SYNOPSIS

Name of Sponsor/Company	Janssen-Cilag International NV
Name of Finished Product	Risperdal® CONSTA®
Name of Active Ingredient(s)	JNJ-410397-AAA (risperidone long-acting injectable)

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Protocol No.: RISSCH4230

Title of Study: InORS - International Observational Registry on Schizophrenia

NCT No.: NCT01026285

Clinical Registry No.: CR016630

Coordinating Investigator(s): This study was conducted at 143 sites across Europe, Middle East and Africa. There was no coordinating or overall principal investigator.

Study Center(s): France (25 sites), South Africa (2 sites), Germany (51 sites), Italy (13 sites), Greece (11 sites), Czech Republic (6 sites), Spain (15 sites), Russia (10 sites), and Turkey (10 sites).

Publication (Reference): Not applicable.

Study Period: 03 June 2009 - 20 March 2012. Database lock was on 22 June 2012.

Phase of Development: Phase 4

Objectives: The primary objective was to prospectively assess medication usage patterns under routine clinical practice, related to initiation of treatment with risperidone long-acting injectable (Risperdal® CONSTA®), hereafter referred to as Consta, (gluteal or deltoid injections; 25, 37.5, and 50 mg every 2 weeks) and oral antipsychotic treatments in subjects with schizophrenia in a naturalistic setting.

Additional objectives of the study were:

1. To collect 6-month retrospective and 1-year prospective data to allow the exploration of treatment outcomes including hospitalizations and rehospitalizations, with Consta and oral antipsychotics, in relation to previous treatments.
2. To evaluate reasons for initiation and/or discontinuation of new antipsychotic medications, including subject satisfaction with treatment.
3. To explore relevant factors for subject adherence to treatment.
4. To document clinical effectiveness and functionality of subjects on Consta and oral antipsychotics (as measured by the Global Assessment of Functioning [GAF] scale).

Additionally, the long-term safety of Consta (25, 37.5, and 50 mg every 2 weeks) and oral antipsychotics was assessed.

Methodology: This was an observational, non-interventional registry designed to assess medication usage patterns and to collect, in routine clinical practice, long-term outcomes and relevant factors for subject adherence to treatment in subjects with schizophrenia receiving antipsychotic treatment with

Consta or oral antipsychotics. Six-month retrospective data and 12-month prospective data were collected. An interim statistical analysis was performed when 600 subjects had completed a period of 3 months. The interim analysis consisted of a limited exploratory statistical analysis of effectiveness and safety data for the first 613 subjects.

Number of Subjects (planned and analyzed): The planned total sample size was 1200 subjects. In total, 1095 subjects were documented in the study. Subjects who received Consta or oral antipsychotics at least once were included in the intent-to-treat [ITT] analysis (n=1084). Subjects who received Consta or oral antipsychotics at least once and provided any post-baseline information were included in the ITT analysis for safety (n=1084).

Diagnosis and Main Criteria for Inclusion: This was a non-interventional study, with treatment decisions made prior to selection of subjects, and minimal selection criteria were applied. To be eligible for documentation, subjects had to be at least 18 years old, have a diagnosis of schizophrenia with at least 6 months of retrospective clinical records, and be newly initiated or switched to Consta or an oral antipsychotic not longer than 2 weeks before. Subjects with established treatment-refractory schizophrenia or with a history of neuroleptic malignant syndrome were not eligible for documentation in the study.

Test Product, Dose and Mode of Administration, Batch No.: No study medication was provided by the sponsor. Subjects received their medication according to usual care in their treatment setting. Dosing and administration of all treatments were at the physician's discretion and according to approved local labels.

Duration of Treatment: At baseline, 6-month retrospective data were collected for each subject. Prospective data were obtained for 12 months. Assessments of clinical outcomes were to be made for the entire duration of the 12-month prospective period, irrespective of further treatment decisions concerning Consta and oral antipsychotic drugs.

Criteria for Evaluation: At the start of the documentation, subject characteristics and retrospective 6-month treatment history were recorded. During the 12-month prospective period, treatment outcomes were evaluated using clinician-administered assessments. Assessments were conducted at baseline and at Months 1, 3, 6, 9, and 12. Psychiatric hospitalizations were recorded for both the retrospective and prospective periods to assess the outcomes of medication strategies. Details of the newly-initiated Consta or oral antipsychotic treatment and concomitant use of other antipsychotic treatment were also documented. Any switch in the subject’s antipsychotic treatment since the last assessment was recorded at each visit. Reasons for initiating and discontinuing antipsychotic treatment were collected from the clinical records. Concomitant use of anticholinergics, antidepressants, mood stabilizers, benzodiazepines, sedatives, anxiolytics, and somatic medication was also recorded.

