CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company:	Ortho-McNeil Janssen Scientific Affairs, L.L.C.	
Name of Finished Product:	RISPERDAL® CONSTA®	
Name of Active Ingredient:	Risperidone	

Protocol Number: RIS-BIP-302

Title of Study: A prospective, randomized, double-blind, placebo-controlled study of the effectiveness and safety of RISPERDAL® CONSTA® augmentation in adult patients with frequently-relapsing bipolar disorder

Coordinating Investigator: Caleb Adler, MD	**Publication (Reference)**: None
Study Period: 20 May 2004 – 09 February 2007	**Phase of Development**: IIIb

OBJECTIVES: The primary efficacy objective of the study was to demonstrate the efficacy of RISPERDAL® CONSTA® augmentation of treatment as usual (TAU), compared with placebo augmentation of TAU, in delaying the time to intervention for any mood episode over 52 weeks in patients with Frequently Relapsing Bipolar Disorder (FRBD) Type I or II who achieved remission during the preceding 4 months open-label (OL) Stabilization phase. The safety objective of the study was to evaluate the short-term (4 months) and longer-term safety and tolerability (12 months) of RISPERDAL® CONSTA® augmentation of TAU in patients with FRBD.

Key secondary efficacy objectives included examination of the effects of RISPERDAL® CONSTA® on the percentage of patients who achieved remission (Clinical Global Impression Scale for Bipolar Disorder – change score [CGI-BP-C], Young Mania Rating Scale [YMRS] and Montgomery-Åsberg Depression Rating Scale [MADRS], and the severity of manic and depressive symptoms (YMRS, MADRS).

METHODOLOGY: This was a prospective, randomized, multicenter study to evaluate the efficacy of RISPERDAL® CONSTA® as adjunctive therapy to TAU in adult patients with FRBD. Enrolled patients entered the 16-week OL Stabilization phase, during which RISPERDAL® CONSTA® treatment was initiated as adjunctive therapy to TAU. Patients taking oral antipsychotics had these tapered off within the first 3 weeks of the study. Patients who achieved stable remission of mood episodes in the OL Stabilization phase qualified for the 52-week double-blind (DB) Relapse Prevention phase. Patients continued taking their TAU and were randomized to receive injections of either RISPERDAL® CONSTA® (at the same dose as at the end of the OL Stabilization phase) or placebo every 2 weeks. One blood sample (10 mL) was collected from patients who had given separate written informed consent for pharmacogenomic research, for genotyping of candidate genes related to risperidone or bipolar disorder.

Stable remission was achieved if all of the following criteria were met during the last 4 weeks of the 16-week OL Stabilization phase: the patient had not met DSM-IV-TR criteria for active mood disorder; the patient had no crisis interventions (eg, no hospitalization or emergency room/crisis center visits for psychiatric reasons); the patient's YMRS and MADRS total scores remained ≤10, and the Clinical Global Impression Scale for Bipolar Disorder severity score (CGI-BP-S) score remained ≤3; and the patient's medications and doses of all psychotropic medications remained unchanged. Patients who failed to meet these remission criteria at the end of the OL Stabilization phase could continue OL RISPERDAL® CONSTA® as adjunctive therapy to their TAU for an additional 36 weeks in the non-remitted continuing (NRC) population. In the DB relapse prevention phase, relapse was defined as the first occurrence of a mood episode, determined in a blinded manner by an independent Relapse Monitoring Board (RMB). Patients who continued in the study after discontinuation of blinded study medication in the DB Relapse Prevention phase could choose to receive OL RISPERDAL® CONSTA® (as adjunctive therapy to their TAU) in the retrieved dropout (RDO) population.

Number of Patients (planned and analyzed): Planned: approximately 276 patients in the OL Stabilization phase, from which at least 138 patients would enter the DB Relapse Prevention phase. Actual: 275 patients enrolled in the OL Stabilization phase, 139 patients enrolled in the DB phase, 70 patients continued in the NRC population, and 41 patients continued in the RDO population.

