SYNOPSIS

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Name of Sponsor/Company	Janssen EMEA
Name of Finished Product	RISPERDAL® CONSTA®
Name of Active Ingredient(s)	Risperidone

Protocol No.: RIS-SCH-4045

Title of Study: Early versus late initiation of treatment with RISPERDAL CONSTA in subjects with schizophrenia or schizoaffective disorder after an acute episode

EudraCT Number: 2005-002304-41

Principal Investigators: This was a multinational, multicenter study with 52 principal investigators at study sites (9 sites in Finland, 8 sites in Italy, 6 sites in Denmark, 6 sites in France, 6 sites in Sweden, 5 sites in Greece, 4 sites in Switzerland, 3 sites in the United Kingdom, 3 sites in Israel, 1 site in Norway, and 1 site in Slovenia). There was no coordinating or overall study principal investigator.

Publication (Reference): None

Study Period: 10 November 2005 to 29 December 2009

Phase of Development: Phase 4

Objectives: The primary objective of this study was to investigate whether early initiation of treatment with RISPERDAL CONSTA (risperidone long-acting injectable [RLAI]) was not inferior to the routine approach (oral treatment for 12 weeks followed by treatment with RLAI). Noninferiority was assessed based on the reduction in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to end point (scheduled after 6 months).

Secondary objectives were to investigate and compare, in the 2 treatment arms:

- Response rates (defined as ≥20%, ≥30%, ≥40% and ≥50% improvement on PANSS total score from baseline to end point);
- Remission rates according to the PANSS severity criteria after 3 and 6 months;
- The number of discontinuations due to lack of efficacy;
- The number of discontinuations due to adverse events;
- Changes in Clinical Global Impression-Severity (CGI-S) scale, Global Assessment of Functioning (GAF) scale, overall health status (SF-12 Health Survey), and patient treatment satisfaction (rated on a 5-point scale; Drug Attitude Inventory [DAI] and/or the Udvalg for Kliniske Undersogelser Consumer Satisfaction [UKU-ConSat] were optional scales);
- Resource use data; and
- Safety/tolerability.

Methods: This was an open-label, multicenter, randomized Phase 4 trial conducted in Europe and Israel that evaluated the efficacy and safety of early versus late initiation of RLAI treatment. Subjects with an acute episode of schizophrenia or schizoaffective disorder (if schizoaffective disorder was a registered indication in the country at the time of the study) who had not been treated for the acute episode for more than 14 days were eligible.

The screening visit (Visit 1) was performed as early as possible after the start of the acute episode. Eligible subjects who were already receiving permitted antipsychotic treatment for the acute episode at Visit 1 were maintained on their existing therapy. Eligible subjects who were not receiving any antipsychotic treatment at Visit 1 were started on oral risperidone immediately after the screening visit. The baseline visit (Visit 2) was performed within 1 week after the screening visit and not later than 14 days after start of treatment for the acute episode. At the baseline visit, subjects were randomized to either early (immediate) start with RLAI or late start of treatment with RLAI at Week 12.

RLAI was started at a dose of 25 mg, administered as an intramuscular gluteal injection every 2 weeks. To ensure adequate antipsychotic coverage during the release phase of RLAI, all subjects continued on their existing antipsychotic medication for 21 days after the first injection of RLAI. The oral medication was then tapered off within the next 7 days.

Subjects were treated for 6 months with further visits at Weeks 6, 12, and 26 or at the time of discontinuation. Extra assessments were performed if a dose change of RLAI was required (PANSS) or if extrapyramidal symptoms required treatment (Extrapyramidal Symptom Rating Scale [ESRS]).

Number of Subjects (planned and analyzed): 220 subjects were planned and randomized. All 220 randomized subjects were included in the Safety analysis set; 216 subjects were included in the Intent-to-Treat (ITT) analysis set, and 140 subjects were included in the Per-Protocol (PP) analysis set (76 subjects were excluded from the PP analysis set due to a major protocol deviation).

