CLINICAL STUDY REPORT SYNOPSIS
STUDY RIS-SCH 3007 R-LAI

PROTOCOL NO.: **CTMS: RIS SCH 3007**

Name of Sponsor/Company	Janssen-Cilag S.p.A. Via M. Buonarroti, 23 20093 Cologno Monzese (Milano) Italy
Name of Finished Product	RISPERDAL® prolonged-release powder and solvent for suspension for intramuscular injection (R-LAI)
Name of Active Ingredient(s)	Risperidone long-acting injectable

Title of Study: Maintenance of clinical response with risperidone long-acting injectable (R-LAI) in subjects with schizophrenia or schizoaffective disorder

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Publication (Reference): none

Study Period: First patient in: January 10th, 2005; Last patient out: April 4th, 2007. Data base locked July 2007

Phase of Development: IIIb

Objectives: Primary – Maintenance of antipsychotic efficacy and safety of R-LAI injected every two weeks over a period of 52 weeks in subjects with schizophrenia or schizoaffective disorder. Secondary – To investigate the prevalence of subjects who met standardized remission criteria and the psychopathological, psychosocial and subjective predictors of achieving remission.

Methods: A 52-week, prospective, open-label, single-arm study performed at 47 Italian sites between January 2005 and April 2007. All efficacy and safety assessments were performed at baseline and after 4, 12, 26, 38, and 52 weeks of treatment with R-LAI administered into the gluteal muscle every two weeks. The recommended starting dose was 25 mg. However, subjects with persistent symptoms or who were known to respond only to higher dosages of antipsychotics could receive initial doses of either 37.5 mg or 50 mg. Subsequently, the dosage could be adjusted according to the patient's symptoms and response to treatment. If necessary, the dosage could be increased 4 weeks after treatment but not earlier than 2 weeks after the previous injection. Tolerability of oral risperidone should be investigated before the first injection of RLAI in patients with no history of previous risperidone use by administering two 1 mg risperidone tablets once daily for 2 days. Patients were switched from their previous antipsychotic agent(s) directly to RLAI without an oral risperidone run in. When switching from an oral antipsychotic, the agent was administered at the same dose for 21 days after the first injection of RLAI, and then stopped or tapered off over 3 days. The treatment regimen of subjects who changed their medication from conventional depot neuroleptics depended upon the injection regimen of the previous medication. Temporary oral supplementation with risperidone (1-2 mg/day) was permitted when considered necessary by the investigator to treat breaktrough psychosis, and also for up to 21 days

following an increase in the dose of RLAI if an immediate clinical effect was needed. Patients could receive other psychotropic medication that had been initiated before the trial for other reasons (e.g. sleep induction or sedation). Anticholinergic medication was allowed up to 8 weeks past baseline with a gradual tapering. Finally, benzodiazepines could be used as rescue medication for a short period.

Number of Subjects (planned and analyzed): Based on the data in the literature (total baseline PANSS score of 67.1) and fixing a 90% power and a one-sided CI of 95%, 270 subjects were needed to show non-inferiority of R-LAI treatment compared to previous standard therapy. With a foreseen drop-out rate of about 20% during the study period, a number of 338 enrolled subjects was planned.

Planned: 338; Enrolled: 347; ITT population: 326; PP population, completers: 243.

Table 1. Number of subjects

	No. of subjects	Percentage
Planned	338	
Enrolled	347	100%
Safety population	347	100%
ITT population	326	93.9%
Discontinued	104	30.0%
PP population, Completers	243	70.0%

ITT = intention-to-treat; PP = per-protocol.

