

CLINICAL STUDY REPORT SYNOPSIS**Issue Date:** 15 July 2008**Document No.:** EDMS-PSDB-8490859

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RISPERDAL® CONSTA® NAME OF ACTIVE INGREDIENT(S): Risperidone depot microspheres	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: RIS-BIM-3003 Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Explore the Efficacy and Safety of Risperidone Long-Acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar I Disorder, With Open-Label Extension		
Coordinating Investigator: Margarita Morozova, M.D., Ph.D - Mental Health Research Center, 34 Kashirskoye sh., Moscow 115522, Russia		
Publication (Reference): None		
Study Initiation/Completion Dates: 31 January 2005 to 20 December 2007		Phase of development: 3
Objectives: The primary objective of this study was to evaluate the efficacy of risperidone long-acting injection (LAI) vs. placebo in the prevention of a mood episode (relapse event) in subjects with Bipolar I disorder after a 26-week (6-month) stabilization period on risperidone LAI, as measured by the time to relapse of a mood episode. Additional objectives were: to evaluate the prevention of a mood episode (sustained efficacy of maintenance treatment) with risperidone LAI vs. placebo, as measured by the time to relapse of an elevated-mood episode (manic, hypomanic, or mixed) and the time to relapse of a depressive episode; to evaluate the overall duration of treatment of risperidone LAI vs. placebo, as measured by the time to discontinuation from study medication for any reason (including relapse) except termination of the study by the sponsor; to evaluate the sustained efficacy of maintenance treatment with risperidone LAI vs. placebo, using the Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), and Clinical Global Impressions – Severity (CGI-S) scale; to evaluate the sustained effect of maintenance treatment with risperidone LAI vs. placebo on mental health status, using the Medical Outcomes Study Short Form 36 (SF-36); and to evaluate the long-term safety of risperidone LAI in subjects with Bipolar I disorder.		
Methodology: The study was conducted in Austria, India, Malaysia, Poland, Russia, Slovakia, Spain, Taiwan, Ukraine, and the United States (U.S.). Following screening, subjects were divided into 3 groups based on their mood and medication status (i.e., acute episode, stable on risperidone, or stable on another antipsychotic or mood stabilizer). Subjects with an acute episode or subjects stable on another antipsychotic were eligible to enter 3 weeks of open-label oral risperidone treatment (Period II). Subjects who met criteria for an initial response during Period II and subjects stable on risperidone at screening were eligible to enter the 26-week (6-month) open-label risperidone LAI stabilization period (Period III). Subjects who maintained a treatment response and received a stable dose of risperidone LAI for the last 8 weeks of Period III were eligible to enter the double-blind treatment period (Period IV), for which they were randomly assigned to receive risperidone LAI or placebo (1:1 ratio) until they completed 24 months of treatment, met relapse criteria, withdrew from the study, or the study was terminated. After at least 1 visit during the double-blind treatment period, subjects were eligible to enter 8 weeks of open-label risperidone LAI treatment in the open-label extension (Period V).		
Number of Subjects (planned and analyzed): The planned sample size was 600 subjects, based on the expectation that 200 randomized subjects would provide 114 relapse events during double-blind treatment. Overall, 559 subjects were treated with study drug, including 440 subjects in the open-label oral risperidone period (Period II) and 119 subjects who entered open-label risperidone LAI stabilization (Period III) directly from screening. A total of 303 subjects were randomly assigned to double-blind treatment with placebo (n=149) or risperidone LAI (n=154); all these subjects were included in the safety analysis set, while 135 subjects in the placebo group and 140 subjects in the risperidone LAI group were included in the primary efficacy analysis set.		

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Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged 18 to 65 years (inclusive) with a diagnosis of Bipolar I disorder who were currently experiencing a manic or mixed episode (YMRS ≥20) or were between mood episodes (stable; CGI-S ≤3 [mild]), did not meet DSM-IV-TR criteria for a depressive episode, and were in good physical health. To enter the double-blind period, subjects were required to have maintained a treatment response during Period III and to have received a stable dose of risperidone LAI for the last 8 weeks of the open-label risperidone LAI stabilization period (Period III).		