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 to 65 years (inclusive) who were eligible for treatment with RLAI according to the registered indication in the country (diagnosis according to Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition [DSM-IV]) and were experiencing an acute episode (PANSS $\geq$80) at baseline. Subjects already receiving treatment for the acute episode at baseline must have been randomized within 14 days after starting treatment.

Test Product, Dose and Mode of Administration, Batch No.: RLAI 25, 37.5, or 50 mg was administered every 14 days as an intramuscular injection in the gluteus. The starting dose was 25 mg.

Subjects randomized to early initiation of RLAI received their first injection at baseline (Week 0) and their last injection at Week 24 (ie, there was a planned total of 13 injections for early initiation of RLAI). Subjects randomized to late initiation of RLAI received their first injection at Week 12 and last injection at Week 24 (ie, there was a planned total of 7 injections for late initiation of RLAI).

Risperidone LAI and oral risperidone were provided by the sponsor. Other oral/short-acting injectable antipsychotic medications were sourced by the clinical site.

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

Duration of Treatment: The treatment period (baseline to end point) was 26 weeks.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated using PANSS, CGI-S, and GAF scales. In addition, overall health status (assessed using the SF-12 Health Survey), patient treatment satisfaction (as rated on a 5-point scale, plus optional assessments using the DAI and/or the UKU-ConSat scales), and resource use data were collected throughout the trial period.

Safety: Safety assessment was based on reported adverse events, vital signs (pulse, blood pressure), body weight, BMI, physical examinations, and the Extrapyramidal Symptom Rating Scale (ESRS). Additional ESRS assessments were performed if extrapyramidal symptoms required treatment (if not started at a regular visit).

Statistical Methods:

Sample size calculation: It was assumed that early initiation of treatment with RLAI would be slightly better than the routine approach. Noninferiority of early initiation treatment was to be assumed if the difference in mean change in PANSS total score was 6 points or less in favor of the routine approach. The standard deviation in previous trials was about 21 (based on preliminary results of RIS-INT-87). Assuming a difference of 3 points in favor of early initiation of treatment with RLAI, a sample size of 87 subjects per treatment arm (N=174) was predicted to have a power of 80% to demonstrate non-inferiority at the 0.025-level (1-sided). It was expected that about 20% of randomized subjects would be excluded from the PP analysis; therefore 220 subjects were included in the study, which was expected to be a sufficient number of subjects to achieve a PP analysis set of at least 174 subjects.

Randomization: Randomization was stratified by:

- Duration of acute treatment of the present acute episode (treatment with antipsychotics for ≤7 days at baseline or treatment for >7 days but ≤14 days at baseline);
- Gender (male or female);
- Years since first psychotic symptoms (≤2 years since first psychotic symptoms at baseline visit or >2 years since first psychotic symptoms at baseline)

Analysis Sets: The Safety analysis set included all randomized subjects. The ITT analysis set included all randomized subjects who received at least 1 dose of open-label study drug and had at least 1 efficacy measurement during the open-label treatment. The PP analysis set contained all patients in the ITT analysis set who met the following criteria: 1) No violation of inclusion or exclusion criteria, and 2) No major protocol violations.

Efficacy Analyses: The primary analysis set for efficacy was the PP analysis set. Efficacy was also analyzed using the ITT analysis set.

The primary endpoint was the change in PANSS total score from baseline to end point, using the last observation carried forward (LOCF) method. Endpoint was defined as the last post-baseline value of each subject. The comparison between the 2 treatment groups was performed based on an analysis of covariance (ANCOVA) model. Non-inferiority of early initiation was inferred if the upper 95% confidence boundary for the difference of change in PANSS total score from baseline in favor of the routine approach was 6 points or less.

