

CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6368882:2.0

<u>Name of Sponsor/Company</u>	Janssen-Cilag EMEA	
<u>Name of Finished Product</u>	Risperdal Consta; Risperdal Quicklet	
<u>Name of Active Ingredient(s)</u>	risperidone	
Protocol No.: RIS-PSY-301		
Title of Study: An open-label trial of risperidone long-acting injectable in the treatment of subjects with recent onset psychosis		
Investigator: R. Emsley, MD, Dept. Psychiatry, University of Stellenbosch, South Africa		
Publication (Reference): -		
Study Period:	First visit of first subject: 13 February 2004 Last visit of last subject: 7 December 2006	Phase of Development: IIIb
<p>Objectives:</p> <p>To assess the efficacy of risperidone long-acting injectable (RLAI) in recent onset psychosis with regard to:</p> <ul style="list-style-type: none"> - total symptoms, positive, negative and general psychopathology; - time to relapse; - co-morbid depressive symptoms; - functional outcome. <p>To assess the tolerability of RLAI in recent onset psychosis with regard to:</p> <ul style="list-style-type: none"> - extrapyramidal symptoms (EPS); - weight, body mass index (BMI), waist and hip circumference; - electrocardiogram (ECG); - prolactin; - other adverse events (AEs). <p>To assess the safety and patient acceptance of fast-dissolving orodispersible risperidone tablets.</p>		
<p>Methodology: This was an open-label, single-site study in subjects with recent onset schizophrenia, schizophreniform disorder and schizoaffective disorder. It was a pilot project, and could lead to a larger multicentre, randomised, controlled trial. The main purpose of the present study was to demonstrate that RLAI could be used safely and effectively in treating patients in the early stage of psychosis. RLAI (25, 37.5, or 50 mg) was given to all participants every two weeks, for a period of 24 months. The trial ended once the last recruited patient completed 24 months of treatment. Results can be indirectly compared to the results of study RIS-INT-35, a multi-site international study which included the same site as the current trial, in which oral risperidone was compared with oral haloperidol in subjects with recent onset psychosis.</p>		
Number of Subjects (planned and analysed): 50 subjects planned / 50 subjects analysed		
<p>Diagnosis and Main Criteria for Inclusion:</p> <ul style="list-style-type: none"> • Male or female in- or out-patient. • Age between 16 and 45 years, inclusive. • Female subjects had to be surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and have a negative urine serum pregnancy test at baseline, before study entry. • Subjects (or their legally acceptable representatives) had to have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study. • Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) diagnosis of schizophreniform disorder, schizophrenia or schizo-affective disorder for no longer than 12 months, and with not more than two hospitalizations for psychosis. • Subjects who had, during their lifetime, been exposed to a maximum of 12 weeks of antipsychotic medication. • Subjects who, in the opinion of the investigator required at least 12 months of treatment with antipsychotic medication. 		

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Test Product, Dose, Mode of Administration, Batch No.: RLAI; 25, 37.5, or 50 mg; intramuscular injection; Batch No.: V03PK8618, V03PK8619, V03PK8620, V04PB8752, V04PB8753, V04PB8754, V04PB8755, V05PK9384, V05PK9385, V05PG9299, V05PA9142, V05PA9143, V05PA9144, V05PA9145

Duration of Treatment: 24 months

Criteria for Evaluation:

- Efficacy:**
- Positive and Negative Syndrome Scale (PANSS);
 - Time to Relapse;
 - Response Rate;
 - Calgary Depression Rating Scale for Schizophrenia (CDSS);
 - Hospitalisation / Health Care Resource Use and Productivity;
 - Social and Occupational Functioning Assessment Scale (SOFAS);
 - SF-12 survey;
 - Clinical Global Impression (CGI);
 - Patient Global Impression (PGI).
- Safety:**
- Extrapyramidal symptoms (EPS);
 - Weight, BMI, waist and hip circumference;
 - Vital signs and electrocardiogram (ECG);
 - Laboratory assessments (including prolactin);
 - AE reporting.

Statistical Methods: Descriptive statistics; frequency tabulations; Wilcoxon-signed-rank test; Wilcoxon-two-sample test; Kaplan-Meier plots; Cox regression analysis; regression analysis; analysis of covariance [ANCOVA]; Fisher's exact test; Spearman correlation coefficient. Cut-off level for statistical significance was set at $p < 0.05$. All comparisons were 2-sided.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Subjects demonstrated significant improvements in mean total PANSS scores, with 78% of subjects achieving at least a 50% reduction in their corrected PANSS total score at endpoint. Subjects achieved a mean (SD) statistically significant reduction in their PANSS total score at endpoint of 39.7 (21.1; $p = 0.0001$). All PANSS factor-derived domains were statistically significantly decreased at endpoint ($p = 0.0001$).

