SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Risperidone 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.: CR002023

Title of Study Risperidone LAI in the treatment of subjects with schizophrenia or schizoaffective disorder – an open-label follow up trial of RIS-INT-57 and RIS-INT-61

Coordinating Investigator: Włodzimierz Chrzanowski , MD - Klinika Psychiatrii AMB, Białegostoku, Poland

Publication (Reference): None

Study Initiation/Completion Dates: 04 February 2000 / 14 March 2005 **Phase of development:** 3

Objectives: The objective of the study was to document the long-term safety of 25, 50 and 75 mg risperidone LAI given every 2 weeks to subjects with schizophrenia or schizoaffective disorder.

Methodology: This was an open-label, international, multicenter study in subjects with schizophrenia or schizoaffective disorder who either completed study RIS-INT-57 or RIS-INT-61 or who dropped out of RIS-INT-61 after the completion of 3 injection cycles. Subjects had to begin this study within 7 days of the final or endpoint visit in the RIS-INT-57 or RIS-INT-61 studies. The end point visit of RIS-INT-57 and RIS-INT-61 served as the first visit (Visit 1) of RIS-INT-63. The last visit of RIS-INT-57 and RIS-INT-61 was considered baseline of the extension study.

Number of Subjects (planned and analyzed): A total of 810 subjects participated in this study.

No formal sample size calculation was done for this open-label, long-term, extension safety study. All subjects from RIS-INT-61 and RIS-INT-57 who were eligible for entering RIS-INT-63 could be included in this study (i.e., a maximum of 1270 subjects).

Diagnosis and Main Criteria for Inclusion: Subjects had a diagnosis of schizophrenia (those from RIS-INT-57 or RIS-INT-61) or schizoaffective disorder (subjects from RIS-INT-57 only) according to the DSM IV criteria.

Inclusion Criteria

Subjects who met all of the following criteria were eligible for this study:

- Aged ≥18 years;
- Subject completed RIS-INT-57 or RIS-INT-61 or dropped out after completion of 3 injection cycles in RIS-INT-61 (i.e. at or after Visit 4);
- Informed consent signed by subject and/or subject's relative, guardian or legal representative;
- Subject was otherwise healthy on the basis of a pre-study physical examination, medical history and anamnesis.

SYNOPSIS (CONTINUED)

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Test Product, Dose and Mode of Administration, Batch No.: Study medication was provided in vials that contained risperidone LAI in concentrations of 25, 50 or 75 mg, prefilled syringes that contained 2 mL of diluent for intramuscular injection and oral tablets containing either risperidone 2 mg, risperidone 4 mg, risperidone 6 mg or no active ingredient (placebo) only for subjects enrolled from RIS-INT-61.

The following batch numbers were used: Risperidone 2 mg tablet - 99H10 F13, 98D22/F13; 4 mg tablet - 99E18/F12; 6 mg tablet - 99E19/F11.

Risperidone LAI 25 mg - 164-2298BC, 164-2060BB, 164-0611AA, 164-0100AB, 164-2928AC, 164-0240DB
Risperidone LAI 50 mg - 164-2438BC, 164-2420CC, 164-164-0240DC164-2060AA 2081BA, 164-0100AA, 164-2928AB.
Risperidone LAI 75 mg - 164-2298AA, 164-2420AA, 164-0751AA, 164-0100CB, 164-0240CB, 164-2060BA.

Subjects who had completed the RIS-INT-57 study were to continue on the same dose of risperidone LAI injections as they had received the last 3 months of that study. Subjects who had completed or dropped out of RIS-INT-61 were to continue on the same or equivalent dose they received during that study. The blind was not broken when the subject terminated RIS-INT-61. Therefore, the subjects entering RIS-INT-63, were to receive, during the first 3 weeks of this study, double-blind oral medication:

- subjects who were treated with placebo tablets and risperidone LAI treatment were to continue to receive placebo tablets;
- subjects who were treated with risperidone tablets and placebo depot treatment were to receive 2, 4, or 6 mg risperidone active tablets according to their previous medication schedule.

During RIS-INT-63, the dose of risperidone LAI could be increased or decreased by 25 mg increments (from 25 to 50 mg, or from 50 to 75 mg or from 25 to 50 to 75 mg or vice versa) at the discretion of the investigator.

Also throughout the study a maximum of 4 mg oral risperidone could be administered as a supplement to the risperidone LAI injections at the discretion of the investigator if clinically needed for a maximum of 2 weeks in a row.

