SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RISPERDAL ®CONSTA™ NAME OF ACTIVE INGREDIENT(S): risperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR002026 **Title of Study:** An Open-Label, Randomized, Multicenter Study Comparing Risperidone Depot Microspheres and Olanzapine Tablets in Subjects with Schizophrenia or Schizoaffective Disorder		
Principal Investigators: N. Keks, M.D. Box Hill Department of Hospital and Community Psychiatry, Australia and A. Pons Villanueva, M.D. – Clinic i. Provincial Hospital, Spain		
Publication (Reference): None		
Study Initiation/Completion Dates: 21 November 2000/ 10 December 2002		**Phase of development:** 3
Objectives: The primary objective was to show that treatment with risperidone long-acting injectable (LAI) was not inferior to treatment with olanzapine tablets in short-term efficacy at Week 13 (Part 1) as rated on the Positive and Negative Syndrome scale (PANSS), when the dose was titrated to the subject's best individual dose. The safety profiles, including weight changes, also were documented for the initial 13-week period. Long-term efficacy, safety, quality of life, and resource use in the 2 groups were documented over the course of 1 year during the second part of the study (Weeks 13 to 53). The complete results from the 13-week period is provided in the Clinical Study Report for CR002026, Part 1: EDMS-PSDB-2272108.		
Methodology: This was an open-label, randomized, international, multicenter, flexible-dose study conducted in 618 schizophrenic or schizoaffective subjects with a total duration of 12 months. The study was divided into 2 parts: the first part included the first 13 weeks of the trial and the second part included Week 13 to Week 53. Subjects were titrated to their optimal oral dose during run-in and converted to a pre-defined dose of risperidone long-acting injections (25, 50 or 75 mg every 2 weeks), or continued on their last run-in dose of olanzapine tablets (5, 10, 15 or 20 mg once daily). Protocol Amendment 2 excluded the 75 mg dose from the study; thus data from subjects who received 75 mg were analyzed separately for efficacy and safety. Subjects were screened for eligibility at Visit 1 and randomized at Visit 2 to either risperidone LAI (depot microspheres) or olanzapine oral treatment. Safety and efficacy assessments were performed at randomization and thereafter on Days 8, 22, 36, 64, 92, 176, 259, and 372 or endpoint.		
Number of Subjects (planned and analyzed): 560 planned; 618 randomized, treated, and analyzed		
Diagnosis and Main Criteria for Inclusion: Schizophrenic or schizoaffective adult subjects; PANSS score ≥50 at randomization; body mass index (BMI) ≤40; hospitalized or required medical intervention for acute exacerbation of psychotic symptoms within 2 months of screening and who had at least 1 other exacerbation during the last 2 years prior to screening that required medical intervention; otherwise, healthy on the basis of physical examination, medical history, ECG, and lab results performed within 2 weeks before the study; and have provided informed consent.		
Test Product, Dose and Mode of Administration, Batch No.: Risperidone LAI intramuscular injection (i.m.) 25 or 50 mg biweekly and oral risperidone tablets 2 mg (maximum 6 mg/day) for first 3 weeks; supplementation for exacerbation of psychotic symptoms thereafter. The 75 mg risperidone LAI dose was discontinued in Amendment 2 of the Protocol.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Oral olanzapine tablet 5 mg (maximum 20 mg/day)		
Duration of Treatment: Run-in period: 1 week Part 1 of open-label treatment: 13 weeks (Weeks 1-13) (risperidone LAI and oral olanzapine) and oral risperidone (Week 1-3) Part 2 of open-label treatment: 40 weeks (Weeks 13-53)		

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Criteria for Evaluation:

Pharmacokinetics: Serum concentrations were evaluated at specified timepoints during Weeks 13-53 of the study and the concentrations of risperidone, active moiety, and olanzapine in plasma were determined by the sponsor using validated drug assay methods.

Efficacy: Evaluations included the change in the total score of the PANSS from baseline to endpoint at Week 13 for Part 1 and during Weeks 1-53 for Part 2, maintenance of effect, overall severity of illness at randomization (Visit 2) and at all subsequent visits using the CGI Severity Scale, and subscale scores of the PANSS as follows: positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Clinical improvement defined as >=20% improvement in Total PANSS was also evaluated.

Safety: Evaluations included assessments of treatment-emergent adverse events, clinical laboratory tests, vital sign measurements, and physical examination results.

