SYNOPSIS

Name of Sponsor/Company: Janssen Pharmaceutica, Inc. Name of Finished Product: Risperdal® Name of Active Ingredient(s): Risperidone (R064766)	

Protocol No.: CR002758

Title of Study: A Six-Month, Double Blind, Randomized, International, Multicenter Trial to Evaluate the Glucoregulatory Effects of Risperidone and Olanzapine in Subjects with Schizophrenia or Schizoaffective disorder.

Coordinating Investigator: Multicenter Study

Publication (Reference): None

Study Period: 29 May 2002 to 12 August 2003	**Phase of development:** 4

Objectives: The primary objective of this small pilot trial was to compare glucoregulatory effects associated with risperidone and olanzapine in the maintenance treatment of patients with schizophrenia or related disorders as measured by change in the disposition index (DI; derived from FSIVGTT) over six months. The secondary objectives of this trial were to compare the short and long term metabolic profile of risperidone vs. olanzapine in subjects with schizophrenia or related disorders as assessed by changes from baseline to study endpoint (6 months) on various metabolic measures; to compare the short and long term efficacy of risperidone and olanzapine in patients with schizophrenia or related disorders; and to compare the safety and tolerability of maintenance treatment with risperidone or olanzapine in subjects with schizophrenia or related disorders

Methodology: This trial was a small randomized, double blind, parallel group comparison of the glucoregulatory and metabolic effects of maintenance therapy with risperidone or olanzapine in subjects with schizophrenia or related disorders. Consenting subjects entered a 45-day screening evaluation phase to determine study eligibility. Following completion of all baseline evaluations, subjects were randomized to either risperidone or olanzapine therapy for the 6-month double-blind treatment phase of the study. Primary evaluations for measurements of glucose and insulin levels were completed at baseline (Day 0), week 6 (visit 8), and month 6 (visit 13).

Number of Subjects (planned and analyzed): Because no prior data were available from which both variability and effect size of the primary endpoint in this population could be accurately estimated and from which a good sample size calculation could be derived, expert consensus was used as a basis for estimation of the number of subjects that would be valuable to include in this pilot trial. 60 subjects were planned, 59 subjects were randomized to treatment (28 risperidone, 31 olanzapine), 58 were analyzed for efficacy in the Intent-to-Treat (ITT) population (28 risperidone, 30 olanzapine) and 59 were analyzed for safety (28 risperidone, 31 olanzapine).

Diagnosis and Main Criteria for Inclusion: Patients with a diagnosis of schizophrenia or schizoaffective disorder between the ages of 18 and 65 who were considered medically and psychiatrically (Clinical Global Impression [CGI] < 4) stable and who would benefit from treatment with an atypical antipsychotic were included. Main exclusion criteria included patients that received risperidone, olanzapine, quetiapine, or clozapine within 30 days of baseline and any patient with a known history or diagnosis at screening/baseline visit of diabetes mellitus, or any illnesses that would bias study evaluations (including patients that were HIV positive at screening).

Test Product, Dose and Mode of Administration, Batch No.: Risperidone was orally administered in 2 mg overencapsulated capsules (batch number 21601C0). Risperidone capsules were administered with identically-appearing placebo (P) capsules (batch number 21601A0) to achieve a final dose of 2 mg (2+P+P+P), 4 mg (2+2+P+P), or 6 mg (2+2+2+P) risperidone.

Reference Therapy, Dose and Mode of Administration, Batch No.: Olanzapine was orally administered in 5 mg overencapsulated capsules (batch number 21601B0). Olanzapine capsules were administered with identically-appearing placebo capsules (batch number 21601A0) to achieve a final dose of 10 mg (5+5+P+P), 15 mg (5+5+5+P), or 20 mg (5+5+5+5) olanzapine.

Duration of Treatment: 6 months.

