SYNOPSIS

NAME OF SPONSOR/COMPANY:

Janssen-Cilag GmbH; Neuss; Germany

NAME OF FINISHED PRODUCT:

Risperdal® Consta®

NAME OF ACTIVE INGREDIENT(S):

Risperidone microspheres

Protocol No.: RIS-SCH-4023

Title of Study: Long-term safety and tolerability of Risperdal® Consta® as compared to oral atypical antipsychotics in the treatment of schizophrenic patients (German original title: LaRA - Langzeitverträglichkeit in der rezidivprophylaktischen Atypikatherapie)

Coordinating Physician: Ibach, Bernd, M.D., P.D.

Publication (Reference): Not applicable.

Study Initiation/Completion Dates: March 16, 2004/ March 5, 2008	**Phase of development:** PMS

Objectives: The primary objective was to obtain data about long-term tolerability and safety of risperidone long-acting injectable (Risperdal® Consta ®) in comparison to the oral atypical antipsychotics amisulpride, aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone.

Secondary objectives were to explore efficacy of the different treatments regarding to the change in psychopathology, relapse rates, retention rates and retention times as well as reduction of the hospitalization rates, change of overall severity of disease in the course of the treatment, adherence to treatment, requirement of additional psychotropic medication, changes in the profile of extrapyramidal side effects, patients' attitude to medication, changes in patients' global functioning, effects of treatment on patients' quality of life and use of further resources of primary or secondary health care section.

Methodology: Prospective, two-arm, non-interventional longitudinal study

Number of Subjects (planned and analyzed): 400 planned; 444 analyzed, 10 patients were excluded from the analysis. Thus, 434 patients were available for analysis. In this ITT-population 177 patients started with risperidone long-acting injectable and 257 patients with one of the oral atypical antipsychotics. In the PP-population 400 patients were included, 167 patients on risperidone long-acting injectable and 233 patients on one of the oral atypical antipsychotics. The data in this report refer to the ITT-population.

Diagnosis and Main Criteria for Documentation: Schizophrenia (F20.x) according to ICD-10 and indication for long-term treatment with an atypical antipsychotic

The patients had to fulfill the following criteria:

- women or men aged 18 to 65 years
- diagnosis of schizophrenia (F20.x) according to ICD-10 and indication for long-term treatment with an atypical antipsychotic drug
- presence of schizophrenic symptomatology for at least 1 year and for not more than 5 years; treatment of newly diagnosed, so far untreated patients was not to be documented in this study
- severity of disease at baseline not worse than "patient is severely ill" according to CGI
- planned treatment in this study should be highly potent antipsychotic monotherapy with either oral amisulpride, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone or with intramuscular risperidone long-acting injectable
- patient's written informed consent to inspection of medical records by authorized monitors was preferred; without this consent monitoring of data was performed according to the "back to back" -procedure
- treatment of patients with an anamnestically known resistance to treatment with risperidone or clozapine was not to be documented in this study

Drug under Observation, Dose and Mode of Administration: Risperidone microspheres (Risperdal® Consta ®), 25 mg to 50 mg every 14 days i.m.

Reference Therapy, Dose and Mode of Administration: Oral atypical antipsychotics amisulpride, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone. Doses were given according to the instructions in the summary of product characteristics of the different antipsychotics.

Duration of Treatment: Two years

Criteria for Evaluation:

Primary endpoints are long-term tolerability and -safety**.**

Efficacy: The efficacy was evaluated by the Positive And Negative Syndrome Scale (PANSS), relapse rate during the study, time until first relapse, Clinical Global Impression Scale (CGI) (Item 1), Global Assessment of Functioning Scale (GAF), Revised Schizophrenia Quality of Life Scale (SQLS-R4) and Drug Attitude Inventory (DAI). Relapses were defined as a) hospitalization due to the underlying psychiatric disease or b) deterioration of the total score of PANSS by more than 25% in comparison to baseline or c) deterioration of the total score of PANSS by more than 10 points, if the baseline value was ≤ 40 points or d) occurrence of clinically significant self-inflicted injuries according to the treating physician's opinion, or of suicidal intentions, or of intimidation of others with physical violence, or of infliction of bodily harm to others, or of causing material damage or e) deterioration of overall clinical status according to CGI-C in comparison to baseline grade 6 ("much worse") or 7 ("very much worse").