Statistical Methods: The primary objective of the study was to demonstrate that risperidone LAI was not inferior to oral olanzapine by showing that the difference in change from baseline to the 13-week endpoint in the Total PANSS score was not more than 8 points in favor of oral olanzapine (a pre-defined non-inferiority margin). The remaining assumptions made for sample size calculation were: that both the risperidone LAI group and the oral olanzapine group would change equally (hence their difference was estimated as almost 0) and that the standard deviation of the mean was 20. Taking these assumptions into account, 132 subjects per group were required to test the noninferiority hypothesis that the average Total PANSS score of the risperidone-treated subjects would be no more than 8 points lower than the average score of the olanzapine-treated subjects at the 0.025 (one sided) significance level with 90% power. Descriptive summaries were used to evaluate the pharmacokinetic profile of risperidone and olanzapine. All analyses of secondary efficacy and safety variables were exploratory in nature. The 95% confidence intervals (CI) of the difference in changes from baseline between the risperidone and olanzapine groups were constructed for the secondary efficacy variables.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Following bi-weekly administration of risperidone LAI, the plasma concentrations for active moiety, risperidone and 9-hydroxy-risperidone were constant throughout Week 13-53 of the trial and in line with previously reported studies (CR006061, CR006055, RIS-INT-57).

Following once-daily oral administration of 5, 10, 15, and 20 mg olanzapine, the trough plasma concentrations for olanzapine and desmethyl-olanzapine were constant throughout Weeks 13-53 of the trial. The olanzapine exposure was in the range of expectation for the doses administered.

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EFFICACY RESULTS: A total of 488 subjects were in the 'per-protocol analysis: OLA-RIS (risperidone) 25/50 mg LAI' data set at 13 weeks. The primary objective was to test non-inferiority to olanzapine at endpoint, up to Week 13. The difference between the changes from baseline on Total PANSS equaled 0.3 with a 95% CI from -2.16 to 2.66. The upper limit of the confidence interval (2.66) between the 2 treatment groups was smaller than the pre-defined margin of 8 points. Thus, the non-inferiority hypothesis was supported by the analyses.

Total PANSS Score and Change from Baseline at 13-Week Endpoint
(Study CR002026: Per-Protocol: OLA-RIS 25/50 mg LAI Data Set)

	Risperidone LAI					Olanzapine					
				Change from baseline					Change from baseline		Difference in Change
	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE	L.S.Mean (95% CI)[a]
Baseline	216	79.1	0.98			271	78.3	0.85			
Endpoint	216	63.7	1.21	-15.4	1.00	271	62.2	1.08	-16.1	0.95	0.3 (-2.16; 2.66)

[a] The difference in change from baseline between risperidone LAI and olanzapine. LS means and their 95% CI was obtained from an ANCOVA model controlling for stratification variables: baseline Total PANSS score, BMI, subject status, number of previous hospitalizations; and country and investigator.

The secondary analysis on data from the 'per-protocol' OLA-RIS 25/50 mg' data set was performed at Week 53. There were 263 subjects in the olanzapine group and 201 subjects in the risperidone LAI 25-50 mg group. After 53 weeks of treatment, the change from baseline in Total PANSS was –19.0 and -18.0 in the risperidone LAI and olanzapine treatment groups, respectively. There was a tendency for separation for the secondary PANSS subscale results from Month 9 to Month 12. The odds of clinical improvement of a decrease of >20% or more on Total PANSS was significantly greater in subjects treated with risperidone LAI.

SAFETY RESULTS: Safety data collected over the 53 weeks of treatment, including adverse events, EPS-related adverse events, clinical laboratory test results, vital signs, and ECGs, demonstrated that risperidone LAI was generally well tolerated in this subject population. No new and unexpected safety concerns for the use of risperidone LAI in this subject population were observed. The pattern and frequency of adverse events reported were similar in the risperidone LAI group and the olanzapine tablet group except for a higher proportion of EPS-related adverse events in the risperidone LAI group and a significantly greater incidence of weight gain in the olanzapine treatment group. Weight, waist circumference, and body mass index were significantly greater in the olanzapine treatment group.

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CONCLUSION: The primary efficacy results of this noninferiority trial demonstrated that during 13 weeks of treatment risperidone LAI treatment was as effective as oral olanzapine treatment in subjects with schizophrenia or schizoaffective disorder. This conclusion was based on Total PANSS scores, and was supported by secondary efficacy analyses including confirmation of the 13-week result at endpoint, subscales of PANSS, and Clinical Global Impression. At 12 months, 2 of the 5 PANSS subscales ('disorganized thoughts' and 'uncontrolled hostility/excitement') showed significant differences in favor of risperidone LAI. There was also a statistically higher incidence of clinical response in the risperidone LAI group over the olanzapine group.

Analyses of safety and tolerability, including adverse events, changes in laboratory findings, vital signs and ECGs provide evidence of the adequate safety and tolerability profile for the risperidone LAI formulation. Safety data with risperidone LAI demonstrated a profile consistent with data from previously conducted clinical studies. Differences between the 2 treatments were noted in weight gain and EPS-related adverse events but not in SARS results, an objective measure of EPS.

Date of the report: 28 August 2003

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