SYNOPSIS

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Name of Sponsor/Company	Janssen-Cilag Medical Affairs EMEA a division of Janssen Pharmaceuticals N.V.
Name of Finished Product	Risperdal® Consta®
Name of Active Ingredient(s)	risperidone

Protocol No.: RIS-SCH-3001

Title of Study: CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness

Principal Investigator: not applicable

Publications Based on the Study:

- Medori R, Wapenaar R, De Arce R, Rouillon F, Gaebel W, Cordes J, Eriksson L, Smeraldi E. Relapse prevention and effectiveness in schizophrenia with risperidone long-acting injectable (RLAI) versus quetiapine. Poster No. 793 63rd Annual Meeting of the Society of Biological Psychiatry (SOBP), Washington, DC, USA, May 1-3, 2008.
- Medori R, Wapenaar R, De Arce R, Rouillon F, Gaebel W, Cordes J, Eriksson L, Smeraldi E. Relapse prevention and effectiveness in schizophrenia with risperidone long-acting injectable (RLAI) versus quetiapine. Poster No.4-042 at the 161th Annual Meeting of the American Psychiatric Association (APA), Washington, DC, USA, May 3-8, 2008.
- Schreiner A, Wapenaar R, De Arce R, Rouillon F, Gaebel W, Cordes J, Eriksson L, Smeraldi E. Relapse prevention and effectiveness in schizophrenia with risperidone long-acting injectable (RLAI) versus quetiapine. Poster No. WPC 946 at the XIV World Congress of Psychiatry, Prague, Czech Republic, September 20-25, 2008.

Study Period: 4 October 2004 – 21 November 2007 [date of first study related procedure - date of last observation for last subject]

Phase of Development: IIIb-IV

Objectives:

The primary objective of this study was:

- to investigate whether risperidone long-acting injectable (LAI) provided better efficacy maintenance over 2 years, in comparison to the newer oral atypical antipsychotic quetiapine, tested in a routine care setting in general psychiatric services.

The secondary objectives were:

- to investigate remission according to the PANSS scale, suicidal ideation and suicidal behaviour, use of health care facilities, tolerability, quality of life (QoL) and subjects' functionality during long-term treatment with risperidone LAI in comparison with the oral atypical antipsychotic quetiapine;
- to analyse efficacy in subjects treated with the oral atypical antipsychotic aripiprazole (if commercially available);
- to assess the overall cost of a relapse.

Methods:

Approximately 691 stable subjects suffering from schizophrenia or schizoaffective disorder, who were treated with oral risperidone, olanzapine, or conventional oral neuroleptic monotherapy at screening, were planned to participate in this open-label, active-controlled, multicentre, randomised study.

Symptomatically stable subjects who were not optimally treated were switched from their antipsychotic treatment (oral risperidone, olanzapine, or conventional oral neuroleptic agent) to either risperidone LAI, quetiapine oral, or aripiprazole oral. Reasons for switching treatment in a stable but not optimally treated subject were insufficient efficacy on symptoms (e.g., negative, positive, general) or side effects (e.g., extra-pyramidal symptoms [EPS]) or subject's request. Countries with 3 arms of treatment could continue to enrol subjects also after the necessary subject quota for risperidone LAI and quetiapine were reached. These subjects were then automatically allocated to aripiprazole treatment.

Apart from the number of subjects included to test the primary outcome parameter, also a limited number of subjects (N = 63) was to be randomised to aripiprazole oral treatment.

The main goal of this study was to investigate whether risperidone LAI provided better efficacy maintenance over 2 years, as measured by the time to relapse, in comparison to the newer oral atypical antipsychotic quetiapine, tested in a routine care setting in general psychiatric services. For this assessment, relapse was defined as meeting any one of the following criteria (adapted from Csernansky et al., 2002):

- psychiatric hospitalisation;
- clinical judgement that an increase in level of care was necessary and an increase in PANSS score of 25% relative to baseline score or an increase of 10 points if baseline score was ≤40;
- deliberate self-injury, in the opinion of the investigator;
- emergence of clinically significant suicidal or homicidal ideation;
- violent behaviour resulting in significant injury to another person or significant property damage, in the opinion of the investigator;
- significant clinical deterioration defined as a Clinical Global Impression of Change (CGI-C) score of 6 ('much worse');
- requiring a dose of study medication that exceeds the registered dose.

