

SYNOPSIS

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<u>Name of Sponsor/Company</u>	Janssen-Cilag International N.V
<u>Name of Finished Product</u>	Risperdal® Consta®
<u>Name of Active Ingredient(s)</u>	Risperidone

Protocol No.: CR011992

Title of Study: A prospective study of the clinical outcome following treatment discontinuation after remission in first-episode schizophrenia

Principal Investigator: Robin Emsley, Prof, University of Stellenbosch Research Unit, Cape Town, South Africa

Publication (Reference): None.

Study Period: 25 April 2006 to 11 March 2010. Database lock date: 1 June 2010.

Phase of Development: Phase 4.

Objectives: The primary objective of the study was to determine the time to relapse after discontinuation of RISPERSDAL® CONSTA® (risperidone long-acting injection [RLAI]) in first-episode subjects who had been successfully treated with RLAI for 2 years.

Secondary objectives were to: evaluate the relapse rate after treatment discontinuation; evaluate the time to response after re-exposure to treatment with RLAI; and evaluate the degree of clinical improvement measured by the Positive and Negative Syndrome Scale (PANSS).

Methods: This was an open label, single-site study in subjects who had completed 2 years of RLAI treatment in the clinical trial RIS-PSY-301. Subjects who completed RIS-PSY-301 were offered treatment discontinuation. If accepted, subjects were entered into the present study.

The study consisted of 2 periods:

- In Period 1, RLAI was tapered and discontinued over a period of up to 6 weeks. Subjects were regularly and carefully followed up for a maximum of 3 years or until their first disease relapse. In case of relapse, patients were transferred to Period 2.
- Period 2 was started when a patient presented with a disease relapse. Upon relapse, treatment with RLAI was immediately re-started. RLAI treatment in Period 2 continued for a maximum of 2 years.

Number of Subjects (planned and analyzed): Thirty-three subjects entered Period 1 and all were included in the analysis of efficacy and safety. Thirty-one subjects entered Period 2; 30 were included in the analysis of efficacy and 31 were included in the analysis of safety. .

Diagnosis and Main Criteria for Inclusion: Men and women who successfully completed 2 years of RLAI treatment in the clinical trial RIS-PSY-301 were recruited.

Test Product, Dose and Mode of Administration, Batch No.: In Period 2, subjects received RLAI 25, 37.5, or 50 mg, every 2 weeks as an intramuscular injection in the gluteus. Supplementation with oral risperidone (oro-dispersible tablets) was administered for 21 days from the first dose of RLAI in Period 2 and tapered off over the next 5 days.

Batch numbers for RLAI = 25 mg: 05AS124K, 05KS157K, 05KS159K, 6ESK004; 37.5 mg: 05AS46K, 05DS76K, 5ISK000, 6GSK000; 50 mg: 05JS53K/A, 05JS53K/B, 05JS53K, 6FSK003.

Batch numbers for oral risperidone = 1 mg: 4NG4640.A, 6BG8093, 6BG8093/2, 7MG3962, 9HZS00E; 2 mg: 5CG5349-X, 6AG7873, 7EG2195, 7EG2465.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: In Period 1, subjects discontinued RLAI and were followed up for a maximum of 3 years until disease relapse. In Period 2, subjects restarted RLAI and were followed up for maximum of 2 years.

Criteria for Evaluation:

Efficacy assessments: Patients' clinical state was monitored throughout the study through evaluation of the following scales: PANSS, Clinical Global Impression of Severity/Change (CGI-S/C), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Assessment Scale (SOFAS), quality of life questionnaire (SF-12), and Patient Global Impression of Severity/Change (PGI-S/C). Hospitalization/health care resource use and productivity were also recorded throughout the study.

The primary efficacy end points were:

- Period 1: time to relapse following RLAI discontinuation; and relapse rate after discontinuation of RLAI
- Period 2: the degree of clinical improvement measured by the PANSS total score after reinitiation of RLAI; the time to response after reinitiation of RLAI.

Safety assessments: Adverse events, clinical laboratory tests (hematology, chemistry, prolactin), vital signs, physical examination, electrocardiograms (ECG), body weight, body mass index (BMI), waist/hip circumference, and the Extrapyramidal Symptom Rating Scale (ESRS) were assessed throughout the study.