For changes from baseline in PANSS total and subscale scores, CGI-S, SF-12, treatment satisfaction, DAI, and UKU-ConSat, the Wilcoxon test was used. Within-group changes from baseline were analyzed using the Wilcoxon signed-rank test. Between-group comparisons were tested using the Wilcoxon 2-sample test. Differences between the 2 treatment arms with regard to response rates (according to percentage improvement from baseline on PANSS total score) and remission rates (according to the PANSS severity criterion) were analyzed using Fisher's exact test. Differences in resource use data between the treatment groups were analyzed using the Wilcoxon 2-sample test.

Safety Analyses: Safety data were summarized using descriptive statistics. For ESRS scores, body weight, and BMI, within-group changes from baseline were analyzed at each assessment time point using the Wilcoxon signed-rank test and between-group comparisons were tested using the Wilcoxon 2-sample test.

RESULTS:

SUBJECT AND TREATMENT INFORMATION:

In total, 220 subjects were randomized to one of 2 treatment groups: early initiation of RLAI (N=110) or late initiation of RLAI (N=110). Of the 220 randomly assigned subjects, 220 were included in the Safety analysis set, 216 were included in the ITT analysis set, and 140 were included in the PP analysis set. A total of 76 subjects in the ITT analysis set (42 patients in the early- and 34 in the late-initiation group) were excluded from the PP analysis set due to a major protocol deviation or a violation of inclusion/exclusion criteria. The main reason for exclusion was due to use of prohibited concomitant medication.

Of the 216 subjects in the ITT analysis set, 135 (62.5%) subjects completed the 26-week open-label treatment period. The percentage of subjects who completed the study was higher in subjects assigned to early start of RLAI (69.4%) than those assigned to late start of RLAI (55.6%); corresponding completion rates for the PP analysis set were 72.7% and 52.7%. The proportion of subjects in the ITT analysis set who were withdrawn due to adverse event(s) or insufficient response and adverse event(s) was higher in the late-start group than the early-start group (10 [9.3%] vs. 6 [5.6%]), as was the proportion of subjects withdrawn for refusing injections (13 [12.0%] vs. 3 [2.8%]). In contrast, more subjects in the early-start group were withdrawn from the study due to insufficient response (9 [8.3%] vs. 4 [3.7%] in the late-start group).

The majority of subjects were male (61.1%), Caucasian (89.4%). Subjects were aged 18 to 63 years (mean age 38 years). A total of 204 subjects in the ITT analysis set were diagnosed with schizophrenia and 9 were diagnosed with schizoaffective disorder (all 9 subjects with schizoaffective disorder were included in the PP analysis set). There were no differences between the early- and late-start treatment groups with regard to baseline demographic or disease characteristics.

Of the 9 subjects with a diagnosis of schizoaffective disorder, 7 were enrolled in countries in which schizoaffective disorder was not a registered indication for RLAI, thereby violating the inclusion criteria that subjects were required to be *eligible for treatment with RLAI according to the registered indication in the country*. Including these 7 subjects in the PP analysis set was not considered to impact the study conclusions, given the number of subjects in the PP analysis set (n=140) was already smaller than estimated in the sample size analysis (n=174).

RLAI was administered at doses of 25, 37.5 or 50 mg every 2 weeks. In the ITT analysis set the mean (SD) mode dose was 36.0 (11.07) mg in the early-start group and 34.46 (10.50) mg in the late-start group. As subjects in the early-start group received RLAI treatment for longer, the mean total dose in this group was larger (399.31 mg) than the late-start group (223.56 mg). In the late-start group, subjects received treatment-as-usual with oral or short-acting injectable antipsychotics for the first 12 weeks of the study. The most common treatments (by generic name) were olanzapine, haloperidol, quetiapine fumarate, aripiprazole, levomepromazine, risperidone, and promazine.