For having relapsed, the subject was to meet the criteria above on 2 consecutive evaluations, 3 to 5 days apart. The first of these visits was considered as the moment of relapse.

To avoid undue prolongation of the study, an interim analysis of efficacy was performed after the last subject had completed one year of treatment. If a difference in efficacy at the 0.1% significance level (two-tailed) was observed, the study was to be terminated.

Note that the following medication was not allowed during the course of the study:

- Antipsychotics other than the study medication, with the exception of antipsychotics administered during the 3 weeks after the first risperidone LAI injection and during the tapering off period;
- Beta-blockers, except for those that were used as antihypertensives (the subject's blood pressure had been stabilised prior to screening visit) or those used for the treatment of treatment-emergent akathisia.

Number of Subjects (planned and analysed):

Sample size determination was based on the expected difference in time to relapse between the risperidone LAI arm and the quetiapine arm. The null hypothesis was that there is no difference in treatment effect between risperidone LAI and quetiapine as measured by the time to relapse. In total 628 subjects were needed to be able to detect a difference in relapse rates between risperidone LAI and quetiapine. Apart from the number of subjects included to test the primary outcome parameter, also a limited number of subjects (N=63) were to be randomised to aripiprazole oral treatment.

The actual number of randomised subjects was 756. The predefined analysis sets consisted of:
- ITT population: 711 subjects, i.e., 329 treated with risperidone LAI, 337 with quetiapine, and 45 with aripiprazole;
- Efficacy Analysis Set: 697 subjects, i.e., 327 treated with risperidone LAI, 326 with quetiapine, and 44 with aripiprazole;
- Safety Analysis Set: 711 subjects, i.e., 329 treated with risperidone LAI, 337 with quetiapine, and 45 with aripiprazole.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

Subjects were to satisfy the following criteria to be enrolled in the study:
- Being male or female;
- Aged at least 18 years;
- Having a diagnosis of schizophrenia or schizoaffective disorder according to the DSM-IV;
- Being treated with oral risperidone, olanzapine, or conventional oral neuroleptic monotherapy at screening (daily doses were not to exceed 6 mg for risperidone, 20 mg for olanzapine, or a conversion dose of 10 mg haloperidol for oral conventional agents).
- Female subjects were to be surgically sterile or were to practice an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intra-uterine device, double-barrier method, contraceptive patch, male partner sterilisation, or abstinence) before entry and throughout the study. Additionally, they were to have a negative serum pregnancy test at baseline, before study entry.
- Subjects were to be stable (judged clinically stable by the investigator and on a stable dose of medication for 4 weeks or longer and living in the same residence for 30 days) but not optimally treated (insufficient efficacy on symptoms or side effects, or subject's request).
- Subjects (or their legally acceptable representatives) were to have signed an informed consent form indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study.
- Subject's relative or caregiver was to have signed an informed consent form indicating that he/she was willing to participate in the study to provide information in case the subject experienced relapse during the evaluation period. If this relative or caregiver consent could not be obtained, the subject could still participate in the study.

Exclusion criteria:

Potential subjects who met any of the following criteria were excluded from participation in the study:
- Having a DSM-IV axis I diagnosis other than schizophrenia or schizoaffective disorder;
- Being treated with other antipsychotics than oral risperidone, olanzapine, or conventional oral neuroleptics;
- Female subjects planning to become pregnant in the coming 2 years from study start;
- Subjects who were known non-responders to previous treatment with at least 2 antipsychotics;
- Subjects who were known non-responders to quetiapine, aripiprazole, or oral risperidone proven by adequate drug plasma levels (non-responders due to non-compliance were not to be excluded);
- Subjects treated with mood stabilisers or antidepressants that were not on a stable dose for at least 3 months prior to study entry;
- Having evidence of alcohol or drug abuse or dependency (except for nicotine and caffeine dependency) according to DSM-IV criteria diagnosed in the last month prior to study entry;
- Being pregnant or breast-feeding;
- Subjects having received an experimental drug or having used an experimental medical device within 30 days before the planned start of treatment with study medication;
- Having a history of severe drug allergy, drug hypersensitivity, or neuroleptic malignant syndrome;
- Having a clinically significant laboratory abnormality;
- Having a known clinically significant electrocardiogram (ECG) abnormality;
- Having a significant physical illness;
- Subjects with mental retardation;

- Subjects with a known hypersensitivity to risperidone, quetiapine, or aripiprazole;
- Subjects with phenylketonuria;
- Subjects with, in the opinion of the investigator, acute risk of suicide at study entry or a history of suicidal attempt(s);
- Employees of the investigator or study centre, with direct involvement in the study or other studies under the direction of that investigator or study centre, as well as family members of such employees or investigators.