Diagnosis and Main Criteria for Inclusion/Exclusion: Adult males and females out-subjects or subjects hosted in residential structures, aged ≥18, with schizophrenia or schizoaffective disorder according to DSM-IV, symptomatically stable (clinical stability is defined as the absence of ospitalizations due to psychiatric causes and a stable dose of antipsychotic medication in the last month prior to screening visit), and requiring long-term antipsychotic therapy were included. Subjects who had received clozapine during the previous 3 months, who had participated in an investigational drug trial in the previous 30 days, or who had previously been shown to be either intolerant or non-responsive to risperidone therapy were excluded. Other exclusion criteria included the presence of a serious unstable medical condition, such as a history or current symptoms of tardive dyskinesia or a history of neuroleptic malignant syndrome. Pregnant or breast-feeding subjects were also ineligible, and all other female subjects of childbearing potential who did not use adequate contraception were excluded.

All subjects or their legal representatives provided their written informed consent prior to enrolment in the study.

Test Product, Dose and Mode of Administration, Batch No.: R-LAI, 25 mg, 37.5 and 50 mg every 2 weeks, by intramuscular administration.

Batch numbers:

25 mg: V04PH8955; V04PJ8991; V05PA9146; V05PA9147; V05PC9186; 05AS124K

37.5 mg: V04PH8956; V04PJ8992; 04LS91K;04KS88K; 05CS69K; 5ISK003

50 mg: V04PH8957; V04PJ8993; 04LS92K; 05AS137K; 04LS92K

Reference Therapy, Dose and Mode of Administration, Batch No.: none

Duration of Treatment: 52 weeks.

Criteria for Evaluation: Primary efficacy: Positive and Negative Syndrome Scale (PANSS) total and subscales score change from baseline to endpoint. Secondary efficacy: Change from baseline to week 52 of Clinical Global Impression (CGI), Global Assessment of Functioning (GAF), Drug Attitude Inventory 30 (attitude towards treatment) scores. Remission criteria. Safety: AE recording, vital sign measurement, and assessment of changes in body weight and body max index (BMI).

Statistical Methods: All patients who received at least one dose of RLAI were included in the safety analysis (safety population). All patients who received at least one dose of RLAI and completed at least one post-baseline efficacy assessment were included in the Intention-To-Treat (ITT) population and analysed for the primary efficacy parameter using a last-observation-carried-forward (LOCF) approach with respect to endpoint visits. Patient demographics were analysed using descriptive statistics. Patients in the ITT population who completed the study according to study protocol (i.e. completers) were included in the Per-Protocol (PP) population. The primary efficacy measure (i.e. PANSS total and subscales score change from baseline to endpoint) was analysed either with ITT and PP analysis. A PP analysis was performed for the secondary efficacy measures (i.e. CGI-C, GAF and DAI30 score change from baseline to week 52, and remission data). Three non-parametric tests were used for comparative statistical analyses of efficacy measures: Wilcoxon Rank-Sum test, Wilcoxon Signed Rank test and Kruskal-Wallis test. A $P<0.05$ was considered statistically significant. The PANSS scores at each visit were analysed (PP population) to determine whether patients met the criteria for remission as defined by the Remission in Schizophrenia Working Group (Andreasen *et al.*, 2005). This definition requires the simultaneous attainment of a score of 3 (mild), 2 (minimal) or 1 (absent) for at least 6 months for all of the following symptoms (PANSS items): delusions (P1); concept disorganization (P2); hallucinatory behaviour (P3); unusual thought content (G9) or mannerisms and posturing (G5); blunted affect (N1); passive/apathetic social withdrawal (N4); and lack of spontaneity and flow of conversation (N6). For visits up to week 26, only the severity criteria were applied, but both severity and duration criteria were applied for subsequent visits (i.e. patients were considered to be “in remission”). A binary logistic regression model was used to test the power of the predictors to estimate the remission.

RESULTS: SUBJECTS CHARACTERISTICS

A total of 347 subjects were included in the study and received at least one dose of R-LAI (safety population), whereas 326 had at least one post-baseline efficacy evaluation (ITT population). Overall, 243 subjects (70%) completed the 52-week study period in accordance with the study protocol (PP population, i.e. completers). The most common reason for discontinuation of R-LAI treatment are described in Table 2.