In total, 64% of subjects achieved remission and 62% of subjects maintained remission throughout the trial. Relapse was assessed for those subjects who initially achieved the response criterion. Four (8%) subjects who had initially responded to treatment relapsed during the trial, including one subject who relapsed twice in the first 12 months. When comparing the baseline features of the remission and non-remission groups, the only statistically significant difference between the groups was that more of the females remitted as compared to males. Time to remission was decreased ($p < 0.05$) by being female, having higher BMI, higher level of depression, lower negative and disorganized PANSS factor scores and higher Anxiety/Depression PANSS factor scores.

Early change of PANSS total scores as a predictor of remission was also examined. A large and significant difference starting at Week 2 of a -12 point advantage for the remission group was observed, which was maintained at Weeks 4 and 6. At endpoint, the PANSS total score change was twice as great in the remission group as compared to the non remission group (-48 vs. -25). Change to Week 2 was significantly associated with remission, with greater reduction on PANSS being associated with reduced time to remission ($p = 0.002$).

The remission and non-remission groups were compared on clinical and functional outcomes. The remission group showed significantly more decline on CGI-S, ESRS and PANSS total and factor scores, required lower doses of RLAI, displayed more improvement on the SOFAS and spent longer time in the study compared to the non-remission group.

At endpoint, only 8 (16%) subjects were judged to be moderately, markedly, or severely ill by the investigator, compared to all subjects being judged moderately, markedly, or severely ill at baseline (as measured by the CGI-S scale). At endpoint, a mean (SD) statistically significant decrease of 3.1 (1.6) from baseline ($p = 0.0001$) was observed in CGI-S score. The CGI-C is designed to assess the change in the clinical condition over time. The CGI-C consists of a 7 point rating of change, questioning if the clinical condition of the subject improved, remained unchanged, or worsened. Most improvement was seen in the first 16 weeks of treatment, with the percentage of subjects showing improvement (minimally, much, or very much improved) ranging from 51% to 78% (as measured by the CGI-C scale).

At endpoint, mean (SD) CDSS score was showed a decrease of 0.9 (3.9) from baseline ($p = 0.0065$).

Subjects' functioning was observed to increase on average by 72% at endpoint (as measured by the SOFAS scale).

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There was a statistically significant negative correlation of medium to large size between SOFAS and total PANSS score ($r = -0.70$; $p < 0.0001$), PANSS positive subscale ($r = -0.46$; $p = 0.0011$), PANSS negative subscale ($r = 0.53$; $p < 0.0001$), and PANSS general psychopathology subscale ($r = 0.71$; $p < 0.0001$). Subjects' attitudes towards their illness also improved significantly, generally shifting towards a less severe perception of their illness (as measured by the PGI-S scale).

When measured by the SF-12 scale, MCS score showed a mean (SD) improvement at endpoint of 13.9 (14.41) from baseline ($p = 0.0001$), while PCS score showed no statistically significant change from baseline (mean [SD] decrease of 2.4 [11.05]; $p = 0.2373$).

At the start of the trial, 38 (76%) subjects were hospitalised because of psychotic disease. Five (10%) subjects were rehospitalised during the trial, one of them twice. All but one of these were hospitalised because of psychotic disease. At baseline, 13 (26%) subjects were employed. Of the subjects unemployed at baseline, 19 (51%) subjects changed occupational status, mainly because of improvement in psychiatric condition.

SAFETY RESULTS:**Subjects With Adverse Events/Reactions During the Trial**

	All subjects (N=50)	
	n	(%)
One or more adverse events/reactions	49	(98.0)
One or more serious adverse events/reactions	5	(10.0)
Deaths	0	(0.0)
Treatment stopped due to adverse events/reactions	2	(4.0)

AEs reported during risperidone treatment (orodispersible risperidone or RLAI) were most often related to the nervous system (60%), investigations (46%), psychiatric disorders (46%), infections and infestations (34%), and gastrointestinal disorders (28%). Blood prolactin increased and headache were the most frequently reported AEs, reported in 36% and 26% of subjects. Other frequently reported AEs (> 10% of subjects) were sedation and influenza (18% each), parkinsonism (14%), and extrapyramidal disorder and aggression (12% each). The majority of AEs during the trial were mild or moderate in severity (97%). Close to half of AEs (45%) were rated at least possibly related to the trial medication. Most of the AEs (76%) had resolved by the end of the trial.