Test Product, Dose and Mode of Administration:

Risperidone long-acting injectable, an extended release microsphere formulation of risperidone containing 25 mg, 37.5 mg, or 50 mg risperidone was administered intramuscularly every 2 weeks and started at 25 mg. During the first 3 weeks, after the first risperidone LAI injection, the subjects continued to receive their previous oral medication (risperidone, olanzapine or conventional neuroleptic) to ensure coverage until the main release phase of risperidone LAI starts leading to effective drug levels. The dose could be increased in increments of 12.5 mg during the study, if the subject experienced a worsening of psychotic symptoms. This increase in dose could only take place at scheduled visits and the subject was to maintain each dose of risperidone LAI for a minimum of 4 weeks before an increase could occur. Dosing was not to exceed the registered maximum dose. Doses of risperidone LAI could be reduced if required due to emergence of safety and/or tolerability problems and according to the investigator's judgement. Additional risperidone oro-dispersible medication could be administered as required, until a dose increase of risperidone LAI became effective.

Reference Therapy, Dose and Mode of Administration:

Quetiapine was supplied for oral administration as 25-mg, 100-mg, and 200-mg tablets. Administration was done according to SmPC, started at 25 mg b.i.d., increased in increments of 25-50 mg b.i.d. or t.i.d. to a target dose range of 300-400 mg daily (given in a b.i.d. or t.i.d. regimen). If indicated, further dose adjustment could occur at intervals of not less than 2 days. Daily doses were not to exceed the registered maximum dose.

In countries where aripiprazole is available, aripiprazole was supplied in tablets for oral administration, in 10-mg, 15-mg, and 30-mg strengths. Administration was done at the recommended dose of 15-30 mg q.d. Daily doses were not to exceed the registered maximum dose.

Duration of Treatment:

2 years; the subject's time in the clinical study from randomisation to the time until he/she has completed a 2-year treatment, has dropped out, or experienced a relapse.

Criteria for Evaluation:

Efficacy

- Time to relapse: relapse was defined according to predefined criteria (adapted from Csernansky et al., 2002)
- Positive and Negative Syndrome Scale
  The PANSS was assessed at:
  - Baseline;
  - Months 1, 3, 6, 9, 12 15, 18, 21 and 24 (endpoint).
- Clinical Global Impression Scale
  The CGI (Severity and Change) was assessed at:
  - Baseline;
  - Months 1, 3, 6, 9, 12 15, 18, 21 and 24 (endpoint).
- Affective symptoms' assessment
  The Montgomery-Asberg Depression Rating Scale (MADRS) were assessed at:
  - Baseline;
  - Months 1, 3, 6, 9, 12 15, 18, 21 and 24 (endpoint).

- Functioning assessment
  The Social and Occupational Functioning Assessment Scale (SOFAS) was assessed at:
    - Baseline;
    - Months 6, 12, 18, and 24 (endpoint).
- Health status and quality of life assessments
  The Short Form Health Survey 12 (SF-12®) and Schizophrenia Quality of Life Scale (revision 4; SQLS-R4) were assessed at:
    - Baseline;
    - Months 1, 3, 6, 12, 18, and 24 (endpoint).
- Information on health care resource use was collected for all subjects throughout the study period. Questionnaires were employed to assess utilisation of resources (hospitalisation [one overnight stay], emergency room visits without hospitalisation, day or night clinic stays, and outpatient treatment) as well as daily living conditions and productivity of the subject.
- Immediately upon identification of a relapse by the investigator, a specific IRUB was implemented (only for those subjects who relapsed). The main objective of this IRUB was to assess the costs of a relapse.