Diagnosis and Main Criteria for Inclusion: Patients were men and women aged 18 to 70 years, with a current diagnosis of Bipolar I or II Disorder, including rapid cycling. Patients must have experienced at least 4 episodes (requiring psychiatric intervention) of a mood disorder in the past 12 months. Patients must not have met any exclusion criteria, which included but were not limited to the following: women who were known or suspected to be pregnant or lactating; patients with a psychiatric diagnosis due to a general medical condition (eg, clinically notable hypothyroidism); patients who were currently taking 2 antipsychotic medications at therapeutic doses.

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Test Product, Dose, and Mode of Administration: RISPERDAL® CONSTA® 25 mg (lot numbers 164-0943BB, 164-0775AA), 37.5 mg (lot numbers 164-2393CA, 164-2194BA), and 50 mg (lot numbers 164-2623BA, 164-2194AB) long-acting injection or placebo (lot numbers 165-1941AA, 248-2272AA) every 2 weeks.

Duration of Treatment: In the OL Stabilization phase, patients received TAU plus injections of RISPERDAL® CONSTA® (25, 37.5, or 50 mg) every 2 weeks for 16 weeks. Investigators could adjust the dose based on their clinical judgement. Patients who entered the DB Relapse Prevention phase received TAU and RISPERDAL® CONSTA® injections or TAU and placebo injections every 2 weeks for 52 weeks after the OL Stabilization phase (at the same dose as at the end of the OL Stabilization phase). If patients withdrew early from the DB Relapse Prevention phase and chose to continue in the RDO population, they received TAU and RISPERDAL® CONSTA® (25, 37.5, or 50 mg) injections up to Week 68; same total study duration as if remaining in DB Relapse Prevention phase. Patients in the NRC population received RISPERDAL® CONSTA®, at the same dose as at the end of the OL Stabilization phase, for up to an additional 36 weeks after the OL Stabilization phase.

Criteria for Evaluation:

Efficacy: The primary efficacy variable in the DB Relapse Prevention phase was time to relapse, where relapse was defined as the first occurrence of a mood episode. The occurrence of relapses and the start dates of relapses were determined by an independent RMB, after review of all available clinical and research data and before database lock. The efficacy endpoint in the OL Stabilization phase was the incidence of stable remission in patients in the ITT-OL population. Remission was assessed by clinical status, changes in rating scales, and stability of medication dosages during the 4 last weeks of the OL study phase.

Secondary endpoint variables were change from OL and DB baseline of the YMRS and MADRS total scores. Additional secondary endpoint measures were the CGI-BP-S scale for overall bipolar disorder, mania, and depression; and the CGI-BP-C scale for overall bipolar disorder, mania, and depression. Other assessments included the patient's global level of functioning (Global Assessment of Function Scale [GAF]); objective and subjective measures of substance use and craving (Timeline Follow-back [TLFB]); patient-reported health status and functional impairment (Short Form 36 Health Survey [SF-36], Sheehan Disability Scale [SDS]); health/social care utilization (Resource Utilization Questionnaire [RUQ]); the change in severity of illness (CGI-BP-S); and the presence and severity of suicidal thoughts (Revised InterSePT Scale for Suicidal Thinking [ISST Revised]).

Safety: The safety assessments conducted throughout this study included the regular monitoring and recording of: adverse events; prior and concomitant medication; clinical laboratory test results, including serum chemistry, hematology, and urinalysis; vital signs; physical examinations; ECGs; and assessments of movement disorders. In addition, a complete medical and psychiatric history, a diagnostic interview (MINI), a medication history, and a urine drug screen test were obtained and recorded during the Pretreatment phase.

Pharmacokinetic/Pharmacodynamic Relationships: The relationship between selected efficacy parameters (YMRS, MADRS, CGI-BP and occurrence of relapse) and plasma exposure were explored by graphical methods.

