Janssen-Ortho Inc., Canada
MEDICAL AFFAIRS

SYNOPSIS RIS-BIP-301

Name of Sponsor/Company:	Janssen Ortho Inc.	Individual Study Table Referring to Part of the Dossier **n/a**	(for National Authority Use only)
Name of Finished Product:	Risperdal Consta	Volume: n/a	
Name of Active Ingredient:	Risperidone microspheres	Page: n/a	
Title of Study:		A randomized open label trial of Risperdal Consta™ versus oral antipsychotic care in subjects with Bipolar Disorder	
Investigators:		[redacted]	
Study centre(s):			
Publication (reference)		Brief report to Amer J. Psychiatry (1500 words max, 1 figure)	
Studied period (years): over 2 years		Phase of development:	Phase 3b
	(date of first enrolment)	13 jan 2004	
	(date of last completed)	26 april 2006	
Objectives:		To determine the safety and effectiveness of Risperdal Consta™ in stable bipolar subjects randomly switched from their current adjunct atypical antipsychotic (olanzapine, risperidone or quetiapine) therapy to Risperdal Consta™ versus subjects who continue on oral antipsychotic treatment.	
Methodology:		This was an open-label, randomized study. Approximately 40 bipolar subjects who were on an atypical antipsychotic (risperidone, quetiapine, olanzapine) plus adjunct bipolar treatment consisting of a combination of one or two of lithium, valproate or lamotrigine; and, if applicable, one antidepressant, were randomized to risperidone long acting injectable (ris LAI) or continuation with current oral atypical antipsychotic (oral AP) treatment.. The screening period was used to perform protocol-required tests. In one arm, 25 mg Risperdal Consta™ replaced the oral atypical antipsychotic as adjunct and in the other arm subjects continued with their current atypical antipsychotic therapy. Trial treatment duration was 6 months. In the Risperdal Consta™ arm, the oral atypical antipsychotic (as supplementation) was continued for 3 weeks after the first injection of Risperdal Consta™ and then discontinued. The protocol contained guidelines for increasing the dose of Risperdal Consta™ to 37.5mg and then to 50 mg.	
Number of patients (planned and analyzed):		40 planned	49 analyzed
Diagnosis and main criteria for inclusion:		Original protocol: Male and female bipolar disorder I & II subjects aged 18-65 years inclusive with YMRS and or MADRS ≥ 13, CGI-S≥3 at screening and baseline. Amendment 2: baseline CGI-S ≤ 4, and YMRS and MADRS ≤ 19, stable psychotropic meds for at least 5 weeks prior to trial entry.	
Test product, dose and mode of administration, batch number:		Risperdal Consta™ 25mg, 37.5mg or 50mg.	
Duration of treatment:		6.5 months, .5 months screening, 6 months active treatment	
Reference therapy, dose and mode of administration, batch number		Comparators: Oral antispyshotics-olanzapine, risperidone, quetiapine prescribed by clinician, filled by retail pharmacy and reimbursed by JOI.	
Criteria for evaluation:			