Duration of Treatment: The total study duration was planned to be at least 1 year. The study was to be stopped when risperidone LAI was registered and commercially available on the market in the respective countries participating in this study or when the development was terminated.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation: The end point visit of the prior studies served as the first visit of the extension study.

Pharmacokinetics: Not applicable

Efficacy:

CGI	- Baseline, and each study visit thereafter

Safety:

Laboratory tests	- Baseline, Months 6, 12, 24, 36 and end point
Vital signs	- Baseline, Month 3, 6, 12, 24, 36 and yearly thereafter and end point
Physical examinations	- Baseline and end point
Body Weight	- Baseline 1 and each study visit thereafter
ECG	- Baseline, Month 3, 6, 12, 24, 36 and yearly thereafter and end point
Injection Site Evaluation	- Baseline 1 and each study visit thereafter and end point
ESRS	- Baseline, Month 3, 6, 12, 24, 36 and yearly thereafter and end point

Pharmacokinetic/Pharmacodynamic Relationships: Not applicable

Statistical Methods:

Descriptive statistics summarized demographic and baseline (from the previous studies RIS-INT-57 and RIS-INT-61, and from this extension study, RIS-INT-63) data and extent of exposure information. Subjects were grouped according to their most frequently used dose of risperidone LAI (i.e., their mode dose): risperidone 25-50 mg LAI and risperidone 75 mg LAI as well as by prior trial and treatment.

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 CGI-severity, the means and the mean changes from both the previous baseline and the extension baseline 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.

SYNOPSIS (CONTINUED)

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Not applicable

EFFICACY RESULTS: During treatment with risperidone LAI during this extension study, 208 out of 741 (28.1%) subjects had a CGI rating at extension end point that indicated that the severity of disease had improved from the start of the extension study. There were 366 of 741 (49.5%) subjects with the same CGI rating at extension end point than at the start of the extension study.

Overall, there was a decrease in the mean CGI severity score during treatment with risperidone LAI compared to the previous baseline, with most of the change occurring during the previous study.

In the group of subjects who used oral risperidone supplementation, a slight increase in mean CGI severity score was observed from extension baseline to extension end point. In the group of subjects who did not use any oral risperidone supplementation during the extension study, a decrease in mean CGI severity score was observed from extension baseline to extension end point.

SAFETY RESULTS: No major safety concerns were observed in this long-term extension study that lasted approximately 2 years. A treatment-emergent adverse event was reported by 86.3% of subjects. Insomnia was the most frequently occurring treatment-emergent event (24.7%) followed by anxiety (21.5%). The overall incidence of EPS-related adverse events with onset during RIS-INT-63 was 24.4%. Tardive dyskinesia was reported in 8 (1.0%) subjects. Serious adverse events occurred in 30.9% of subjects.

There were 422 (52.1%) of subjects who discontinued study treatment; the most common reason for discontinuation was withdrawal of consent (19.5%). Overall, 7.0% of subjects discontinued with treatment-emergent adverse events, 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 8.1% of subjects.

Seventeen deaths (2.1%) occurred in this study. Cardiovascular reasons and suicide were the most frequent cause of death. Four subjects committed suicide (3 in 50 mg risperidone LAI and 1 in 75 mg risperidone LAI mode dose). Two subjects died of myocardial infarction (both in 50 mg mode-dose group) and 2 subjects died of cardiac failure (1 in 50 mg and 1 in 75 mg mode-dose group). The adverse events with outcome of death were assessed by the investigator as not related to study medication except 1 death due to cardiac failure which was considered doubtfully related.

There was no pattern of laboratory findings, ECG data, or vital signs that were of new concern in this study. From extension baseline to end point, the mean weight increase was 1.3 kg (SD 8.4) and BMI 0.5 kg/m^2 (SD 2.9). The total weight increase for the duration of risperidone use from previous baseline to end point was an average (SD) of 2.7 (9.51) kg. The increase was similar for both the mode-dose groups and overall.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: Not applicable

CONCLUSION: Risperidone LAI (25, 50, and 75 mg) intramuscular injection, given every 2 weeks, was safe, well tolerated, and effective in the treatment of subjects with schizophrenia or schizoaffective disorder. Efficacy was maintained for up to 4.8 years with treatment with risperidone LAI.

Date of the report: 9 JANUARY 2006

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