Statistical Methods: The statistical analyses were descriptive and of exploratory nature.

Efficacy: The changes from baseline to endpoint for efficacy scales (PANSS, CGI-S, CDSS, SOFAS, SF-12, PGI-S) were tested for differences using the Wilcoxon signed rank test (ordinal/continuous data). Statistical tests for differences between endpoint and baseline were interpreted at the 5% significance level (two-tailed). For time to relapse, survival analysis techniques were used.

Safety: Treatment-emergent adverse events, clinical laboratory analyte values, vital sign measurements, ECG data, body weight, BMI, waist/hip circumference, and ESRS results were summarized. The changes from baseline to endpoint for body weight, BMI, waist/hip circumference, and ESRS subscales were tested for differences using the Wilcoxon signed rank test.

RESULTS:

At Period 1 baseline, there was a generally even proportion of female (42%) and male (58%) subjects and the median age was 24 years. Approximately half the subjects had a DSM-IV diagnosis of schizophrenia (48%) and the other half had a diagnosis of schizophreniform disorder (52%).

A total of 33 subjects entered Period 1; none of these subjects completed the full 36-month follow-up period (32 subjects relapsed before 36 months and 1 was lost to follow-up).

A total of 31 subjects entered Period 2. Two subjects in Period 1 did not enter Period 2 (1 lost to follow-up during Period 1 and 1 did not enter due to a positive drug screen). A total of 14 (45%) subjects completed the 24-month treatment period. The mean (SD) number of RLAI injections per subject was 29.0 (21.8) [range, 1 to 54] and the mean (SD) number of days of RLAI use was 392.0 (305.1) days [range, 0 to 743]. The most common mode dose was 25 mg (in 17 [54.8%] subjects).

EFFICACY RESULTS:

Period 1: A total of 32 of 33 subjects experienced a relapse during Period 1. The Kaplan-Meier estimate of the median time to relapse was 163 (95% CI, 96; 199) days. The mean (SD) time to relapse was 206.9 (186.7) days, with values ranging from 34 to 880 days. The predominant reasons for diagnosing relapse in Period 1 were a significant clinical deterioration based on CGI-C (100%) and an increase in PANSS total score (72%).

Consistent with a diagnosis of relapse in the majority of subjects at endpoint, mean PANSS total and subscale scores showed a statistically significant increase (ie, worsening) from baseline to endpoint. Mean

(SD) PANSS total score increased from 44.8 (7.4) at baseline to 86.6 (15.7) at end point, ie, a mean (SD) increase of 41.8 (15.0) [$p<0.0001$].

At baseline, 28 of 33 subjects were in remission according to PANSS criteria. This number dropped rapidly as Period 1 progressed. The mean (SD) time to loss of remission status was 202.7 (193.7) days, with values ranging from 35 to 889 days.

Statistically significant changes from baseline to endpoint consistent with an overall deterioration in clinical state were also observed for the secondary efficacy variables, including PANSS Marder factors, CGI-S, PGI-S, SOFAS, CDSS, and SF-12 (physical and mental component) scores.

Period 2: A statistically significant decrease (ie, improvement) in PANSS total and subscale scores was observed during Period 2. Mean (SD) PANSS total score decreased from 86.5 (14.4) at baseline to 59.0 (23.7) at end point, ie, a mean (SD) decrease of 27.7 (20.6) [$p<0.0001$]. The effect was rapid: a statistically significant difference versus baseline was observed for the PANSS total score and all PANSS subscales from the first assessment time point (Week 2) and every time point thereafter.

Based on corrected response rates, a total of 26 (86.7%) patients achieved a 20% or greater reduction in PANSS total score during Period 2; 25 (83.3%) achieved a $\geq 30\%$ reduction, 24 (80%) achieved a $\geq 40\%$ reduction, and 23 (76.7%) achieved a $\geq 50\%$ reduction in PANSS total score. In addition, a total of 14 (45%) subjects met PANSS remission criteria during Period 2.