Table 2. Reasons for discontinuation of R-LAI treatment

	N	%
Total number of subjects	347	100.0
Completed 52-week treatment (PP)	243	70.0
Discontinued	104	30.0
Reasons for discontinuation		
Withdrawal of consent	54	15.6
Adverse event	11	3.2
Subjects lost to follow-up	11	3.2
Insufficient response	10	2.9
Non-compliance	10	2.9
Death	1	0.3
Other	7	2.0

Of the 347 subjects, the majority were male (61.9%). Mean ± SD age was 44.2 ± 11.4 years. On the basis of DSM-IV criteria, subjects were diagnosed with schizophrenia (n = 260; 74.9%) or schizoaffective disorder (n = 87; 25.1%). The mean age at first onset of symptoms was 26.9 ± 9.4 years and mean age at

first antipsychotic treatment was 28.6 ± 9.5 years. Subjects had an average of 4.6 ± 5.9 hospitalizations over a period of 6 months prior to inclusion in the study.

The demographic parameters of the PP population were comparable to those of the overall population.

Table 3. Demographic and baseline characteristics

Characteristic	Overall Population
Gender, no. (%) No. of pts. Male Female	 347 215 (61.9) 132 (38.1)
Age (years) No. of pts. Mean (SD)	 347 44.2 (11.4)
Systolic Blood pressure No. of pts. Mean (SD)	 320 126.7 (15.5)
Diastolic Blood pressure No. of pts. Mean (SD)	 320 80.0 (9.6)
Heart rate No. of pts. Mean (SD)	 320 78.9 (9.6)
Weight (kg) No. of pts. Mean (SD)	 340 81.3 (16.1)
BMI (kg/m^2) No. of pts. Mean (SD)	 340 28.7 (5.5)

SD = standard deviation; BMI = body mass index

More than the half of the 347 patients were on monotherapy at baseline (n=201; 57.9%). The most common antipsychotic medications were atypical antipsychotics (n=190; 94.5%), which were mainly risperidone (n=71; 35.3%) or conventional depot neuroleptics (n=55; 27.4%).

At the onset of RLAI treatment, the vast majority (97.1%) of patients received 25 mg as the initial dose, whereas the remainder received 37.5 mg. At the endpoint, 41.2% of patients were receiving the 25 mg dose, whereas 30.0% and 28.8% were receiving 37.5 mg and 50 mg, respectively. The modal dose at each visit was 25 mg. During the 52-week study period excluding the first 3 weeks, 23.3% of patients received oral risperidone supplementation at a mean dose of 2.1 ± 0.1 mg and for a mean duration of 46.0 ± 5.1 days. This supplementation was given to manage a brief burst of symptoms.

RESULTS: EFFICACY

The mean change from baseline to endpoint in the PANSS total score was reduced significantly (P<0.001) at week 52 and at the endpoint. Table 4 shows values at baseline and at each time point in the two analysed population (ITT and PP). A significant improvement was seen as early as the 4th week of treatment with RLAI, and further improvements were observed continuing the treatment throughout the one-year study period (Table 4). Significant improvements from baseline to endpoint were observed in all the subscores for the PANSS positive, negative, general psychopathology subscales and in the PANSS cognitive cluster score (Table 4). When subjects who completed the 52-week study period (PP population; PANSS data for 12 subjects were not available at all time points and therefore excluded from

analysis) were stratified on the basis of their improvement in PANSS total score from baseline to week 52, 57.6% (n=133) had >20% improvement. Of these patients, 16% (n=37) showed ≥30% improvement, 6.1% (n= 4) had ≥40% improvement, and 5.6% (n=13) achieved ≥50% improvement.