Statistical Methods: Continuous variables were summarized using descriptive statistics and categorical variables were summarized using counts and percents. All statistical tests were 2-sided, and the type I error was fixed at 0.05. All confidence intervals (CIs) were 2 sided with 95% coverage. All group comparisons from analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models were based on Type III sum of squares. An independent committee (RMB) regularly reviewed patient data in a blinded manner and determined whether or not an event (mood episode) was a relapse event, on the basis of blinded data provided by the investigators. The primary analysis of time to relapse was analyzed using a log-rank test, controlling for geographic regions. Kaplan-Meier survival curves were presented. In addition, Cox proportional hazard models were performed with factors treatment and country. All secondary analyses were supportive in nature and the OL and DB objectives were separate; therefore, no adjustments for multiplicity were planned.

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RESULTS:

Disposition and Demographics: Of the 313 patients who were screened, 275 patients were enrolled in the OL Stabilization phase of the study and received at least 1 dose of study medication, comprising the ITT group. Of the 275 patients, 218 (79.3%) patients completed the 16-week OL Stabilization phase, and 139 (50.5%) patients were randomized into the DB Relapse Prevention phase. A total of 57 (20.7%) patients discontinued the OL Stabilization phase. Seventy (25.5%) patients continued in the NRC population. Nine (3.3%) patients completed the OL phase and did not enter either the DB Relapse Prevention phase or the NRC group. Demographic characteristics of patients randomized to the DB Relapse Prevention phase were similar to those in the OL Stabilization phase. A greater percentage of patients were males than females and were predominantly enrolled at Indian sites. Mean age, weight, and body mass index (BMI) were similar between the patients in the OL phase and the DB phase and between the treatment groups in the DB phase.

Efficacy Results (for OL Stabilization Phase): Stable remission was achieved by 50.5% (139/275) of the patients, who were then randomized into the DB Relapse Prevention phase. Point remission, defined as having both a YMRS total score ≤10 and a MADRS total score ≤10 at a single visit, was met by 24.4% of patients at OL baseline and by 67.4% of patients at the Week 16 last observation carried forward (LOCF) endpoint. Statistically significant ($p<0.001$) improvements in the total YMRS and MADRS scores (decrease in the total scores) were shown at every time point. Results of the secondary endpoint rating scales indicated improvements in the severity of illness. Patients taking oral antipsychotics were tapered off within the first 3 weeks of the study. Valproic acid derivatives and lithium were the most common mood stabilizers, while SSRIs were the most common antidepressants taken as TAU.

Efficacy Results (for DB Relapse Prevention Phase):

Primary Analysis: Kaplan-Meier survival curves for the 2 treatment groups showed a longer time to relapse ($p=0.004$, log-rank stratified by pooled center) for the RISPERDAL® CONSTA® group, compared with placebo during the DB Relapse Prevention phase.

Analysis of Relapse – Based on Independent RMB Decision, in the DB Relapse Prevention Phase (ITT Population)

	RIS CONSTA (N=72)	Placebo (N=67)
Relapsed, n (%)	16 (22.2)	32 (47.8)
Kaplan-Meier 25th Percentile, days (95% CI)	NA (129, NA)	134 (77, 207)
Kaplan-Meier median, days (95% CI)	NA	305 (207, NA)
Log-rank p-value stratified by pooled site	0.004	

Patients in the placebo group were more than twice as likely to experience a relapse compared with patients in the RISPERDAL® CONSTA® group (hazard ratio 2.438 for treatment). The hazard ratio for country was not statistically significant.