Statistically significant changes from baseline to endpoint consistent with an overall improvement in clinical state were also observed for the secondary efficacy variables, including PANSS Marder factors, CGI-S, PGI-S, SOFAS, CDSS, and SF-12 (physical and mental component) scores.

RESOURCE USE: There were 4 subjects who were hospitalized during Period 1 (all due to psychotic disorder) and 9 subjects who were hospitalized during Period 2 (7 for psychotic disorder, 1 following a motorcycle accident, and 1 for diabetes mellitus and related care). The mean (SD) time to first hospitalization in Period 2 was 96.8 (114.4) days (range, 7 to 344 days).

During Period 1, 3 subjects visited the emergency room with a reason of psychotic disease, 3 subjects visited the day clinic, and no subjects visited the night clinic. In Period 2, no subjects visited the emergency room, day clinic, or night clinic.

Changes in accommodation status were reported for 0 subjects in Period 1 and 1 subject in Period 2. Ten subjects experienced a shift from employed to unemployed status during Period 1 versus 5 subjects in Period 2.

SAFETY RESULTS:

Safety was analyzed using the Safety Analysis Set (N=33 for Period 1 and N=31 for Period 2).

	Subjects With Adverse Events/Reactions During the Trial ^a			
	Period 1 (N=33)		Period 2 (N=31)	
	n	(%)	n	(%)
One or more adverse events/reactions	33	(100)	25	(80.6)
One or more serious adverse events/reactions	5	(15.2)	9	(29.0)
Deaths	0	(0.0)	0	(0.0)
Treatment stopped due to adverse events/reactions	0	(0.0)	4	(12.9)

^a Only adverse events/reactions with onset during each treatment period are summarized.

Period 1: At the start of Period 1, 21 (63.6%) of 33 subjects had an adverse event that was ongoing from the previous study, RIS-PSY-301, the most common of which was blood prolactin increased (12 [36%] subjects).

Following discontinuation or RLAI, all 33 (100%) subjects experienced an adverse event with onset during Period 1. The most common AEs with onset during Period 1 were psychotic disorder (97.0%), restlessness (24.2%), insomnia (21.2%), weight decreased (18.2%), and blood cholesterol increased (12.1%). The majority of AEs with onset during Period 1 were mild or moderate in severity (99%) and most were

considered by the investigator to be unrelated to study medication (88%). Most of these AEs (77%) were ongoing at Period 1 end point. There were no deaths during Period 1. Five (15.2%) subjects experienced a serious AE (psychotic disorder).

Adverse events of potential clinical importance with onset during Period 1 included 3 subjects with a glucose-related AE (1 subject with blood glucose decreased, and 2 subjects with blood glucose increased), 8 subjects with an EPS-related AE (restlessness in 8 subjects, and tardive dyskinesia in 1 subject), and 2 subjects with a potentially prolactin-related AE (menorrhagia). No subject experienced an injection-related AE.

There was a statistically significant decrease in prolactin levels from baseline to endpoint (mean levels decreased from 54.4 to 10.6 µg/L, representing a mean change of -43.7 µg/L [$p < 0.0001$]). Small but statistically significant mean changes were observed for various other clinical laboratory parameters, but the clinical significance of these findings is considered unlikely.

Vital signs data showed a small but statistically significant increase from baseline to end point in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during Period 1 (mean increase of 6.6 mmHg [$p = 0.015$] and 5.4 mmHg [$p = 0.003$], respectively). No statistically significant changes from baseline to end point were observed for pulse rate, respiration rate, or temperature.

Body weight and BMI were statistically significantly ($p < 0.0001$) decreased versus baseline. Mean change in body weight and BMI from baseline to endpoint was -7.1 kg and -2.6, respectively. Weight decrease was reported as an AE for 6 (18.2%) subjects. A statistically significant decrease from baseline to end point in waist circumference and hip circumference was also observed.

There were no statistically significant changes from baseline to end point in any of the ESRS subscales. Median scores for all ESRS subscales were 0 at baseline and end point. According to Schooler and Kane criteria, 1 subject experienced emergent and persisting dyskinesia during Period 1.

Period 2: At the start of Period 2, all 31 (100%) subjects entering Period 2 had an adverse event that was ongoing from Period 1. The most common AE that was ongoing from Period 1 was psychotic disorder (31 [100%] subjects).