Safety

- Adverse events: AEs were reported for the duration of the study
- Extra-pyramidal symptoms
  The Extra-Pyramidal Symptom Rating Scale (ESRS) was assessed at:
    - Baseline;
    - Months 3, 6, 12, 18, and 24 (endpoint).
- Laboratory safety:
  Blood samples for serum chemistry, prolactin, and haematology assessments were taken at:
    - Screening;
    - Months 12 and 24 (endpoint).
- Vital Signs
  Blood pressure and heart rate measurements were taken at:
    - Screening;
    - Baseline;
    - Months 3, 6, 12, 18, and 24 (endpoint).
- Other safety parameters:
  Weight, waist and hip circumference were measured at:
    - Baseline;
    - Months 6, 12, 18 and 24 (endpoint).

Statistical Methods

Descriptive statistics, intent-to-treat, Fisher-exact test, Kaplan-Meier, Wilcoxon signed-rank test, Wilcoxon two-sample test

RESULTS:

STUDY POPULATION:

The actual number of randomised subjects was 756. During the study, one centre was disqualified because of GCP non-compliance and the 25 subjects recruited by the centre were excluded from the ITT population. Another 20 randomised subjects were excluded from the ITT population since they did not receive any study medication.

On 23 October 2007, an independent scientific board reviewed the results of an interim analysis performed after the last subject had completed one year of treatment. Since the stopping criteria based on difference in efficacy at the 0.1% significance level of risperidone LAI compared to quetiapine were met and no other concerns emerged, the study was stopped as per recommendation of the independent scientific board. Thirty-four subjects (5%) were ongoing at the time of study stop and were discontinued by the sponsor per amendment 5. The last subject had a last visit on 21 November 2007. Prior to study stop, 168 subjects (24%) had discontinued study medication because they met the criteria for relapse and 229 subjects (32%) had withdrawn from the study for reasons other than relapse. Main reason for premature discontinuation other than relapse was withdrawal of consent. Two hundred eighty subjects completed the 2-year treatment period with risperidone LAI, quetiapine, or aripiprazole.

Study Completion/Withdrawal Information
(Study RIS-SCH-3001: *ITT Population*)

Parameter, n (%)	Risperidone LAI N=329	Quetiapine N=337	Aripiprazole N=45	Total N=711
Completed	**151 (45.9)**	**120 (35.6)**	**9 (20.0)**	**280 (39.4)**
Ongoing until study stop by sponsor	**19 (5.8)**	**8 (2.4)**	**7 (15.6)**	**34 (4.8)**
Discontinued	**159 (48.3)**	**209 (62.0)**	**29 (64.4)**	**397 (55.8)**
Relapse	**54 (16.4)**	**102 (30.3)**	**12 (26.7)**	**168 (23.6)**
Reasons other than relapse	**105 (31.9)**	**107 (31.8)**	**17 (37.8)**	**229 (32.2)**
Withdrawal of consent	59 (17.9)	72 (21.4)	9 (20.0)	140 (19.7)
Lost to follow up	10 (3.0)	9 (2.7)	1 (2.2)	20 (2.8)
Adverse event(s)	6 (1.8)	10 (3.0)	1 (2.2)	17 (2.4)
Refuses injection	11 (3.3)	0	0	11 (1.5)
No more in need of treatment	3 (0.9)	4 (1.2)	1 (2.2)	8 (1.1)
Insufficient response	4 (1.2)	3 (0.9)	0	7 (1.0)
Non-compliance	0	4 (1.2)	1 (2.2)	5 (0.7)
Higher dose/extra medic. required	2 (0.6)	0	2 (4.4)	4 (0.6)
Death	2 (0.6)	0	0	2 (0.3)
Pregnancy	0	1 (0.3)	1 (2.2)	2 (0.3)
Administrative reasons	1 (0.3)	1 (0.3)	0	2 (0.3)
Other[a]	7 (2.1)	3 (0.9)	1 (2.2)	11 (1.5)

N=number of subjects in the treatment arm, n=number of subjects with observation
[a] 'other' includes 'protocol violations' and 'moving'.

The study population was predominantly Caucasian (98%) with a median age of 39, 42, and 38 years in the risperidone LAI, quetiapine, and aripiprazole treatment arms, respectively (overall range: 17-89 years). A slight majority of subjects was male (58%).

