dose of either 25, 37.5, or 50 mg of risperidone LAI every 2 weeks for the duration of the study (at least 1 year or until the approval of risperidone LAI in the respective country). The dose could be increased or decreased by 12.5 mg every 2 weeks to a maximum dose of 50 mg based on the investigator's evaluation of the subject's clinical status. Subjects who received 75 mg during RIS-INT-62 could continue on this dose, however, an attempt was made to decrease the dose to 50 mg within 3 months. Throughout the duration of the study, treatment with risperidone LAI could be supplemented by oral risperidone at the discretion of the investigator.

Criteria for Evaluation: The end point visit of the preceding study (either RIS-INT-62 or RIS–INT-85) served as the first visit of RIS-INT-80.

Efficacy: Positive and Negative Syndrome Scale (PANSS; Visits 3 and 5 through 10 [end point (ext)]) and Clinical Global Impression (CGI; Visits 2 through 10 [end point]) scores. PANSS and CGI assessments done at the end point visit of the preceding study (RIS-INT-62 or RIS-INT-85) were used as baseline assessments for this extension study.

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Safety: Laboratory tests (Visits 6, 8, 9, and 10 [end point (ext)]), vital signs (Visits 2 through 10 [end point (ext)]), physical examination (Visit 10 [end point (ext)]), body weight (Visits 2 through 10 [end point (ext)]), and ECGs (Visits 6, 8, and 10 [end point (ext)]). Safety assessments performed at the end point visit of the preceding study (RIS-INT-62 or RIS-INT-85) were used as baseline assessments for this extension study.

Statistical Methods: Demographics and treatment-emergent adverse events, as well as baseline and end point visit-based data (including efficacy, laboratory, vital signs, ECG, and physical examination data) from the previous studies were included in the analysis data sets of RIS-INT-80. The end point visit (Visit 10) from the previous studies served as the first visit (Visit 1) for RIS-INT-80, with the exception of a blood draw for prolactin at Visit 1 of RIS-INT-80 for subjects entering the study from RIS-INT-62. Efficacy and safety were evaluated relative to both the baseline of the previous studies and the extension baseline of RIS-INT-80. Continuous variables were summarized using N, mean, standard deviation (SD), median, and range. For categorical variables, the number and percentage of subjects in each category were provided. The denominator for percentages was the number of subjects with data (i.e., subjects with missing data were excluded).

Efficacy: The intent-to-treat (ITT) analysis set was used in all efficacy analyses and included data from all subjects who received at least 1 dose of study drug. Results are provided for the observed case data and using the last-observation-carried-forward (LOCF) approach.

Safety: Safety analyses included data from all subjects who received at least 1 dose of study drug. 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. Other safety parameters were summarized over time.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS (for the subset of subjects diagnosed with schizophrenia):

- The means at the extension end point represented small increases from the extension baseline, but were well below the mean scores from the previous baseline for the mean total PANSS and subscale scores, and the mean CGI-S scores.
- At the extension end point, 60.8% of the subjects demonstrated a clinical improvement (decrease of ≥20%) in their total PANSS score from the previous baseline, and 29.4% from the extension baseline.
- There were 57.2% of the subjects who had CGI-S ratings at the extension end point indicating that the severity of disease had improved from the previous baseline, while 22.4% had CGI-S ratings indicating that the severity of disease had improved from the extension baseline.
- Among the RIS LAI OL subjects, 9.6% and 21.6% met the most conservative criteria for clinical worsening (i.e., ≥20% increase in total PANSS and ≥1 point increase in CGI-S) at the extension end point relative to the previous baseline and the extension baseline, respectively.
- The last observation carried forward (LOCF) results were similar to those from the observed case.
- For the subgroup who did not receive oral risperidone supplements at any time during the extension study, the total PANSS and the CGI-S results at the extension end point were more favorable than for the subgroup that received oral risperidone.
- The overall incidence of discontinuation due to insufficient response was 9.5%. The rates were 3.4% for those subjects previously in RIS-INT-62 and 17.4% for those who were previously in RIS-INT-85.
- Although there were differences noted between the RIS-INT-62 and RIS-INT-85 subject groups for the previous baselines and for the extension baselines, the mean PANSS and CGI-S scores at the extension end point were generally similar between the 2 subject groups.

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SAFETY RESULTS:

The mean (SD) duration of risperidone LAI treatment in this extension study, defined as the number of days from the first to the last injection of risperidone LAI in RIS-INT-80, was 522.9 (295.11) days (i.e., 17.2 months or 1.4 years), the median was 505 days and the range was 1 to 1136 days.

No major safety concerns were observed in this extension study that lasted approximately 3 years and 4 months. A treatment-emergent adverse event was reported by 82.9% of subjects. Hyperprolactinemia was the most frequently occurring treatment-emergent event (27.9%) followed by psychosis (21.6%). The overall incidence of extrapyramidal symptom (EPS)-related adverse events with onset during RIS-INT-80 was 7.0%. There were no reports of tardive dyskinesia in this study.

Serious adverse events occurred in 22.5% of subjects. Most serious adverse events were of a psychiatric nature and were most likely due to the underlying disease condition. One death (0.3%) occurred in this study. Death was due to a chest injury caused by a traffic accident. The investigator assessed the injury as not related to study drug. Ten (3.2%) subjects reported a total of 11 suicide attempts (verbatim terms included "suicide attempt" [x2], "suicidal tendency" or "suicidal tendencies" [x3], "suicidal ideations" [x2], "intoxification of caustic product of unknown origin" [x1], "tentamen suicide" [x1], suicidal thoughts [x1], and suicide obsession [x1]). Nine of 11 suicide attempts (9 subjects) were considered serious.

One hundred ten (34.9%) of 315 subjects discontinued study treatment; the most common reason for discontinuation was withdrawal of consent (11.7%). Overall, 5.4% of subjects in the ITT population discontinued with treatment-emergent adverse events (5.7% discontinued due to an adverse event), the majority of which were classified as psychiatric disorders. The majority of treatment-emergent adverse events were of mild or moderate intensity as determined by the investigators. Discontinuation due to insufficient response was reported in 9.5% of subjects.

Increases in mean (SD) body weight (1.2 [6.18] kg) and mean body mass index (BMI) (0.4 [2.14] kg/m^2) were observed from the extension baseline to extension end point. The increases were slightly greater in the RIS-INT-85 group (1.4 kg and 0.5 kg/m^2, respectively) compared with the RIS-INT-62 group (1.0 kg and 0.3 kg/m^2, respectively). There were no changes from previous baseline or extension baseline in laboratory findings, ECG data, or vital signs that were of concern in this study.

CONCLUSION:

Risperidone LAI IM injection (median modal dose: 37.5 mg), given every 2 weeks, was safe and well tolerated in long-term use in the treatment of subjects with schizophrenia or schizoaffective disorder. The results of this study are consistent with those of prior open-label, long-term, follow-up studies with risperidone LAI using comparable doses. The results confirm the long-term safety and tolerability of Risperdal LAI, suggest that stable subjects remain stable during treatment, and are consistent with information in the current label.

Date of the report: 31 MAY 2006

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