Summary of Relative Risk, Based on RMB Decision, Cox Regression Model in the DB Relapse Prevention Phase (ITT Population)

	Hazard Ratio	95% CI	p-value
Treatment	2.438	[1.337, 4.447]	0.004
Country	0.615	[0.297, 1.273]	0.190

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Secondary Analyses: In a secondary analysis of relapses determined by investigators, good concordance was seen between these relapse events and those determined by the RMB. Similar to what was observed in time to relapse based on the independent RMB decision, Kaplan-Meier survival curves for the 2 treatment groups showed a statistically significant (p=0.023) longer time to relapse for the RISPERDAL® CONSTA® group, compared with placebo. A lower percentage of patients relapsed in the RISPERDAL® CONSTA® group compared with placebo based on investigator's decision (20.8% vs. 40.3%, respectively). Results for the secondary endpoints further supported the efficacy of RISPERDAL® CONSTA® in maintaining clinical improvement achieved in the OL Stabilization phase.

Efficacy Results (for NRC Population): In the 70 patients who chose to continue in the study in the NRC population, the percentage of patients who met both YMRS and MADRS point remission criteria increased from baseline to Week 52 (15.7% to 70.0%) and was 65.7% at Week 52 LOCF endpoint. Results from the secondary endpoints further supported the efficacy of RISPERDAL® CONSTA® in combination with TAU in stabilizing patients' mood disorders.

Overall Safety Results:

Treatment-emergent adverse events (TEAEs) are presented below:

Summary of Number (Percent) of Patients With Treatment-Emergent Adverse Events

	OL Phase	DB Phase		NRC Population	RDO Population	
	Overall (N=275)	RIS CONSTA (N=72)	Placebo (N=67)	Overall (N=70)	RIS CONSTA/ RIS CONSTA (N=15)	Placebo/ RIS CONSTA (N=26)
Patients with at least 1 TEAE, n(%)	212 (77.1)	51 (70.8)	51 (76.1)	69 (98.6)	8 (53.3)	20 (76.9)
Deaths, n(%)	0	1 (1.4)	1 (1.5)	0	0	1 (6.6)
Patients with 1 or more SAEs, n(%)	25 (9.1)	10 (13.9)	13 (19.4)	15 (21.4)	0	3 (11.5)
Patients who were discontinued due to an AE, n(%)	16 (5.8)	3 (4.2)	1 (1.5)	5 (7.1)	0	2 (7.7)

Safety Results (for OL Stabilization Phase): The most commonly-reported TEAEs by MedDRA preferred terms were tremor (23.3%), muscle rigidity (14.5%), weight increased (12.7%), and insomnia (10.2%). No deaths occurred during the OL Stabilization phase. SAEs reported by more than 1 patient were psychiatric disorders, which included mania in 7 (2.5%) patients, depression in 6 (2.2%) patients, suicidal ideation in 3 (1.1%) patients, and aggression and agitation in 2 (0.7%) patients each. TEAEs causing permanent discontinuation of study medication experienced by more than 1 patient included weight increased (0.7% of patients), dizziness (0.7%), tremor (0.7%), depression (0.7%), and galactorrhoea (0.7%) Changes in clinical laboratory tests, vital signs, ECG parameters, and rating scales for movement disorders were generally small or within the known safety profile of RISPERDAL® CONSTA®

Safety Results (for DB Relapse Prevention Phase): The most commonly-reported TEAEs reported in the RISPERDAL® CONSTA® group and placebo group, respectively, were tremor (23.6% vs. 16.4%), insomnia (19.4% vs. 23.9%), muscle rigidity (11.1% vs. 6.0%), and mania (4.2% vs. 11.9%). Two deaths occurred during the DB Relapse Prevention phase (hypertensive heart disease in 1 RISPERDAL® CONSTA® patient and road traffic accident in 1 placebo patient). The most common SAEs reported in the RISPERDAL® CONSTA® group compared with the placebo group, respectively, were psychiatric disorders, including mania in 3 (4.2%) vs. 4 (6.0%) patients, depression in 0 vs. 4 (6.0%) patients, bipolar Type 1 disorder in 0 vs. 2 (3.0%) patients, suicidal ideation in 0 vs. 1 (1.5%) patients, and suicide attempt in 1 (1.4%) vs. 0. TEAEs causing permanent discontinuation of study medication experienced by more than 1 patient included hypokinesia (1.4%), tardive dyskinesia (1.4%), and hypertensive heart disease (1.4%) in RISPERDAL® CONSTA® patients; and mania (3.0%) in placebo patients. Mean weight change to LOCF endpoint was 0.7 kg in the RISPERDAL® CONSTA® group and –1.8 kg in