Safety: The safety was documented by the Extrapyramidal Symptom (EPS) scale, the reported adverse events (AEs) and serious adverse events (SAEs) as well as the body weight.

Statistical Methods:

The retention rates, the proportion of patients without change of therapy, were presented at each visit. Differences between the two treatment groups and between the various oral atypical antipsychotics were analyzed using Fisher's exact test.
For each patient the number of relapses during the entire study, prior to the first change of therapy and prior to the first change of the treatment group were determined and counted.
Time to first relapse was calculated separately for the 3 relevant periods (overall, until first change of therapy, until first change of treatment group) by the product-limit-method according to Kaplan-Meier. Differences between the 2 treatment groups were analyzed with the log-rank-test. Differences between the various oral atypical antipsychotic drugs were analyzed with the log-rank-test.
For the PANSS, CGI, GAF, SQLS-R4 and DAI distribution of the baseline score, the last documented score, the last score prior to the first change of therapy, and the last score prior to the first change of the treatment group were determined. Distribution parameters at baseline, at the end and the differences between these scores were presented. Within each treatment group these differences (pre-post) were analyzed with the 1-sample t-test. For the analyses of the differences between the two treatment groups (patients assigned to receiving long-term monotherapy with either risperidone long-acting injectable or with an oral atypical antipsychotic) the 2-sample t-test was applied to the differences. Differences between the various oral atypical antipsychotic drugs were analyzed with one-way analysis of variance (ANOVA).
EPS was evaluated in the same way.
Frequency counts were calculated for AEs and SAEs. Distribution parameters for body weight were determined and presented for all visits.

SUMMARY - CONCLUSIONS

DEMOGRAPHY OF TRIAL POPULATION: In the ITT population 36.2% (N=64 of 177) of the patients in the risperidone long-acting injectable group and 46.3% (N=119 of 257) of the patients in the group starting treatment with oral atypical antipsychotics were male. The mean age was 33.9±11.1 (risperidone long-acting injectable) and 35.1±12.0 years (oral atypical antipsychotics). Socioeconomic data (living situation, educational status, professional education) were fairly similar for all patients, although more patients of the risperidone long-acting injectable group had a legal custodian (20.9% vs. 14.0%) and were unemployed (31.1% vs. 24.9%).

The prevalence of the different types of schizophrenia (F20.x acc. ICD-10) in the two treatment groups was comparable. Duration of disease in the two treatment groups was 2.76±1.82 years vs. 2.56±1.61 years. Less favorable courses of schizophrenia (continuous, episodic with progressive residual) in the past appeared to be more common in the risperidone long-acting injectable than in the oral atypical antipsychotics group (37.9% vs 28.8%), as was the case in additional axis Ia-disorders and use of psychotropic substances (F10.1-F19.1) (23.7% vs. 12.1%). In addition, mean number of relapses since first diagnosis (2.12±2.22 vs. 1.78±1.77) and of hospitalizations since first diagnosis (1.74±1.81 vs. 1.36±1.57) were higher in the risperidone long-acting injectable than in the oral atypical antipsychotics group.