The Clinical Global Impression - Schizophrenia (CGI-SCH) scale was used to evaluate severity and treatment response and the GAF scale was used to rate subjects' overall level of functioning. The subjects’ satisfaction with antipsychotic treatment was evaluated using the Medication Satisfaction Questionnaire (MSQ), a single-item global subject-rated scale. Adherence to treatment was recorded using the 7-point observer-rated Compliance Rating Scale (CRS). Safety evaluations included adverse event (AE) data, injection site pain scores, and body weight.

Statistical Methods: The sample size calculation indicated that a sample size of 128 subjects was required to investigate maintained effectiveness using the CGI-SCH parameter in a single group. Assuming that a change of 0.4 points versus baseline on CGI-SCH is a minimum clinically relevant difference, a standard deviation of 1.6 and a one-sided significance level of 0.025 would have 80% power to test equivalence. Hence, it was estimated that a total of approximately 1200 subjects would be sufficient to construct at least 6 to 10 clinically relevant subgroups of subjects and to enable separate analysis of these subgroups.

Baseline was defined as the day of initiation of Consta or a new oral antipsychotic treatment, which defined entry into the study. All subjects were analyzed by the antipsychotic medication that subjects were taking at the onset of the study (ie, their baseline medication). Subjects were grouped into baseline Consta or baseline Oral therapy groups. The period of observation began at the start of the study and continued until the end of Consta/oral therapy. The baseline oral antipsychotic therapy period ended if a subject changed medication (molecule), even if the new medication was an oral antipsychotic medication.

Subjects who received Consta at the onset of the study were further analyzed by injection site. Subjects who received Consta by gluteal injection at the start of the study were analyzed as the baseline Consta-Gluteal group. Subjects who received Consta by deltoid injection at the start of the study were analyzed as the baseline Consta-Deltoid group.

For the Medication Switch Pattern I (C:O pattern) analysis, medication periods were categorized as either C- (Consta) or O- (NonConsta) periods. C-periods were defined as periods during which the subjects received Consta therapy, regardless of injection site (gluteal or deltoid). Since supplemental oral antipsychotic medication should be given during the first 21 days of Consta therapy, the first 28 days of Consta plus supplemental oral therapy were considered as a C period. O periods were defined as periods during which subjects received single or multiple therapies including oral or depot antipsychotic medication but not Consta.

Medications started prior to the prospective period were considered concomitant medications, and therefore were not considered to be part of the study medication. The definition of medication switches included addition or deletion of antipsychotic medication after baseline, changes to another antipsychotic medication within the same class, or stopping an antipsychotic medication while another medication was ongoing.

If a subject switched his/her medication across the C- or O- category after baseline, the series of medication category was created to define the medication switch pattern. Hence, potential observable treatment patterns by the end of the 12-month study period included, but were not limited to: C; O; C-O; O-C; C-O-C; O-C-O, etc. Discontinuation of antipsychotic treatment did not result in discontinuation from documentation. Therefore, any subject who discontinued antipsychotic treatment before the end of the prospective period was analyzed according to the medication switch pattern up to the point of stopping treatment.

Additionally, a medication category (II) analysis was used to examine switches between antipsychotic monotherapy and polytherapy.

RESULTS:

STUDY POPULATION

A subject was considered to have completed the study if he/she completed the 12-month prospective period. Among the 1095 subjects documented, 935 (85.4%) subjects completed the study. Reasons for drop-out are summarized below:

Reason for drop-out	Total (N=1095)
Death	11 (1.0%)
Lost to follow-up	86 (7.9%)
Withdrawal of consent	30 (2.7%)
Other	33 (3.0%)

There were 93 subjects with one or more major protocol deviations during the study. No subject was excluded from the study and only one subject (see below) was excluded from the baseline and baseline medication period analyses due to protocol deviation(s). One subject received only a conventional depot antipsychotic medication (fluphenazine decanoate) within the 14 day period either side of baseline; as this treatment was neither Consta nor an oral antipsychotic, this subject was excluded from the baseline and baseline medication period analyses. However, this subject was included in analyses by medication switch pattern.