The majority of subjects (82%) had been diagnosed with schizophrenia, most commonly with schizophrenia of the paranoid type (75% of schizophrenia subjects). The remaining subjects (18%) suffered from schizoaffective disorder. Median duration of illness prior to the study was 7 years for subjects in the risperidone LAI and quetiapine arms, and 5 years for subjects in the aripiprazole arm.

Baseline disease characteristics in the risperidone LAI treatment arm were not significantly different from those in the quetiapine treatment arm.

Demographic And Baseline Characteristics
(Study RIS-SCH-3001: *ITT Population*)

	Risperidone LAI	Quetiapine	Aripiprazole
Sex, n (%)			
N	329	337	45
Male	195 (59.3)	191 (56.7)	25 (55.6)
Female	134 (40.7)	146 (43.3)	20 (44.4)
Age, years			
N	329	337	45
Mean (SD)	40.6 (12.48)	42.6 (13.14)	40.9 (12.94)
Median	39	42	38
Range	18;81	17;89	21;81
Height, cm			
N	329	337	45
Mean (SD)	170.6 (9.06)	171.1 (9.55)	169.9 (8.56)
Median	170	171	170
Range	150;190	146;196	157;188
Weight, kg (at baseline)			
N	328	335	44
Mean (SD)	80.4 (16.93)	79.0 (17.75)	82.8 (17.63)
Median	80	78	80
Range	43;145	44;141	49;125

EFFICACY RESULTS:

Efficacy analysis (with the exception of resource use) was performed on the efficacy analysis set, i.e., all subjects who received at least one dose of study medication and that had at least one efficacy assessment after baseline. Analysis of resource use was performed on the ITT population. All except 14 subjects of the ITT population were included in the efficacy analysis set. This set thus consisted of 697 subjects, of whom 327 were randomised to risperidone LAI treatment, 326 to quetiapine, and 44 to aripiprazole.

PRIMARY EFFICACY PARAMETER - TIME TO RELAPSE:

In total 168 subjects (24%) discontinued study medication because they met at least one of the pre-defined criteria for relapse (adapted from Csernansky et al., 2002[25]) on 2 consecutive evaluations during treatment, 3 to 5 days apart. This fraction of subjects having relapsed was significantly lower in the risperidone LAI arm than in the quetiapine arm, i.e., 17% (54 subjects) compared to 31% (102 subjects). In the aripiprazole group, 27% (12 subjects) relapsed during treatment.

Kaplan-Meier estimate of the relapse rate in each treatment arm provided a mean (± SE) relapse free period of 607 (± 11.4) days in the risperidone LAI arm, 533 (± 15.6) days in the quetiapine arm, and 314 (± 20.4) days in the aripiprazole arm (note that this estimate and its standard error were underestimated since the largest observation was censored and the estimation was restricted to the largest event time). The survival curves for the treatment arms risperidone LAI and quetiapine were compared by means of a log-rank test with two-sided 5% significance level; the test showed that the curves were significantly different. As the test's p-value (<0.0001) was lower than the critical alpha value (3%), the null hypothesis that there is no difference in treatment effect between risperidone LAI and oral quetiapine as measured by the time to relapse, was rejected. The hazard ratio using quetiapine treatment as the reference equalled 0.464, indicating that the relative risk for relapse in the risperidone LAI treatment arm was less then half the risk for relapse in the quetiapine treatment arm. Conversely, taking the quetiapine treatment arm as index group and the risperidone LAI arm as reference group, the hazard ratio equalled 2.154, indicating that the risk for relapse in the quetiapine arm is more than twice the risk in the risperidone LAI arm.