Test Product, Dose and Mode of Administration, Batch No.: During the open-label oral risperidone period, subjects received oral risperidone film-coated tablets (1 mg; flexible dose in the range of 1 to 6 mg/day). During open-label risperidone LAI stabilization and open-label extension, oral risperidone tablets (1 to 6 mg/day) were used as supplementation for the first 3 weeks of treatment. If an increase in the dose of risperidone LAI was necessary, oral risperidone (1 to 2 mg/day) was added for up to 3 weeks after the first injection of the higher dose (batch numbers 1-mg tablet, 04D14/F005, 04H10/F005, and 05G12/F005). During the open-label risperidone LAI stabilization period, double-blind treatment period, and open-label extension, subjects received risperidone LAI microspheres injected intramuscularly into the gluteal muscle every 2 weeks at the study center. Four strengths (12.5, 25, 37.5, and 50 mg) were used during open-label risperidone LAI stabilization and double-blind treatment, and 3 strengths (25, 37.5, and 50 mg) were used during open-label extension treatment. During open-label risperidone LAI stabilization, subjects stable on risperidone LAI who entered this period directly from screening received risperidone LAI on Day 1 at the same dose (25 mg, 37.5 mg, or 50 mg) as that received at the screening visit. All other subjects received 25 mg of risperidone LAI on Day 1. The 12.5-mg dose was available for subjects who were unable to tolerate the 25-mg starting dose. Dose titration (in 12.5 mg increments) was allowed at 4-week intervals only. Up to 2 increases and 1 decrease in risperidone LAI doses were allowed. Titration was allowed during the first 18 weeks of the stabilization period; however, a dose change was not allowed during the last 8 weeks of treatment. Subjects randomized to risperidone LAI during the double-blind treatment period continued to receive the dose they had received during the last 8 weeks of stabilization (12.5, 25, 37.5 or 50 mg) and dose titration was not allowed. Subjects entering open-label extension from double-blind treatment received 25 mg of risperidone LAI on Day 1. Dose titration (in 12.5-mg increments) was allowed at 2-week intervals, based on the judgment of the investigator. Batch numbers for risperidone LAI were 164-2194CA for 12.5 mg; 164-0943BB, 164-2194BB, and 164-0775-AA for 25 mg; 164-2393CA and 164-2194BA for 37.5 mg; and 164-2623BA, 164-2194AB, and 164-0775AC for 50 mg.		
Reference Therapy, Dose and Mode of Administration, Batch No.: During the double-blind period, subjects assigned to placebo received injections of placebo microspheres matching the risperidone LAI injection that was administered i.m. every 2 weeks (batch numbers, 248-2272AA and 285-1195AA).		
Criteria for Evaluation: <u>Efficacy:</u> Time to relapse of a mood episode in the double-blind period was the primary efficacy variable. The following parameters were used to evaluate efficacy throughout the study: YMRS, MADRS, and the CGI-S scale. Additionally, the Personal and Social Performance scale and SF-36 were administered throughout the study, except during open-label oral risperidone treatment. The Resource Use Questionnaire (RUQ) was administered during double-blind treatment and the Intensive Resource Use Questionnaire (IRUQ) was administered during open-label extension treatment. <u>Safety:</u> The following parameters were used to evaluate safety: adverse events, clinical laboratory tests, vital signs, weight and body mass index (BMI), electrocardiograms (ECGs), physical examinations, and the Extrapyramidal Symptoms Rating Scale (ESRS).		