Among 1083 subjects, 561 started Consta at baseline and 522 started oral medication, predominantly oral atypical antipsychotics. Approximately 62% of subjects starting Consta and approximately 50% of those starting oral medication at baseline were men. Mean ages were similar between the Consta and Oral groups: approximately 43 and 42 years, respectively.

Before baseline, during the 6-month retrospective period, a greater proportion of subjects in the Consta group had been hospitalized, for longer intervals, compared with the Oral group. At baseline, subjects in the Consta group had lower MSQ scores ($p=0.014$), lower mean CRS scores ($p<0.001$), higher CGI-SCH overall severity scores ($p<0.001$), and lower GAF scores ($p<0.001$) compared with the baseline Oral group. These observations suggest greater severity of illness, worse symptoms, a lower level of functioning and intrinsically less treatment adherence in the subjects prescribed Consta at baseline.

BASELINE MEDICATION TREATMENT PERIOD:

In the baseline Consta group, the ratio of Consta-Gluteal to Consta-Deltoid use was approximately 3:2, while a small subgroup of 10 subjects alternated injection sites. The duration of the baseline medication treatment period was approximately 261 days for both the Consta and Oral treatment groups. Similar proportions, approximately 35% and 38%, respectively, of the Consta and Oral groups had discontinuations or changes in the dose of their baseline medication. Reasons for dose change or discontinuation of baseline medication were similar between groups. Concomitant medication usage was comparable between the 2 baseline treatment groups.

OBSERVABLE TREATMENT PATTERNS:

During the 12-month prospective period, approximately 39% of subjects remained on Consta therapy (C-pattern), 45% remained on NonConsta therapy(ies) (O-pattern), and 10% started on Consta but changed to NonConsta therapy for the remainder of the prospective period (C-O pattern). The remaining 6 treatment patterns were grouped together as 'Other' category (63 subjects; <6%). Only 3% of subjects started on NonConsta therapy and switched to Consta during the prospective period. Analyses of mono/polytherapy switch patterns indicated that more than half of subjects received either Consta or NonConsta monotherapy during the prospective period.

Interestingly, oral antipsychotic supplementation, which is required upon initiation, was not taken by 133 (22.4%) subjects who initiated Consta during the prospective period.

EFFICACY RESULTS:

Over the course of the baseline Consta treatment period, duration per stay, total length of stay, and proportion of hospitalized days data all indicated reduced hospitalization time during the prospective compared with the retrospective period. In contrast, for subjects in the baseline Oral medication group, these data were similar during the retrospective and prospective periods. Medication satisfaction (MSQ) and adherence to treatment (CRS) improved significantly over the course of the baseline treatment period for both the Consta and Oral groups ($p<0.001$). However, a between-group comparison indicated greater improvement in the Consta group than in the Oral group for both medication satisfaction ($p=0.013$) and adherence to treatment ($p<0.001$). The Consta-Gluteal and -Deltoid subgroups were comparable in terms of medication satisfaction and treatment adherence scores.

Reductions in symptom severity were demonstrated by significant decreases in CGI-SCH scores at the end of the baseline treatment period for both the baseline Consta and Oral treatment groups ($p<0.001$). The CGI-SCH scores for overall severity showed greatest decreases (ie, improvements) in the baseline Consta group ($p=0.004$). GAF scores demonstrated improved functioning after the baseline treatment period for both Consta and oral antipsychotic medications ($p<0.001$). However, this improvement was significantly greater for the Consta than the Oral group ($p<0.001$).

Greatest treatment effectiveness was seen in subjects remaining on Consta (C-) or NonConsta (O-) therapy during the prospective period. In particular, C-pattern subjects showed marked improvements in functioning rated by GAF scores. In contrast, treatment outcomes were consistently less favorable for subjects with more complex medication switch patterns. The percentages of subjects who clinically deteriorated during the prospective period were substantially higher in the C-O (24.6%) and 'Other' (35.2%) patterns than among C- (8.2%) or O- (11.0%) patterns. Overall, subjects in the C-O and 'Other' categories demonstrated smaller decreases in CGI-SCH symptom severity and less improvement in functioning compared with the remaining treatment patterns. Benzodiazepine/sedative/anxiolytic use was highest in the C-O (41.9%) and 'Other' (55.6%) groups.