SECONDARY EFFICACY PARAMETERS:

Secondary Efficacy Parameters
(Study RIS-SCH-3001: *Efficacy Analysis Set Population*)

Parameter	Risperidone LAI N=327	Quetiapine N=326	Aripiprazole N=44
Reasons for relapse, n (%)[a]			
Clinical deterioration (CGI-C score of 6)	41 (75.9)	80 (78.4)	8 (66.7)
Psychiatric hospitalisation	33 (61.1)	54 (52.9)	2 (16.7)
Increased level of care + % PANSS score increase[b]	33 (61.1)	69 (67.6)	7 (58.3)
Requiring a dose higher than the registered dose	10 (18.5)	22 (21.6)	1 (8.3)
Emergence of suicidal or homicidal ideation	8 (14.8)	4 (3.9)	0
Violent behaviour in the opinion of the investigator	6 (11.1)	12 (11.8)	1 (8.3)
Deliberate self-injury in the opinion of the invest.	5 (9.3)	2 (2.0)	0
PANSS total score[c]			
Actual value at baseline, mean (SD)	72.7 (21.01)	73.2 (22.24)	76.1 (24.99)
Change from baseline to Month 24 (value), mean (SD)	-22.6 (18.55)	-18.6 (18.87)	-33.7 (24.71)
Change from baseline to Month 24 (%), mean (SD)	-28.2 (18.08)	-22.2 (19.33)	-37.1 (22.33)
Marder factors[c]			
Positive symptoms factor			
Actual value at baseline, mean (SD)	18.8 (6.68)	18.6 (6.72)	19.4 (6.99)
Change from baseline to Month 24, mean (SD)	-6.1 (5.63)	-4.6 (5.82)	-7.4 (6.04)
Negative symptoms factor			
Actual value at baseline, mean (SD)	20.6 (6.83)	20.6 (7.28)	21.7 (8.36)
Change from baseline to Month 24, mean (SD)	-6.7 (5.86)	-5.8 (5.92)	-12.1 (10.78)
Disorganised thoughts factor			
Actual value at baseline, mean (SD)	17.0 (5.56)	17.3 (5.99)	18.1 (7.03)
Change from baseline to Month 24, mean (SD)	-5.0 (4.96)	-4.0 (4.66)	-7.8 (5.52)
Uncontrolled hostility/excitement factor			
Actual value at baseline, mean (SD)	6.9 (3.04)	7.1 (3.28)	6.8 (3.37)
Change from baseline to Month 24, mean (SD)	-1.7 (2.56)	-1.3 (3.02)	-1.9 (2.57)
Anxiety/depression factor			
Actual value at baseline, mean (SD)	9.4 (3.57)	9.6 (3.48)	10.2 (3.35)
Change from baseline to Month 24, mean (SD)	-3.1 (3.47)	-2.8 (3.30)	-4.4 (3.87)
No. of subjects with response at Month 24 (based on improvement in PANSS total score)			
≥ 20%	116 (67.1)	78 (59.5)	8 (66.7)
≥ 30%	87 (50.3)	46 (35.1)	7 (58.3)
≥ 40%	45 (26.0)	20 (15.3)	5 (41.7)
≥ 50%	23 (13.3)	10 (7.6)	4 (33.3)
PANSS remission			
No. of subjects achieving remission during study	167 (51.1)	128 (39.3)	15 (34.1)
No. of subjects maintaining remission until end	144 (86.2)	102 (79.7)	13 (86.7)
Mean (SD) duration of remission, days	540.8 (181.43)	508.1 (187.98)	559.9 (157.20)
CGI-S[c]			
Actual value at baseline, mean (SD)	2.8 (1.01)	2.7 (0.97)	2.8 (0.99)
Change from baseline to Month 24, mean (SD)	-0.9 (0.99)	-0.6 (0.90)	-1.1 (0.90)
CGI-C			
Actual value at Month 24, mean (SD)	0.54 (0.88)	0.38 (0.90)	0.33 (0.78)

N=number of subjects in the treatment arm, n=number of subjects with observation

[a] percentages based on the number of relapsed subjects

[b] increase of 25% OR increase of 10 point if baseline PANSS score was ≤40

[c] lower scores indicate improvement in condition.

Secondary efficacy parameters, continued:

Secondary Efficacy Parameters
(Study RIS-SCH-3001: *Efficacy Analysis Set Population*)