During the course of RLAI treatment, there was a statistically significant mean increase in prolactin levels. Twenty-three (46%) subjects experienced 31 AEs possibly related to prolactin levels. AEs possibly related to prolactin included blood prolactin increased (note that this is an AE, not a prolactin related laboratory abnormality) experienced by 18 (36%) subjects, amenorrhoea experienced by 4 (8%) subjects, galactorrhoea by 3 (6%) subjects, loss of libido by 2 (4%) subjects, and anorgasmia, hyperprolactinaemia, menses delayed, and metrorrhagia in 1 (2%) subject. The most commonly experienced EPS related AEs were extrapyramidal disorder and parkinsonism, each by 8 (16%) subjects. Two (4%) subjects experienced an AE related to glucose levels. No AEs related to injection site were reported.

Laboratory results indicated that, in addition to prolactin levels, there was a statistically significant mean increase during the course of RLAI treatment in alkaline phosphatase levels and GGT levels as compared to baseline values.

Clinically significant laboratory values above normal limits were observed at Visit 18 (24 months) in 5 (10%) subjects for cholesterol. Other clinical significant laboratory abnormalities above normal limits were observed in at most 2 (4%) subjects. The most commonly reported AEs related to laboratory abnormalities were blood prolactin increased, reported by 18 (36%) subjects, and blood cholesterol increased, reported in 5 (10%) subjects. No discontinuations due to laboratory-related AEs were reported.

Small but statistically significant mean changes in vital signs parameters versus baseline at endpoint were observed for temperature ($p = 0.003$) and respiration rate ($p < 0.001$). No AEs related to vital signs abnormalities were observed.

Small but statistically significant mean changes in ECG parameters versus baseline at endpoint were observed for QT interval ($p = 0.0032$). There were no subjects with a QTc interval > 500 msec during the trial. At baseline, 3 male subjects were observed with a QTc interval ≥ 430 msec and ≤ 450 msec. At endpoint, this was the case for 2 subjects. One female subject was observed with a QTc interval ≥ 450 msec and ≤ 470 msec at endpoint. There were no subjects with an increase of the QTc interval of > 60 msec. Five (10%) subjects were observed with an increase of the QTc interval of 30 to 60 msec during the trial.

Body weight and BMI were statistically significantly increased versus baseline at all visits during treatment. Mean change in body weight from baseline to endpoint was 13.5 kg. At endpoint, 16 (32%) subjects had an unhealthy weight change versus baseline, defined as movement into a higher BMI category, excluding those subjects who moved from being underweight to normal, or who moved into the underweight category. Female subjects showed

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a larger shift versus baseline in waist-to-hip ratio at endpoint than male subjects, i.e., a mean (SD) increase of 0.063 (0.057) in females ($p = 0.0001$) compared to a mean (SD) increase of 0.031 (0.084) in males (not statistically significant). There was a medium to large size statistically significant positive correlation of baseline BMI with both waist circumference ($r \geq 0.67$) and waist-to-hip ratio ($r \geq 0.32$) at all visits. From Visit 14 (12 months) onward, there was a medium size statistically significant positive correlation of BMI change versus baseline with waist circumference ($r \geq 0.40$). Weight increase was reported as an AE for 3 (6%) subjects during the trial.

There were no statistically significant changes from baseline in any of the ESRS subscales at endpoint. Shifts versus baseline at maximum were statistically significant for total ESRS ($p = 0.0001$) and for the Parkinsonism, Dystonia, Dyskinesia, and Akathisia subscale, and Parkinsonism, CGI-S of Parkinsonism, Stage of Parkinsonism, and Hypokinesia subscales ($p \leq 0.001$). Tardive dyskinesia was reported as an AE in 2 (4%) subjects. One of these subjects experienced probable tardive dyskinesia from Visit 16 (18 months) onward and new-onset tardive dyskinesia from Visit 17 (21 months) onward.

CONCLUSION:

Results of this 2-year trial with RLAI in subjects with recent onset psychosis showed that RLAI was effective and generally well tolerated. The safety results were in line with the known safety profile of risperidone.

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