EFFICACY RESULTS: For all patients completing the study after two years or earlier improvements were significant for all scores in the PANSS ($p<0.0001$) for both treatment groups, but there were no significant differences between the two treatment groups (risperidone long-acting injectable 23.06±26.95 vs. oral atypicals 22.01±26.31, $p=0.69$) although mean improvements were slightly higher in the patients with long-acting risperidone. With regard to the various oral atypical antipsychotics differences for positive symptoms and highest mean improvements were observed for patients starting with olanzapine. In case of relapses the yearly relapse rate prior to change of therapy was lower in the risperidone long-acting injectable group but the differences were not significant (risperidone long-acting injectable 0.48±1.48 vs. oral atypicals 0.71±2.63 relapses per year, $p=0.28$). For patients the retention rate with regard to change of therapy after 2 years were 41.2% (risperidone long-acting injectable) vs. 36.6% (oral atypicals) ($p=0.37$). With regard to treatment group, significant differences between the treatment groups were observed after 2 years (risperidone long-acting injectable 41.2% vs. oral atypicals 52.1%, $p=0.03$) For CGI, GAF, SQLS-R4 and DAI improvements were significant for both treatment groups (CGI: risperidone long-acting injectable 0.70±1.01 vs. oral atypicals 0.64±1.01, $p=0.0001$; GAF: risperidone long-acting injectable 11.63±16.08 vs oral atypicals 10.89±15.76, $p=0.0001$, SQLS-R4: risperidone long-acting injectable 37.22±17.71 vs oral atypicals 38.44±19.77, $p=0.0001$; DAI: risperidone long-acting injectable 3.54±10.49 vs. oral atypicals 2.67±10.66, $p=0.001$) but there were no significant differences between the two treatment groups or between the various oral atypical antipsychotics. Additionally no differences were found in the number of days of unemployment and the days spent in an institution (in-patient clinic, day clinic, night clinic, out-patient clinic) between the two treatment groups.

SAFETY RESULTS: At least one AE was reported by 125 of the 177 patients (70.6%) in the risperidone long-acting injectable group and by 169 of the 257 patients (65.8%) in the group starting treatment with oral atypical antipsychotics. Overall AEs related to the underlying disease – agitation (13% vs. 19.5% of patients) and psychosis (17.5% vs. 14.0% of patients) were most commonly. Among the related adverse events weight increase (13.0% vs. 9.7%), fatigue (5.7% vs. 9.7%) and extrapyramidal disorders (7.9% vs. 5.5%) were the most common occurring AEs.

A total of 184 SAEs (risperidone long-acting injectable group 86 vs. oral atypicals group 98 oral atypicals group) were reported in 104 patients (risperidone long-acting injectable group 48 vs. oral atypicals group 56). Causal relationship with the administration of long-acting risperidone was assessed at least as possible for 16 SAEs. Three patients died during the study. One patient died because of unknown cause, one patient died after an epileptic seizure, and one patient died after a myocardial infarction, respectively. The 3 fatal events were judged to be not or doubtfully related to antipsychotic treatment .

A significant weight gain of 1.7± 4.7 and 0.6± 3.4 kg was observed in the risperidone long-acting injectable and the oral atypical group ($p<0.0001$; $p<0.0142$), respectively, with a significant difference between the two treatment groups ($p<0.0044$) and no significant differences between the various oral atypical antipsychotics.

CONCLUSION:

The long-term tolerability of long-acting risperidone was convincing in the present study. During the two year observational period, no unexpected AEs or SAEs were reported. Overall this non-interventional study in an everyday practice setting provides further support for the long-term tolerability and efficacy of risperidone long-acting injectable in patients with schizophrenia.

This non-interventional study in patients suffering from chronic schizophrenia and being treated with risperidone long-acting injectable showed numerically higher retention times and retention rates in comparison to treatment with oral atypical antipsychotics (amisulpride, aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone) without reaching statistical significance. Likewise, the relapse rate was lower in the risperidone long-acting injectable group but again the between group difference was not significant. The other secondary efficacy parameters showed significant improvements versus baseline for both groups, but not between the groups.

Due to the nature of a non-interventional study, it is obvious that the groups under investigation are not homogenous at baseline and may differ strongly in multiple domains, e.g. in the portion of patients that was submitted to a new antipsychotic treatment due to a lack of compliance. In order to evaluate this potential bias and to analyze more homogenous patient groups, a post-hoc analysis will be performed, as already specified in the study protocol. The resulting addendum will be filed subsequently to this medical report.

Date of the report: 10.10.2008