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<p>Statistical Methods: The primary efficacy variable was the time to relapse of a mood episode during double-blind treatment, where relapse was defined based on pre-specified criteria. The power and sample size calculations were based on a 2-sided hypothesis with a 5% significance level. The cumulative distribution function of the time to relapse for each treatment group was estimated by the Kaplan-Meier method and treatments were compared using a log-rank test, controlling for country. The hazard ratio for relapse was assessed graphically by plotting the Kaplan-Meier estimates using a log-log scale. Secondary analyses included sensitivity analyses and time to relapse by subject type at screening, time to relapse by type of relapse event (elevated mood or depressive episodes), and subgroup analyses. During the course of the study, one Good Clinical Practice (GCP) non-compliant site was identified. After database lock and study unblinding, one site with alleged research misconduct was identified. The primary and all secondary efficacy analyses excluded subjects from both sites (11 per treatment group and 3 per treatment group at the respective sites). The safety analysis included subjects from these sites. An additional sensitivity analysis including these 2 sites was performed. For the secondary efficacy variables, YMRS, MADRS, CGI-S, and PSP, using an analysis of covariance (ANCOVA) model with treatment and country as factors and double-blind baseline score as a covariate, the change from baseline to end point between the risperidone LAI and placebo groups was compared based on the least-squares means obtained from the ANCOVA model. The least-squares mean difference between treatment groups and the associated 95% confidence intervals were estimated. A similar analysis of the SF-36 domains and component summary scores was performed. Frequency distributions for the RUQ and IRUQ variables were provided.</p> <p>A planned interim analysis was performed after 66 relapse events during double-blind treatment, at approximately 50% of the information time, for assessment by the Independent Data Monitoring Committee (IDMC). The study was to be terminated based on the interim analysis results if the comparison between risperidone LAI and placebo for time to relapse during double-blind treatment was statistically significant ($p \leq 0.0020$), both with and without the GCP non-compliant site. The IDMC recommended that the study continue without modification. The p-values for the primary efficacy analysis were 0.027 excluding the GCP non-compliant site and 0.093 including the GCP non-compliant site, with subjects in the risperidone LAI group having a longer time to relapse compared with those in the placebo group.</p> <p>For the primary variable, the final significance level was 0.0493. All other statistical tests were interpreted at the 5% significance level (2 sided). Nominal unadjusted p-values are reported.</p>		
<p>SUMMARY – CONCLUSIONS:</p> <p><u>SUBJECT AND TREATMENT INFORMATION:</u> Overall, 51% of subjects randomized to double-blind treatment were males and 49% were females. The mean age of subjects at screening (study entry) was 39.2 years (range, 18 to 65 years), and most subjects were Caucasian (80%). At screening, 40% of subjects had an acute episode, 24% were stable on risperidone, and 35% were stable on another antipsychotic. The median number of manic and depressive episodes was 3.0 and 2.0, respectively. Based on these data, the population studied had a history of more manic than depressive episodes during their course of bipolar disorder. Most (77%) subjects in the risperidone LAI group received a mode dose of 25 mg (range: 12.5 mg to 50 mg) during double-blind treatment.</p> <p><u>EFFICACY RESULTS:</u> Time to relapse of a mood episode during double-blind treatment (Period IV) in the primary efficacy analysis set (randomized, treated subjects in Period IV excluding subjects at the GCP non-compliant site and the site with alleged research misconduct) was significantly delayed for subjects in the risperidone LAI group compared with the placebo group. Median time to relapse was 219 days for subjects in the placebo group, but could not be defined for subjects in the risperidone LAI group since less than 50% of subjects had experienced a relapse. The 25th percentile of time to relapse (estimated time point at which 25% of subject had experienced a relapse) was 82 days for subjects in the placebo group and 173 days for subjects in the risperidone LAI group. The Kaplan-Meier estimates of the 9-month relapse rate were 30% for subjects in the risperidone LAI group and 60% for the placebo group. Results of the analysis of time to relapse including the 2 excluded sites were consistent with results that excluded these sites.</p>		