Table 4. PANSS total and subscale scores[a] and PANSS cognitive cluster score[b] at each time point

		Baseline	4 weeks	12 weeks	26 weeks	38 weeks	52 weeks	Endpoint
Subscales	ITT	(*n*=326)	(*n*=326)	(*n*=298)	(*n*=265)	(*n*=248)	(*n*=231)	(*n*=326)
	PP	(*n*=243)	(*n*=242)	(*n*=239)	(*n*=236)	(*n*=232)	(*n*=231)	(*n*=242)
Positive	ITT	17.9±6.3	16.9±6.4*	15.7±6.0*	15.5±6.5*	14.8±5.9*	13.7±5.7*	14.5±6.3*
	PP	18.0±6.1	17.3±6.4*	16.0±6.1*	15.5±6.4*	14.6±5.7*	13.7±5.7*	13.9±6.0*
Negative	ITT	24.24±8.0	23.4±8.0*	22.5±7.8*	22.1±7.4*	21.1±7.5*	19.9±7.4*	20.3±7.7*
	PP	25.2±7.8	24.2±7.6*	23.0±7.6*	22.1±7.5*	20.9±7.4*	19.9±7.4*	20.1±7.3*
Cognitive[b]	ITT	21.2±6.9	20.3±6.8*	19.4±6.5*	19.2±6.7*	18.4±6.5*	17.4±6.5*	17.9±6.8*
	PP	21.6±6.7	20.9±6.5*	19.8±6.4*	19.2±6.6*	18.2±6.3*	17.4±6.5*	17.6±6.5*
General	ITT	44.9±11.9	42.7±12.3*	40.6±11.7*	40.0±12.8*	38.2±12.1*	36.1±12.2*	37.6±12.7*
	PP	45.2±11.8	43.6±12.2*	40.9±11.7*	40.0±12.9*	37.7±12.0*	36.1±12.2*	36.6±12.4*
Total	ITT	87.2±22.5	83.0±23.3*	78.8±22.3*	77.6±23.8*	74.1±22.9*	69.6±22.9*	72.5±24.1*
	PP	88.4±22.1	85.1±22.8*	79.9±22.1*	77.6±23.9*	73.2±22.5*	69.6±22.9*	70.6±23.1*

PANSS=Positive and Negative Syndrome Scale; [a] Scores are expressed as mean ± SD
ITT= Intention To Treat population; PP= Per Protocol Population
**Wilcoxon Signed Rank Test, P< 0.001, shifts versus baseline*
*** Wilcoxon Signed Rank Test, P< 0.05, shifts versus baseline*

At baseline, 46.5% of subjects (n=113, PP population) were considered to be “moderately ill” at the CGI-S. The percentage of subjects who experienced any degree of improvement according to the CGI-Change between visits significantly increased from 34.8% (V2-V1) to 65.8% (V6-V5) (P<0.05).

Psychosocial functioning as measured by GAF improved significantly from baseline (49.1 ± 11.2) to week 52 (58.9 ± 13.3; PP population, P<0.001).