SAFETY RESULTS:

Weight increased (7.2%), psychotic disorder (5.1%), schizophrenia (4.2%), anxiety (3.2%), insomnia (2.3%), and extrapyramidal disorder (2.2%) were the only individual AE preferred terms reported in more than 2% of all subjects during the 12-month prospective period. Weight increased, psychotic disorder, schizophrenia, anxiety, insomnia, and somnolence were the only individual preferred terms reported in more than 2% subjects in the baseline Consta or baseline Oral treatment groups. Evaluation of AEs by Medication Switch Pattern I (C:O pattern) revealed a higher incidence of AEs in the NonConsta (O-) group than in the Consta (C-) group. This may be related to differences in effectiveness, or to exposure to more medications in the O-group. However, the more complex treatment patterns (C-O and 'Other' patterns) were associated with highest relative frequencies of AEs, severe AEs, serious AEs (SAEs) and AEs requiring discontinuation of antipsychotic treatment, as shown in the table below.

Frequency of AEs, Severe AEs, SAEs and AEs Requiring Treatment Discontinuation by Medication Switch Pattern I (C:O Pattern)

Number of Subjects With:	**O (n=490)**	**C (n=426)**	**C-O (n=105)**	**Other (n=63)**
≥1 AE	214 (43.7%)	132 (31.0%)	67 (63.8%)	44 (69.8%)
≥1 Severe AE	34 (6.9%)	20 (4.7%)	18 (17.1%)	13 (20.6%)
≥1 SAE	66 (13.5%)	43 (10.1%)	32 (30.5%)	27 (42.9%)
Treatment stopped[a] due to AE	67 (13.7%)	21 (4.9%)	42 (40.0%)	17 (27.0%)

[a] Permanent stop of antipsychotic treatment

In total, 11 deaths occurred during the prospective period. Prior to death, 6 subjects had received Consta (2 of whom were also receiving oral antipsychotic treatments), 4 subjects had received oral antipsychotic medication, and one subject had discontinued antipsychotic treatment several months before death. Completed suicide (6 subjects) was the most common cause of death. Only the death of one subject who committed suicide while receiving Consta, oral flupentixol and oral ziprasidone was reported as possibly causally related to antipsychotic medication.

Injection site pain, scored according to a 10-point categorical scale, indicated a low level of pain for both gluteal and deltoid Consta administration sites. However, the results revealed higher pain scores for subjects receiving deltoid than gluteal injections ($p<0.001$). This is consistent with observations from other studies with injectable antipsychotics.

Available data indicated mean increases in body weight of less than 1 kg at the end of the baseline treatment period. For subjects who remained on the same baseline antipsychotic medication during the prospective period, greatest mean increases were observed in the baseline Consta group (0.89 kg) compared with the Oral group (0.55 kg), although the difference between groups was not clinically relevant. Comparable small proportions of each group reported weight gain as an AE.

STUDY LIMITATIONS:

Since this was not a randomized study, there could be treatment assignment bias and baseline differences between groups, which can make interpretation of comparisons between groups difficult. Another limitation was that data capture was at fixed time points, separated by 3-monthly intervals. This made documentation and interpretation of treatment switch data from the intervening periods difficult. While providing insight into real-world clinical practice, the non-interventional design resulted in heterogeneous data, encompassing multiple treatment changes, which are more difficult to analyze and interpret than data derived from randomized clinical trials.

CONCLUSIONS:

- During the 12-month prospective period, the majority of subjects were treated according to the C- (39.3%), O- (45.2%) or C-O (9.7%) pattern.
- At baseline, subjects prescribed Consta had: more hospitalization days in the previous 6 months, worse symptom severity, a lower level of functioning, and less treatment adherence than subjects prescribed oral antipsychotic therapy at baseline.
- Subjects prescribed Consta at baseline subsequently had reductions in days spent in hospital compared with the retrospective period; little change in hospitalization days was observed for subjects prescribed oral therapy at baseline.
- Greater improvements in symptomatic and functional outcomes, satisfaction with medication, and adherence to treatment were observed in subjects treated with Consta at baseline than in those treated with oral antipsychotics.
- However, subjects starting oral antipsychotics were more likely to switch between NonConsta therapies than to switch to Consta. This is surprising given the potential benefit of a long-acting injectable therapy in schizophrenia, a population characterized by high partial- and non-adherence rates.
- The complex switch patterns observed for a subset of subjects during this study suggest heterogeneous decision processes in the search for an effective treatment. Overall, these more complex treatment patterns were associated with less favorable outcomes.
- There were no unexpected safety findings.

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