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the placebo group. Changes in clinical laboratory tests, vital signs, ECG parameters, and rating scales for movement disorders were generally small or within the known safety profile of RISPERDAL® CONSTA®

Safety Results (for NRC Population): The most commonly-reported TEAEs by MedDRA preferred terms were tremor (40% of patients), muscle rigidity (30%), insomnia (24.3%), and weight increased (24.3%). No deaths occurred in the NRC population. SAEs reported by more than 1 patient were depression and suicide ideation in 5 (7.1%) patients each, mania in 3 (4.3%) patients, and aggression and agitation in 2 (2.9%) patients each. AEs that caused permanent discontinuation of RISPERDAL® CONSTA® included akathisia, amenorrhea, galactorrhea, hypotension, suicidal ideation, and weight increased (each in 1 patient), and anemia and thrombocytopenia (both in 1 patient). Changes in clinical laboratory tests, vital signs, ECG parameters, and rating scales for movement disorders were generally small or within the known safety profile of RISPERDAL® CONSTA®.

Safety Results (for RDO Population): TEAEs reported by preferred terms in the RISPERDAL® CONSTA®/ RISPERDAL® CONSTA® group (patients who were randomized in the DB phase to RISPERDAL® CONSTA®, then treated with OL RISPERDAL® CONSTA® after they relapsed) and placebo/ RISPERDAL® CONSTA® group (patients who were randomized in the DB phase to placebo, then treated with OL RISPERDAL® CONSTA® after they relapsed), respectively, were tremor in 3 (20.0%) vs. 9 (34.6%) patients, insomnia in 1 (6.7%) vs. 4 (15.4%) patients, somnolence in 0 vs. 4 (15.4%) patients, and amenorrhea in 0 vs. 4 (15.4%) patients. One death occurred in the RDO population (suicide in a RISPERDAL® CONSTA®/ RISPERDAL® CONSTA®patient). No patients in the RISPERDAL® CONSTA®/ RISPERDAL® CONSTA® group experienced SAEs. SAEs reported in the placebo/ RISPERDAL® CONSTA® group were pneumonia, depression (each in 1 patient), and completed suicide and intentional self-injury (both in 1 patient). One AE of depression caused permanent discontinuation of RISPERDAL® CONSTA® in a patient in the placebo/ RISPERDAL® CONSTA® group. There were no clinically meaningful changes in clinical laboratory tests, vital signs, ECG parameters, and rating scales for movement disorders.

Other Results:

Pharmacokinetic/Pharmacodynamic Relationships: These data will be reported separately.

Pharmacogenomics: Genotyping of *CYP2D6* was performed. A composite genotype and predicted phenotype (where possible) were derived from the raw genotyping data in each patient. Of the predicted phenotypes determined from the composite genotypes, most (N=55) of the 72 patients were determined to be extensive metabolizers. The other patients were categorized as follows: ultrarapid metabolizers (N=2), intermediate metabolizers (N=5), poor metabolizers (N=4); and no results could be determined for 6 patients. Although mutations were detected, for most of the patients the activity of the composite *CYP2D6* enzyme was unaffected.

CONCLUSION: RISPERDAL® CONSTA® at dosages of 25, 37.5, and 50 mg was effective as adjunctive treatment in delaying the time to relapse to a mood episode in patients with FRBD. Secondary endpoints supported the efficacy of RISPERDAL® CONSTA® in this population. RISPERDAL® CONSTA® was generally safe and well tolerated in this population with no unexpected safety concerns or trends compared to the known safety and tolerability profile of RISPERDAL® CONSTA®.

Issue Date of the Clinical Study Report: March 10, 2008

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