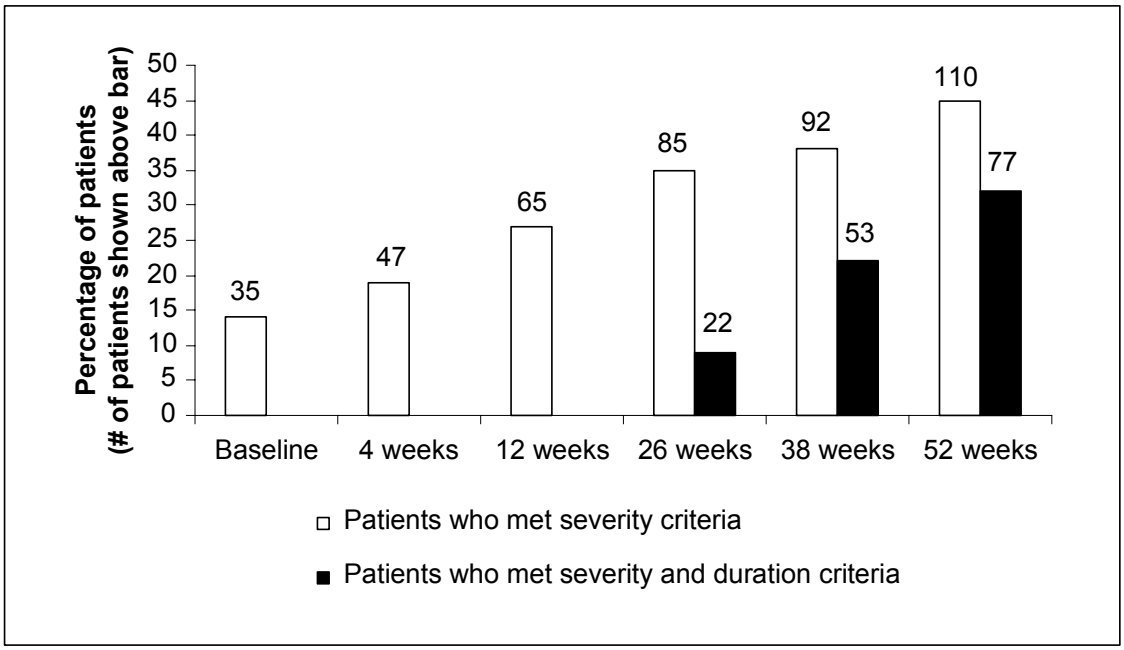
There was an overall improvement in the personal attitude towards medication during treatment with RLAI, as demonstrated by the significant increase vs baseline in DAI30 total scores observed at week 12 and thereafter up to week 52 (baseline, n=215, 42.6 ± 5.1; week 12, n=199, 43.7 ± 5.1; week 52, n=180, 43.7 ± 5.5; PP population, P<0.05). This improvement was also observed in both Attitude towards Medication (baseline, 18.7 ± 2.5; week 12, n=199, 19.1 ± 2.4; week 52, 19.2 ± 2.6; PP population, P<0.05) and Subjective Response DAI30 scores (baseline, 23.9 ± 3.2; week 12, n=199, 24.6 ± 3.2; week 52, 24.5 ± 3.5; PP population, P<0.05).

A total of ten subjects (2.9%) discontinued R-LAI treatment due to insufficient response. Half of these were receiving the 37.5 mg dose at the time of leaving the trial, while the remainder were receiving the 50 mg dose.

RESULTS: REMISSION

In the PP population (n=243), the PANSS severity criteria for remission, measured at each time point, was met by 35 subjects (14.4%) at baseline with an increase to 110 subjects (45.3%) at week 52 (Figure 1). Additionally, 22 of 35 patients (62.9%) who met the severity criteria at baseline also met them at week 52 (Figure 1). The number of subjects who met both severity and duration criteria increased from 22 (9.1%) at week 26 to 77 (31.7%) at week 52 (Figure 1). Of the 208 subjects who did not meet the severity criteria at baseline, 88 (42%) met them at week 52, and 55 (26.4%) reached and maintained remission (both severity and duration) at week 52.

Figure 1. Percentage of subjects (PP population n = 243) who met remission criteria at each time point.



The number of patients who met severity criteria or who met both severity and duration criteria at each time point is indicated above each bar

Subjects completers (PP population) who remitted during the study had significantly lower baseline PANSS total scores than did non-remitted subjects (Wilcoxon Rank-Sum Test, z = -6.9, P<0.001; Table 5). In addition, the improvement in PANSS cognitive cluster score including PANSS insight item G12 was higher among remitted subjects compared with non-remitted subjects (Wilcoxon Signed Rank Test, z = -5.3, P <0.001; Table 5). The difference in baseline CGI-S and GAF scores between groups was statistically significant (Wilcoxon Rank-Sum Test, P<0.001) with more severe scores in the non-remitting population (Table 5). Baseline DAI30 scores did not differ between groups, although DAI30 change (i.e. from baseline to week 52) was significantly (P<0.05) greater among remitted subjects versus non-remitted subjects (Table 5).