EFFICACY RESULTS:

The mean (SD) changes from baseline to end point (LOCF) in the primary and secondary efficacy parameters are summarized for the PP and ITT analysis sets in the table below:

Mean (SD) Change from Baseline to Endpoint (LOCF) for Primary and Secondary Efficacy Parameters

	PP Analysis Set		ITT Analysis Set	
	Early Start with RLAI (N=66)	Late Start with RLAI (N=74)	Early Start with RLAI (N=108)	Late Start with RLAI (N=108)
Primary Parameter				
PANSS Total score[a]	N=65 -38.37 (23.10)*	N=74 -37.24 (25.02)*	N=105 -39.27 (25.49)*	N=106 -35.05 (27.48)*
Secondary Parameters				
PANSS Positive subscale[a]	N=65 -10.94 (6.93)*	N=74 -11.07 (7.57)*	N=105 -10.89 (7.21)*	N=106 -10.28 (8.00)*
PANSS Negative subscale[a]	N=65 -9.51 (7.48*)	N=74 -8.38 (7.95)*	N=105 -9.55 (8.29)*	N=106 -7.78 (8.84)*
PANSS General Psychopathology subscale[a]	N=65 -17.92 (11.82)*	N=74 -17.79 (13.00)*	N=105 -18.83 (13.38)*	N=106 -16.98 (13.91)*
CGI-S	N=65 -1.91 (1.35)*	N=74 -2.03 (1.27)*	N=105 -1.90 (1.38)*	N=106 -1.75 (1.30)*
GAF	N=65 19.65 (14.20)*	N=74 18.72 (16.76)*	N=105 21.04 (15.68)*	N=106 17.33 (16.38)*
SF-12 Physical Component	N=57 2.76 (10.73)*	N=63 1.75 (7.93)*	N=88 1.80 (9.96)*	N=89 0.41 (8.10)*
SF-12 Mental Component	N=57 3.25 (9.19)*	N=63 2.96 (10.76)*	N=88 4.18 (8.56)*	N=89 3.46 (10.22)*
Patient Satisfaction	N=65 0.58 (1.32)*	N=75 0.41 (1.37)*	N=105 0.63 (1.26)*	N=106 0.33 (1.37)*
DAI	N=26 -0.77 (4.30)	N=36 -0.64 (4.54)	N=48 -0.83 (4.03)	N=50 -0.52 (4.30)*
UKU-Con-Sat	N=26 2.15 (14.49)*	N=36 -0.14 (15.30)*	N=48 3.52 (13.50)*	N=51 0.51 (14.70)*

[a] Absolute change.
* Statistically significant change from baseline ($p<0.05$; Wilcoxon signed rank test)
For all parameters, scores indicate an improvement from baseline.

Primary Endpoint:

In the PP analysis set, the mean (SD) change in PANSS total score from baseline to end point was -38.37 (23.10) for the early-start group and -37.24 (25.02) for the late-start group, indicating improvements in the severity of symptoms associated with schizophrenia in both treatment groups. The difference between early versus late start of RLAI in LS means for the absolute change in PANSS total score was -1.1287 (95% CI: -9.2431; 6.9857). As the upper limit of the 95% CI (6.9857) was greater than 6, early start of RLAI was not demonstrated to be noninferior to late start of RLAI for the PP analysis set.

In the ITT analysis set, the mean (SD) change in PANSS total score from baseline to end point was -39.27 (25.49) for the early-start group and -35.05 (27.48) for the late-start group. The difference between early

versus late start of RLAI in LS means for the absolute change in PANSS total score was -4.2214 (95% CI: -11.4166; 2.9738). As the upper limit of the 95% CI was below the predefined noninferiority margin of 6, early start of RLAI was demonstrated to be noninferior to late start of RLAI for the ITT analysis set.

The lack of noninferiority observed for the PP analysis set was considered mostly due to the fact that the PP analysis set for the primary endpoint (n=140) was smaller than the number estimated in the sample size analysis (n=174).

Secondary endpoints:

Change in PANSS Total and PANSS Subscale Scores Over Time: Statistically significant reductions from baseline to Week 26/end point ($p<0.001$, Wilcoxon signed rank test) in PANSS total score and PANSS subscale scores (Positive, Negative, and General Psychopathology subscales) were observed for both treatment groups in the PP and ITT analysis sets (based LOCF and Observed values). Based on the Wilcoxon 2-sample test, no statistically significant differences were observed between the treatment groups for the change from baseline at Week 26/end point for any of the PANSS scores (PP and ITT analysis sets).