	Efficacy:	The efficacy rating instruments and related scales used in the study are Clinical Global Impression of Severity (CGI-S) scale;Young Mania Rating Scale (YMRS);Montgomery-Asberg Rating Scale (MADRS); EuroQol Q-5D Questionnaire (Quality of Life questionnaire);Resource Utilization Questionnaire; Hamilton Anxiety Rating Scale (HAM-A) Subject satisfaction with treatment scored on a 10 cm visual analog scale (VAS); Time to intervention where intervention is defined by any of the following: Psychiatric hospitalization due to worsening symptomatology (not for social reasons); An increase in the dose of the atypical antipsychotic or Risperdal Consta™ after week 20 due to the emergence of mood symptoms (mood symptoms that cause clinically significant distress or impairment in social, occupational or other important areas of functioning) as judged by the investigator;An increase in the dose of mood stabilizers (other than to modulate serum levels) and antidepressants from baseline, or the addition of psychotropic medications, other than listed in Concomitant Medication Section.Discontinuation due to inefficacy; Discontinuation due to deliberate self-harm, suicidal or homicidal ideation that is clinically significant as determined by the Investigator, or violent behavior resulting in clinically significant injury to another person or property damage.
	Safety:	Adverse events, fasting laboratory tests, vital signs, physical exam, AIMS, BARS, SAS
Statistical Methods:		This is a pilot study to primarily assess the safety of Risperdal Consta™ compared with oral antipsychotic treatment and a formal sample size calculation has not been performed. A total of approximately 40 subjects (20 per treatment arm) will be enrolled. Statistical analysis will be performed by Covar Inc. All statistical tests are two-sided, and the Type I error is fixed at 0.05. All confidence intervals are two-sided with 95% coverage. In the case of non-normality of continuous data, parametric tests will be replaced by non-parametric tests. Descriptive statistics will be provided for each treatment group. Summary by centre will be provided for the key effectiveness outcomes. Centres with small sample sizes may be pooled for summary. Possible different treatment effects among centres will be explored using descriptive statistics, graphical methods or hypothesis tests. Descriptive statistics for continuous variables will include the mean, standard deviation, minimum, maximum and number of observations. Categorical data will be summarized by frequency counts and percentages. Line graphs, bar charts, scatter plots, and other graphs may be displayed when a detailed description of the data necessitates. No adjustments for multiplicity are planned.
SUMMARY – CONCLUSIONS		

Subject Flow	**Risperdal Consta™**	**Oral AP**
	N (%)	**N (%)**
Randomized	23	26
Received at least one dose	23	26
Completed study	12 (52%)	21 (81%)
Early discontinuation	11 (48%)	5 (19%)
Subject choice (consent withdrawn)	0	2 (8%)
Lost to follow-up	0	1 (4%)
Lack of efficacy	4 (17%)	1 (4%)
Adverse event	2 (9%)	0
Subject non-compliant	1 (4%)	0
Protocol violation	1 (4%)	0
Other reason	3 (13%)	1 (4%)

There were 11 Risperdal Consta™ patients and 15 oral atypical antipsychotic patients who met the per protocol amendment 2 criteria and all protocol inclusion/exclusion criteria. Since the results for the per protocol population was similar to the safety population, it was decided to base the publication on the safety population.

Treatment group	**Age (year)**					
	N	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
Risperdal Consta™	23	41.8	13.1	41	22	69
Oral antipsychotics	26	40.1	12.6	43.5	20	60

EFFICACY RESULTS

		Risperdal Consta™	**Oral antipsychotics**
Characteristic		**N (%)**	**N (%)**
Gender:	Male	12 (52)	12 (46)
	Female	11 (48)	14 (54)
Race:	Caucasian	21 (91)	25 (96)
	Other	2 (9)	1 (4)

Trial medication last dose for the oral comparator and Risperdal Consta™ arms shown below.

	N	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
Risperdal Consta™	23	26.1	3.6	25	25	37.5
All ORALS (risperidone equivalent dose)	26	2.0	1.6	1.4	0.2	6.7
Olanzapine	5	8.0	6.5	5	2.5	15
Quetiapine	11	352.3	309.5	300	25	1000
Risperidone	10	1.4	0.5	1.25	1	2

LOCF CGI-S between group change from baseline was not significant (p=0.67). Within group change of –0.4(SD 1.5, within group p=0.04) for Risperdal Consta™ was statistically significant but not within the oral AP (–0.4 (SD 1.1, within group p=0.13)).

LOCF mean YMRS change for Risperdal Consta™ was –3.3 (SD 4.4, within group p=0.0016), oral AP was –1.6(SD 6.2,within group p=0.23) and was not statistically significant between groups (p=0.31).

LOCF mean MADRS change for Risperdal Consta™ was –1.0 (SD 9.9, within group p<0.62), oral AP was –3.1(SD 8.3,within group p<0.09) and was not statistically significant between groups (p<0.45).