Table 5. PANSS, CGI-S, GAF and total DAI30 scores at baseline and DAI30 change between baseline and week 52 in remitted subjects versus non-remitted subjects[a] (PP population)

	Non-remitted subjects (n=166)	Remitted subjects (n=77)
PANSS Total	94.7 ± 19.6	74.6 ± 20.9*
PANSS Positive	19.5 ± 5.5	14.8 ± 6.2*
PANSS Negative	27.5 ± 6.9	20.2 ± 7.4*
PANSS Cognitive cluster score	23.1 ± 6.2	18.3 ± 6.7*
PANSS Insight item G12	3.5 ± 1.5	2.8 ± 1.4*
PANSS General Psychopathology	47.7 ± 11.5	39.6 ± 10.5*
CGI-S	4.7 ± 0.8	4.3 ± 0.9*
GAF	46.5 ± 10.2	54.6 ± 11.4*
DAI30 Total	42.5±5.0 (n=152)	43.0 ± 5.5 (n=63)
DAI30 change[§]	0.51 ± 4.9 (n=115)	2.70 ± 5.3 (n=53)**

[a] Data are expressed as mean ± SD.
[§] DAI30 change = week 52 – baseline.
** Wilcoxon Rank-Sum Test, P< 0.001 versus non-remitted subjects.*
*** Wilcoxon Rank-Sum Test, P< 0.05 versus non-remitted subjects.*

RESULTS: SAFETY AND TOLERABILITY

347 subjects were treated and included in the safety analysis. A total of 231 AEs was observed in 105 subjects (30.2% of subjects experienced one or more AEs during the 52-week treatment period). The majority of these events were considered to be mild (120; 51.9%) or moderate (87; 37.7%) in severity, and 81.0% of these events required no change in study treatment.

The most frequently (>5%) reported treatment-emergent adverse events that occurred in ≥5% of subjects were exacerbation of disease (n=23; 9.9%), endocrine-related (n=18; 7.7% including amenorrhea,

galattorrhoea, and impotence), extrapyramidal symptoms (n=17, 7.3%), insomnia (n=14; 6.0%), cardiovascular and respiratory disorders (both n=13; 5.6%), and mood disorders (n=12; 5.2%).

Thirty-two SAEs were observed in 25 (7.2%) subjects. 59 out of 231 AEs (25.5%) were possible, probable or very likely related to study drug administration. These events were observed in 42 (12.1%) subjects. Four (12.5%) SAEs, which were observed in 4 subjects (1.2%), were considered as possible (light fever), probable (distonia and psychotic symptom exacerbation) or very likely (acathisia) related to study treatment.

The number and frequency of AEs and SAEs are summarised in Table 6.

Table 6. Treatment-emergent AEs and SAEs (safety population)

	No. (%)
Total no. of AEs	*231*
Subjects with at least one AE	105 (30.2)
No. of treatment-related AEs	59 (25.5)
Subjects with treatment-related AEs	42 (12.1)
Total no. of SAEs	*32*
Subjects with at least one SAE	25 (7.2)
No. of treatment-related SAEs	4 (12.5)
Subjects with treatment-related SAEs	4 (1.2)
No. of deaths	1 (0.3)

% denominator: no. of subjects by safety population, no. of events by total AEs, no. of events by total SAEs, no. of deaths by safety population. AE = adverse event, SAE = serious adverse event

Eleven (3.2%) subjects discontinued treatment due to a reported treatment-emergent AE, with extrapyramidal symptoms (4/11) as the most frequent reported reason for discontinuation.

One (0.3%) patient died during the study for suicide. The patient was 54-year old male, affected by schizophrenia. The patient ingested a caustic substance, which caused diffused coagulation in the oesophageal and gastric mucosa and sub-mucosa, leading patient to death. The event was considered by the Investigator to be unrelated to treatment with R-LAI. The patient had received 4 injections of 25 mg dose.

There were no clinically significant changes in vital signs over the 52-week study period.

Overall, there was no significant increase in mean body weight from baseline (81.3 ± 16.1 kg) to week 52 (82.1±16.5 kg, paired *t*-test; $P = 0.093$) and in mean body mass index (BMI; 28.7 ± 5.5 kg/m^2 vs. 28.9 ± 5.4 kg/m^2; $P = 0.102$).

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