PANSS response rate: The number of subjects experiencing at least a 20%, 30%, or 40% reduction in PANSS total score from baseline to endpoint was similar between the early-start and late-start treatment groups in the PP and ITT analysis sets. Based on LOCF values, 75.8% of subjects in the early-start group and 78.4% in the late-start group achieved at least a 20% reduction in PANSS total score in the PP analysis set; corresponding values in the ITT analysis set were 73.1% and 71.3%, respectively. The proportion of subjects achieving at least a 50% reduction in PANSS total score (LOCF) was higher in the early-start group than the late-start group in the PP analysis set (28.8% vs. 25.7%, respectively) and ITT analysis set (33.3% vs. 20.4%); the between-group difference was statistically significant for the ITT analysis set ($p=0.0314$) but not the PP analysis set ($p=0.7045$) [Fisher exact test].

PANSS Remission: The proportion of subjects who met PANSS remission criteria was evaluated at Week 12 and Week 26. At Week 12 (ie, prior to initation of RLAI treatment in the late-start group), the percentage of subjects meeting remission criteria was higher in the early-start group than the late-start group in the PP analysis set (40.9% and 27.0%, respectively) and ITT analysis set (40.7% and 23.1%, respectively); the between-group difference was statistically significant for the ITT analysis set ($p=0.0127$) but not the PP analysis set ($p=0.4403$) [Fisher exact test]. At Week 26, there was no statistically significant difference observed between the early-start and late-start groups in the ITT analysis set (44.4% and 36.1%, $p=0.2538$) or PP analysis set (45.5% and 41.9%, $p=0.8609$).

Time to reach remission and duration of remission were analyzed in subjects who met the remission criteria. Based on Kaplan-Meier estimates, the median time to remission (the estimated time point at which 50% of subjects achieved remission) was 175 (95% CI: 84; 185) days in the early-start group and 118 (95% CI: 84; 182) in the late-start group in the PP analysis set; corresponding values in the ITT analysis set were 86 (95% CI: 84; 182) and 182 (95% CI: 105; 183), respectively There was no statistically significant difference between the 2 treatment groups in the analysis of time to remission for the ITT or PP analysis sets using Cox regression models. The mean duration of remission was longer in the early-start group than the late-start group in the PP analysis set (124.7 vs. 95.7 days) and the ITT analysis set (125.7 vs. 97.5 days). The difference in LS means were 28.1980 (95% CI, 8.8097; 47.5862) [$p=0.0047$] for the ITT analysis set and 29.0088 (95% CI, 6.0380; 51.9796) [$p=0.0140$] for the PP analysis set.

Other: In both the PP and ITT analysis sets, comparable improvements in CGI-S, GAF, SF-12 (physical and mental components), treatment satisfaction, DAI, and UKU-ConSat scores were seen in both treatment groups (see table above). Based on the Wilcoxon 2-sample test, no statistically significant differences were observed between the 2 treatment groups at end point (LOCF) for any of these parameters.

Resource Use: Resource use (hospitalizations, daily living, and productivity) was comparable between the 2 treatment groups throughout the study.

SAFETY RESULTS:

Safety was analyzed using the Safety analysis set (N=110 for both treatment groups). A summary of adverse events observed during the study is provided below:

Subjects With Adverse Events/Reactions During the Trial

	Early Start with RLAI (N=110)	Late Start with RLAI (N=110)
One or more treatment-emergent adverse events	58 (52.7%)	66 (60.0%)
One or more serious adverse events	18 (16.4%)	22 (20.0%)
Deaths	0	0
Treatment permanently stopped due to adverse event(s)	7 (6.4%)	10 (9.1%)

There were no major differences between the treatment groups in the adverse event profile.The most common TEAEs in the early- and late-start treatment groups were insomnia (9 [8.2%] and 12 [11%] subjects), anxiety (9 [8.2%] and 10 [9.1%] subjects) weight increased (8 [7.3%] and 8 [7.3%] subjects), akathisia (8 [7.3%] and 7 [6.4%] subjects), and extrapyramidal disorder (6 [5.5%] and 9 [8.2%] subjects), respectively. Other TEAEs observed in ≥5% of patients in either treatment group included depression, sedation, tremor, schizophrenia, and somnolence.