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<p>The effect of risperidone LAI in prevention of relapse was greatest among subjects with an acute episode (24% relapsed vs. 67% of placebo subjects) compared with subjects who were stable on risperidone (37% relapsed vs. 56% of placebo subjects) or stable on another antipsychotic or mood stabilizer (32% relapsed vs. 44% of placebo subjects) at screening. In the risperidone LAI group, the type of relapse episode was evenly divided between elevated mood (manic or mixed) (16%) and depressive mood (14%) episodes. However in the placebo group, a greater percentage of subjects had an elevated mood (46%) episode than a depressive mood (10%) episode.</p> <p>During double-blind treatment, initial improvements observed during 26 weeks of open-label risperidone LAI stabilization (Period III) were better maintained in subjects who continued treatment with risperidone LAI than in subjects who were switched to placebo across a range of measures designed to assess manic and depressive symptoms and global functioning: YMRS (manic symptoms), MADRS (depressive symptoms), CGI-S (overall global evaluation), and PSP (personal and social functioning) efficacy scales.</p>		
<p>SAFETY RESULTS: Three subjects died during the study (1 subject died during open-label oral risperidone treatment, due to duodenal ulcer perforation and peritonitis, and 2 subjects died during the open-label risperidone LAI stabilization period [1 death due to chemical poisoning and completed suicide and 1 death due to accidental death that resulted from a fall, hemorrhage, hepatic rupture, and multiple injuries]). No deaths occurred in the double-blind treatment or open-label extension periods.</p> <p>Serious treatment-emergent adverse events were reported in 2% of subjects in the open-label oral risperidone treatment period, 8% of subjects in the open-label risperidone LAI stabilization period, 17% (placebo) vs. 8% (risperidone LAI) of subjects in the double-blind treatment period, and 3% of subjects in the open-label extension. Most serious events reported across study periods were associated with worsening of the subjects' baseline condition. The number of discontinuations (excluding those who discontinued due to adverse events associated with non-response/relapse) due to adverse events was low ($\leq 4\%$) across all periods. During double-blind treatment only 2 (1%) subjects (1 per treatment group) discontinued due to an adverse event.</p> <p>During double-blind treatment, the most frequently ($\geq 3\%$ difference) reported events with risperidone LAI vs. placebo were depression (6% vs. 2%) and weight increased (5% vs. 1%). Those that occurred more frequently ($\geq 3\%$ difference) with placebo than risperidone LAI were mania (11% vs. 5%), Bipolar I disorder (7% vs. 2%), agitation (5% vs. 1%), and irritability (4% vs. 1%). Except for weight increased, these events were likely related to exacerbation of the underlying bipolar disorder.</p> <p>Suicide/self-injury related adverse events were reported for 8 subjects across all periods. EPS-related adverse events were reported at frequencies of 11% in open-label oral risperidone treatment, 9% in open-label risperidone LAI stabilization, 2% (placebo) vs. 3% (risperidone LAI) in double-blind treatment, and 3% in open-label extension treatment. Glucose metabolism-related adverse events were reported at frequencies of 2% in open-label oral risperidone treatment, 11% in open-label risperidone LAI stabilization, 3% (placebo) and 10% (risperidone LAI) in double-blind treatment, and 2% in open-label extension treatment.</p> <p>Serum prolactin concentrations increased from baseline by a mean of 17.1 ng/mL during the open-label risperidone LAI stabilization period, and decreased from double-blind baseline by a mean of 27.3 ng/mL (placebo) vs. a mean of 8.8 ng/mL (risperidone LAI) in the double-blind treatment period. There was a low incidence of potentially prolactin-related adverse events in both female ($\leq 8\%$) and male ($\leq 8\%$) subjects across all periods.</p> <p>During open-label risperidone LAI stabilization (Period III), the mean increase in body weight and BMI from baseline (Period III) to end point was 1.6 kg and 0.6 kg/m², respectively. Abnormal weight increases ($\geq 7\%$) from baseline (Period III) to end point were noted in 14.5% of subjects, while increases ($\geq 7\%$) from double-blind baseline to end point were noted in 11.6% (risperidone LAI) vs. 2.8% (placebo) during double-blind treatment.</p> <p>No subjects had orthostatic hypotension according to predefined criteria. No subjects had a QTcF or QTcLD increase >60 ms from baseline in any period. No subjects had a potentially clinically important QTc interval (≥ 500 ms) in any period.</p>		
<p>CONCLUSION: Treatment with risperidone LAI significantly delayed the time to relapse of mood episodes after 26 weeks of stabilization treatment in subjects with Bipolar I disorder. Overall, the findings from this study provide support that long-term risperidone LAI treatment is efficacious, and generally safe and well-tolerated.</p>		
<p>Date of the report: 15 July 2008</p>		

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