Parameter	Risperidone LAI N=327	Quetiapine N=326	Aripiprazole N=44
SF-12®: PCS score[a]			
Actual value at baseline, mean (SD)	44.9 (8.82)	45.0 (8.79)	44.6 (9.26)
Change from baseline to Month 24, mean (SD)	3.4 (9.18)	2.8 (9.58)	6.1 (12.17)
SF-12®: MCS score[a]			
Actual value at baseline, mean (SD)	40.8 (11.36)	40.2 (10.65)	39.0 (10.50)
Change from baseline to Month 24, mean (SD)	4.6 (10.91)	6.0 (10.67)	4.3 (11.84)
SOFAS score[a]			
Actual value at baseline, mean (SD)	56.6 (13.14)	57.4 (14.81)	55.0 (16.64)
Change from baseline to Month 24, mean (SD)	12.8 (11.58)	11.0 (11.26)	16.8 (19.61)
MADRS score[b]			
Actual value at baseline, mean (SD)	12.7 (7.63)	13.6 (7.71)	13.3 (7.13)
Change from baseline to Month 24, mean (SD)	-6.5 (6.65)	-6.7 (5.95)	-10.9 (9.27)
SQLS-R4 score[b]			
Actual value at baseline, mean (SD)	39.7 (17.17)	39.9 (16.90)	46.1 (17.69)
Change from baseline to Month 24, mean (SD)	-8.0 (14.77)	-9.7 (15.00)	-13.3 (17.57)

N=number of subjects in the treatment arm
[a] higher scores indicate improvement in quality of life.
[b] lower scores indicate improvement in quality of life.

RESOURCE USE RESULTS:

Hospitalisation: Comparing the number of hospitalisation days during the study to the number of days prestudy, a decrease by 0.85 days per 90 days was calculated in the risperidone LAI arm while the number of days increased by 0.33 days per 90 days in the quetiapine arm.

Emergency room visits: Fourteen subjects (4%) in the risperidone LAI arm and 10 subjects (3%)in the quetiapine arm had an emergency visit during the study. In the aripiprazole arm, no observations of emergency room visits were made during the study.

Partial Hospitalisation: During the study, 5 subjects (2%) in the risperidone LAI arm, 8 (2%) in the quetiapine arm, and 3 (7%) in the aripiprazole arm had a partial hospitalisation. All were visits to the day clinic.

*Outpatient consultation*s. The mean number of outpatient psychiatrist consultations (in subjects with such consultations) was 2.7 per 90 days in the risperidone LAI arm, 3.2 per 90 days in the quetiapine arm, and 4.1 per 90 days in the aripiprazole arm (range: 0.1-32.4 per 90 days). No statistically significant between-group differences were observed.

INTENSIVE RESOURCE USE BATTERY (IRUB):

Two thirds of the subjects who participated in the IRUB collection, i.e., 9 (75%), 34 (67%), and 1 (17%) subjects in the risperidone LAI, quetiapine, and aripiprazole arm, respectively, were hospitalised during IRUB.

The majority of hospitalisations during IRUB were ascribed to an increased care for psychotic disease (for 60% of hospitalised subjects in the risperidone LAI arm and 87% in the quetiapine arm) and reflected admissions to a psychiatric hospital (for 44% of hospitalised subjects in the risperidone LAI arm and 60% in quetiapine arm, and 50% in the aripiprazole arm).

On average, subjects in the risperidone LAI and the quetiapine arm had 28.7 and 27.8 hospitalisation days per 90 days during IRUB, respectively (range: 0-90 days).

Two thirds of the subjects who participated in the IRUB collection, i.e., 7 (58%), 31 (61%), and 4 (67%) subjects in the risperidone LAI, quetiapine, and aripiprazole arm, respectively, had at least one outpatient consultation during IRUB. Although the mean number of outpatient consultations in the risperidone LAI arm was half that in the quetiapine arm, the difference between both treatment arms was not statistically significant (17.8 per 90 days in the risperidone LAI arm and 37.3 per 90 days in the quetiapine arm; range: 1-612).

In total 42 risperidone LAI- or quetiapine-treated subjects were matched in order to compare the health care costs of relapsed subjects to routine health care costs of non-relapsed subjects.

On average, resource use during relapse amounted to £8492 in the risperidone LAI arm and to £10525 in the quetiapine arm, while routine health care costs for non-relapsed subjects were estimated to be £138 and £241, respectively.

SAFETY RESULTS:

Safety analysis was performed on the safety analysis set, i.e., all subjects that received at least one dose of study medication and that had at least one safety assessment after baseline. All subjects of the ITT population were included in the safety analysis set. This set thus consisted of 329 subjects randomised to risperidone LAI, 337 subjects to quetiapine, and 45 subjects to aripiprazole treatment.