Adverse events that occurred more frequently in the late- versus the early-start treatment group included sedation (7 vs. 2 subjects) and somnolence (6 vs. 1 subject). In contrast, the early-start group showed a higher incidence of dystonia (4 vs. 0 subjects) and aggression (4 vs. 0 subjects) compared with the late-start group.

Most adverse events reported during the study were mild (42.6%) or moderate (44.4%) in severity; 10.3% were classified as severe. The majority of events (59.7%) were assessed by the investigators as not related or doubtfully related to study drug; 17.1% were considered possibly related, 10.9% were considered probably related, and 9.4% were considered very likely related to study drug.

There were no deaths during the study and the incidence of serious adverse events was generally similar between treatment groups. The most common SAEs in the early-start and late-start treatment groups included anxiety (4 [3.6%] and 4 [3.6%] subjects), schizophrenia (3 [2.7%] and 5 [4.5%] subjects), schizophrenia, paranoid type (1 [0.91%] and 3 [2.7%] subjects), overdose (2 [1.8%] and 2 [1.8%] subjects), suicidal ideation (0% and 3 [2.7%] subjects), and extrapyramidal disorder (3 [2.7%] and 0% subjects), respectively. All other SAEs were reported in 1 or 2 subjects only. A total of 7 (6.4%) subjects in the early-start group and 10 (9.1%) in the late-start group were withdrawn from the study due to an adverse event.

No clinically meaningful changes from baseline to end point were observed for vital signs (pulse, systolic and diastolic blood pressure). The change in pulse rate was statistically significantly greater in the late-start treatment group compared with the early-start group (p=0.0346), but the actual mean changes were small (-3.82 vs. -0.73 bpm, respectively). No statistically significant differences were observed between the treatment groups for systolic or diastolic blood pressure at end point.

Both the early and late-start treatment groups showed modest and comparable mean increases from baseline to end point in body weight (+2.49 and +2.25 kg, respectively) and BMI (+0.80 and +0.75 kg/m^2, respectively). No statistically significant differences in body weight or BMI were observed between the treatment groups at Visit 4 (Week 12) or end point.

Both the early- and late-start treatment groups showed a reduction from baseline to end point in total ESRS score (mean change of -3.06 and -1.88, respectively) and the Parkinsonism/Dystonia/Dyskinesia/Akathisia score (mean change of -1.26 and -0.89, respectively), indicating an improvement in EPS symptoms during the open-label treatment period. Median scores for most other subscales were 0 at baseline and end point. No statistically significant differences were observed between the treatment groups for any of the ESRS subscales at end point.

STUDY LIMITATIONS: Due to the substantial number of protocol deviations (mainly due to prohibited concomitant medication), the study did not have the required power to demonstrate noninferiority in the PP population.

CONCLUSION: Based on the predetermined noninferiority margin of 6 points for the change in PANSS total score from baseline to end point, early initiation of treatment with RLAI was not shown to be noninferior to the routine approach (oral treatment for 12 weeks followed by treatment with RLAI) in the PP analysis set. However, noninferiority was demonstrated in the ITT analysis set. The lack of noninferiority observed for the PP analysis set was considered mostly due to the fact that the PP analysis set for the primary variable (n=140) was smaller than the number estimated in the sample size analysis (n=174), as a result of the high number of protocol deviations observed in the study.

There were no major differences between the treatment groups with regards to safety and tolerability. Both treatments were generally safe and well tolerated, and no new safety signals were detected.

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