LOCF mean HAM-A change for Risperdal Consta™ was –1.7 (SD 5.6, within group p=0.17), oral AP was –4.5 (SD 5.8,within group p=0.0015) and was not statistically significant between groups (p<0.10).

The repeated measures (mixed model) between group calculations confirmed the t-test results for YMRS, MADRS and HAM-A.

		VAS patient satisfaction with treatment was slightly higher in the oral AP group at endpoint (mean 7.9 at baseline vs 7.6 at endpoint) than the Risperdal Consta™ group (mean 7.7 at baseline vs 6.4 at endpoint) with no statistical within or between group differences. The quality of life scales (EuroQol thermometer and the EQ-5D) did not show any statistically significant differences within or between groups even though the oral AP patients on the EuroQol showed a mean 2.7 improvement and the Risperdal Consta™ patients showed a mean 2.2 decrease. The Resource Use questionnaire did not show any statistically significant differences between the groups. There were 5 patients in each group with interventions. Survival curve indicates oral AP have higher probability of not having an intervention than the Risperdal Consta™ group but there is no statistically significant difference between groups.
	SAFETY RESULTS	Mean change in AIMS score did not show any statistically significant difference within or between groups. Baseline means at baseline for both groups were <1. Mean change in BARS did not show any statistically significant difference within or between groups. Baseline means for Risperdal Consta™ was .3(SD.8) and oral AP was 1.1 (SD 2.0). Mean change in SAS for Risperdal Consta™ did not show any statistically significant difference between group or within Risperdal Consta™ group. There was a statistically significant difference within group for oral AP ($p<0.04$). Baseline mean for Risperdal Consta™ was 1.2 (SD 1.5) and for oral AP was 1.1 (SD 1.6). Mean weight gain of .1kg (SD 2.4) in the Risperdal Consta™ group and mean weight loss -0.1(SD 3.4) in the oral AP group. Mean 1.9 bpm heart rate increase for Risperdal Consta™ and mean –1.1bpm decrease in the oral AP group. There was a mean decrease in systolic and diastolic blood pressure for the Risperdal Consta™ group (within group diastolic BP for Risperdal Consta™ was statistically significantly decreased at endpoint by –5.2 mmHg(SD=11,p=0.033) with a higher numeric decrease for systolic pressure (-4.1mmHg, SD =13.3, p=0.15).. There were 16 Risperdal Consta™ and 19 oral AP patients who reported at least 1 TEAE. **TEAE >10%** For Risperdal Consta™: insomnia, nausea, fatigue, headache (all 13%). For oral AP: influenza-like symptoms (19%), somnolence (12%). One serious AE occurred in subject [redacted] on Risperdal Consta™: post-operative hemorrhage following tubal ligation and curettage; recovered; not related to Risperdal Consta™. Physical exam: Only one oral AP subject had physical examination findings changing from normal to abnormal (subject [redacted], ring worm left inner arm at final visit). There were no clinically significant changes in laboratory tests in either group.

	CONCLUSION:	The primary hypothesis is that subjects switched to Risperdal Consta™ will be able to tolerate Risperdal Consta™ and maintain or even improve bipolar symptomatology compared to baseline and compared to the oral antipsychotic arm. The mean CGI-S and YMRS scores were statistically significant for within group (baseline to endpoint change) in the Risperdal Consta™ group. The mean YMRS change score indicated a numerically greater treatment improvement with Risperdal Consta™ than oral AP. The MADRS and HAM-A showed a numerically greater mean improvement for the oral AP group and a statistically signficant within oral group improvement. However, between group comparisons showed similar efficacy on all efficacy scales and no statistically significant difference between groups at endpoint. The number of interventions was equal in both groups with no statistically significant difference in time to intervention. There were less subjects with TEAEs in the Risperdal Consta™ group than the oral AP group. In general, side effects were rated as mild to moderate in severity for both groups with the Risperdal Consta™ group experiencing a within group statistically significant decrease in diastolic pressure. Weight gain and change in BMI were similar between the groups and no clinically significant changes in laboratory tests were noted.
Date of this report:		July 31, 2006