Following re-introduction of RLAI treatment, a total of 25 (80.6%) of 31 subjects in Period 2 reported at least 1 treatment-emergent AE (TEAE). The most common TEAEs were psychotic disorder (38.7%), weight increased (25.8%), blood prolactin increased (19.4%), restlessness (22.6%), and insomnia (19.4%). The majority of TEAEs during Period 2 were mild or moderate in severity (96%) and most were considered by the investigator to be unrelated or doubtfully related to study medication (73%). Most of the TEAEs (69%) had resolved by the end of the trial. Nine (29.0%) subjects experienced a treatment-emergent SAE (TESAE) during Period 2 (psychotic disorder [6 subjects], and road traffic accident, suicidal ideation and diabetes mellitus [1 subject each]). One subject was withdrawn from the study due to TEAEs of blood prolactin increased, blood creatine phosphokinase increased, hypothyroidism, and blood pressure abnormal; 4 subjects were withdrawn from the study due to a TESAE of psychotic disorder.

An examination of adverse events of potential clinical importance revealed 1 subject with a glucose-related TEAE (diabetes mellitus), 12 subjects with an EPS-related TEAE (restlessness in 7 subjects, musculoskeletal stiffness in 3 subjects, Parkinsonism in 3 subjects, tremor in 2 subjects, and extrapyramidal disorder in 1 subject), and 7 subjects with a potentially prolactin-related TEAE (blood prolactin increased in 6 subjects and loss of libido in 1 subject). No AEs related to the injection site were reported.

During the course of RLAI treatment, there was a statistically significant mean increase in prolactin levels (mean levels increased from 10.9 to 45.8 µg/L, representing a mean change of 34.9 µg/L [$p < 0.0001$]). Small but statistically significant mean changes were observed for various other clinical laboratory parameters, but the clinical significance of these findings was unlikely.

There were no statistically significant changes from baseline to end point in any of the vital sign parameters. However, statistically significant decreases in SBP and DBP versus baseline were observed at several time points over the first 6 months of treatment. One subject had a TEAE of blood pressure abnormal; no other AEs related to vital sign investigations were observed.

There were no statistically significant changes from baseline to end point in any ECG parameter. There was 1 subject with a QTc value >500 msec (at baseline) and no subject experienced an increase in QTc of >60 msec during the study. No TEAEs related to ECG abnormalities were reported.

Body weight and BMI were statistically significantly increased versus baseline at all visits during RLAI treatment. Mean change in body weight and BMI from baseline to endpoint was 6.5 kg and 2.4 kg/m², respectively. Weight increase was reported as a TEAE for 8 (25.8%) subjects during Period 2. A statistically significant increase from baseline to end point in waist circumference, hip circumference, and waist-to-hip ratio was also observed.

There were no statistically significant changes from baseline to end point in any of the ESRS subscales. Median scores for all ESRS subscales were 0 at baseline and end point. According to Schooler and Kane criteria, 1 subject experienced treatment-emergent and persistent dyskinesia.

CONCLUSION: Results of this study showed relapse occurred rapidly following discontinuation of RLAI treatment in subjects with recent-onset schizophrenia or schizophreniform disorder who had been successfully treated with RLAI for 2 years. The Kaplan-Meier estimate of the median time to relapse was 163 (95% CI, 96; 199) days. These results suggest maintenance treatment of durations >2 years and possibly indefinitely is required to maintain adequate symptom control in these patients. The results also suggest that rapid re-introduction of antipsychotic treatment after relapse results in good clinical responses.

Subjects who re-started RLAI treatment after psychotic relapse showed improvements in the severity of symptoms associated with schizophrenia (PANSS), depression (CCDS), social and occupational functioning (SOFAS), clinician- and patient-rated global severity of illness (CGI-S and PGI-S), and quality of life (SF-12). Whether the response to RLAI was diminished versus the initial antipsychotic treatment period (RIS-PSY-301) remains to be determined; this will be evaluated in a secondary analysis, to be reported separately.

The safety results were in line with the known safety profile of RLAI and risperidone.

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