Criteria for Evaluation:

Glucoregulatory: The primary study endpoint was the disposition index over 6 months as derived from the frequently-sampled intravenous glucose tolerance test (FSIVGTT). Other FSIVGTT data included insulin sensitivity, fasting glucose, fasting insulin, first phase insulin response (AIR), 20-minute glucose, 20-minute insulin, glucose distribution

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volume, insulin clearance, glucose disappearance (Kg) and glucose effectiveness (SG) for Week 6 and Week 24.

Efficacy: The efficacy variables were the Positive and Negative Syndrome Scale (PANSS) and Clinician Global Impression (CGI) scores. The PANSS was administered at baseline (visit 2), after 6 weeks (visit 8) and 6 months (visit 13) of study medication. In addition, Global Assessment of Functioning (GAF) was administered at baseline (visit 2), after 6 weeks (visit 8), and 6 months (visit 13) of study medication. The CGI, both Severity (CGI-S) and Clinical Improvement (CGI-I) was administered at each study visit. For this study, a CGI-I score of 1 or 2 at study endpoint was considered evidence of a clinical response.

Safety: Adverse events, clinical laboratory testing (including clinical chemistry, electrolytes, liver function tests, and hematology), vital signs, physical examination, ECG, extrapyramidal symptom (EPS) rating scales (including Abnormal Involuntary Movement Scale [AIMS], the Barnes Akathisia Scale, and the Simpson-Angus Scale), waist-to-hip ratio, lipid profile, and Insulin Resistance Index were assessed.

Statistical Methods: The change in the disposition index from baseline over 6 months was analyzed using a repeated measures analysis model including treatment, time, treatment by time interaction and subject as main effects, and baseline as a covariate. The subject was treated as a random effect to build up a within subject correlation between observations at two points of week 6 and week 24.

The slopes for observed DI scales from three time points: baseline, week 6, and week 24 were analyzed using a random regression model including treatment and subject as the main effect, and time as a covariate. A random regression over time was built by setting random intercept and time effects for each subject.

The change from baseline to Week 24 using analysis of covariance (ANCOVA) model including the baseline score (the covariate), center and treatment. A preliminary model included a term for baseline by treatment interaction to test the assumption of parallel slopes. When a significant baseline by treatment interaction was observed from the preliminary model, an analysis of variance (ANOVA) model with center and treatment as the main effects was used to analyze the treatment difference on DI value with no adjustment for baseline. For the model specified above, the least square means was provided for each treatment group and the 95% confidence interval was provided for the difference in the least square means between the two treatment groups. Change from baseline to Week 6 in DI was analyzed similarly.

Due to the extreme variability observed in DI values, the natural log transformation on the DI+1 was examined for normalization of the data. The repeated measures analysis, the random regression analysis, and the by time point ANCOVA analysis on the transform DI scale was also conducted.

The change from baseline to visits (Week 6 and Week 24) and/or endpoint analyses for insulin sensitivity, fasting glucose, fasting insulin, first phase insulin response, 20-minute glucose, 20-minute insulin, glucose distribution volume, insulin clearance, glucose disappearance, and glucose effectiveness was analyzed using analysis of covariance (ANCOVA) models as described above.

The repeated measures analysis, the random regression analysis, and the by time point ANCOVA analysis was also conducted for insulin sensitivity (SI) and first phase insulin response (AIR). In addition to the original SI and AIR scales, the natural log transformation on the SI+1 and the square root transform on AIR were examined for normalization of the data. The repeated measures analysis, the random regression analysis, and the by time point ANCOVA analysis on those transformed scales were also conducted.

SUMMARY - CONCLUSIONS

Of 59 subjects randomized to treatment, 45 completed treatment (21 risperidone, 24 olanzapine). Subjects ranged from 20 to 59 years of age, with a mean age of 39.7 years of age.

GLUCOREGULATORY RESULTS

Extreme variability in FSIVGTT results were observed at a magnitude not anticipated when the sample size of this pilot study was determined. No statistically significant differences in glucoregulatory parameters were observed between treatment groups. The direction and magnitude of the changes from baseline in the highly variable glucoregulatory parameters varied based on whether observed mean values, natural log transformed mean values, or ANCOVA mean values were used. No difference over time was observed in the repeated measures or random regression models. Also, as is the case with weight gain associated with antipsychotic treatment, it is likely that some specific at-risk patients experience aberrations in glucose metabolism while others remain unaffected.

Therefore, conclusions from the small sample size included in this pilot study cannot be drawn based on mean values and regression analysis alone. For this reason, multiple post-hoc analyses to evaluate the relationship between these treatments and glucoregulation will be conducted and presented in a separate report.

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EFFICACY RESULTS:

This trial was not statistically powered to measure differences between treatments in efficacy. Furthermore, patients entering the trial were psychiatrically stable, thus improvement in efficacy scores was not expected to be substantial. Nevertheless, mean PANSS, CGI, and GAF scores numerically improved in both treatment groups. Patients in the risperidone group had greater improvement numerically in the PANSS total score and statistically in the hostility/aggression subtotal score compared to patients in the olanzapine group. Most importantly, both treatments adequately controlled patients' symptoms throughout the trial such that a high completion rate was observed.

SAFETY RESULTS:

Adverse events (AE) Most frequently reported AE:	Risperidone (n = 28)	Olanzapine (n = 31)
Dry mouth	6 (21.4)	10 (32.3)
Feeling hot	6 (21.4)	8 (25.8)
Somnolence	6 (21.4)	6 (19.4)
Insomnia	6 (21.4)	5 (16.1)
Toothache	6 (21.4)	2 (6.5)
Anxiety	4 (14.3)	10 (32.3)
Weight increase	2 (7.1)	11 (35.5)
No. (%) with one or more AE	27 (96.4)	27 (87.1)
No. (%) of deaths	0 (0.0)	0 (0.0)
No. (%) with one or more serious AE	2 (7.1)	3 (9.7)
No. (%) treatment stopped due to AE	1 (3.6)	2 (6.5)

In general, both study medications were well tolerated. Few serious adverse events or adverse events that led to discontinuation were reported. No patient discontinued due to lack of efficacy, and only 1 patient reported a serious adverse event of worsening psychiatric symptoms. No adverse events of diabetes were reported; however, 2 patients (one in each treatment group) had fasting blood glucose levels in the diabetic range but did not report symptoms. Consistent with the known tolerability profile of olanzapine, percentage of patients reporting weight gain was higher in the olanzapine group compared to the risperidone group. On average, patients in both treatment groups appeared to gain body fat, including abdominal and visceral abdominal fat. No consistent trends in changes in lipid profile parameters were observed between treatments in this small study. Adverse events of EPS and scores on the EPS rating scales were similar between treatment groups, with the exception of mean change in AIMS score at week 24, which was improved from baseline in the olanzapine group. No clinically significant changes in laboratory parameters (clinical chemistry, hematology, electrolytes or liver function tests) were observed between treatments. No clinically significant changes in mean QTc interval were observed for either group.

CONCLUSION:

Overall, both treatments were well tolerated with no adverse events of overt diabetes mellitus reported. However, fasting blood glucose values were reported in the diabetic range for two patients, one in each treatment group. Neither patient reported symptoms of diabetes. Based on the planned analysis, no differences between treatments were observed on the primary or secondary glucoregulatory outcome, though a very high and unanticipated level of measurement variation was found. Additionally, apart from greater weight gain in the olanzapine group compared to the risperidone group, no clinically significant trends were observed in other metabolic parameters in this small sample.

Definitive conclusions from this sample cannot be drawn based on usual comparative data analyses. Due to large inter-patient variability, analysis of group means was virtually uninterpretable. Additional analyses are to be conducted and presented in a separate report.

Date of the report: 20 JANUARY 2004

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