ADVERSE EVENTS (AEs):

Six AEs led to the death of 5 subjects (1%) during treatment or shortly after, i.e., for 3 subjects in the risperidone LAI arm and for 2 subjects in the quetiapine arm. Causes of death were completed suicide for 3 subjects, myocardial infarction for one subject, and deep vein thrombosis and peptic ulcer perforation for one subject. None of these AEs leading to death were considered related to the study medication.

Although the efficacy results of the current study indicated a statistically significantly higher incidence of relapse due to emergence of suicidal or homicidal ideation or due to deliberate self-injury in the risperidone LAI arm compared to the quetiapine arm, these findings were not reflected in the safety results. Incidences of death due to suicide are moreover not higher than was expected in the population and duration of the current study.

Nineteen percent of subjects in the risperidone LAI arm, 23% in the quetiapine arm, and 16% in the aripiprazole arm experienced at least one treatment-emergent SAE during the study. These were most frequently (in at least 2% of subjects in the risperidone LAI or quetiapine arm) schizophrenia and psychotic disorder.

During the study, 68% of subjects in the risperidone LAI arm, 70% of subjects in the quetiapine arm, and 76% of subjects in the aripiprazole arm experienced at least one AE. Most frequently mentioned AEs in the risperidone LAI and quetiapine treatment arms (in more than 5% in either treatment arm) were hyperprolactinaemia (reported as AE based on laboratory results), anxiety, insomnia, schizophrenia, somnolence, weight increased, headache, psychotic disorder, and depression.

Incidences of AEs in the risperidone LAI and quetiapine treatment arms were similar, except for a higher incidence of hyperprolactinaemia (reported as AE based on laboratory results) in the risperidone LAI arm (14%) compared to the quetiapine arm (3%), and a lower incidence of somnolence and schizophrenia in the risperidone LAI treatment arm compared to the quetiapine arm (2% versus 11% for somnolence and 5% versus 11% for schizophrenia).

The majority of treatment-emergent AEs were mild or moderate in severity. Treatment-emergent AEs leading to permanent stop were most often (in at least 2% of subjects in the risperidone LAI or

quetiapine arm) schizophrenia and psychotic disorder. Most commonly reported (in more than 5% of risperidone LAI-treated subjects) treatment-emergent AEs considered at least possibly related to risperidone LAI treatment by the investigator were hyperprolactinaemia (reported as AE based on laboratory results) and weight increased. Most commonly reported (in more than 5% of quetiapine-treated subjects) treatment-emergent AEs considered at least possibly related to quetiapine treatment were somnolence and schizophrenia.

Subjects With Adverse Events
(Study RIS-SCH-3001: *Safety Analysis Set*)

	Risperidone LAI N=329	Quetiapine N=337	Aripiprazole N=45
One or more AE(s)	225 (68.4)	235 (69.7)	34 (75.6)
One or more treatment-emergent AE(s)	222 (67.5)	231 (68.5)	31 (68.9)
One or more severe treatment-emergent AE(s)	43 (13.1)	59 (17.5)	9 (20.0)
One or more related treatment-emergent AE(s)	107 (32.5)	151 (44.8)	23 (51.1)
Deaths	3 (0.9)	2 (0.6)	0
One or more serious treatment-emergent AE(s)	63 (19.1)	77 (22.8)	7 (15.6)
One or more treatment-emergent AE(s) leading to permanent discontinuation	51 (15.5)	81 (24.0)	6 (13.3)

EXTRA-PYRAMIDAL SYMPTOM RATING SCALE (ESRS):

ESRS total scores decreased statistically significantly from baseline to endpoint in all 3 treatment arms. Decreases in total score from baseline were moreover statistically significant from the first post-baseline assessment onwards (Month 3) in all 3 treatment arms (with exception of Month 24 in the aripiprazole arm). Between-group comparison of risperidone LAI and quetiapine ESRS actual values and changes from baseline revealed no significant differences between both treatments. A similar trend was observed at the level of the subscale scores.

CLINICAL LABORATORY EVALUATIONS:

Mean changes from baseline over time were small and comparable in the 3 treatment arms. In particular, comparable values for blood glucose were seen in all 3 treatment arms throughout the study. Although for some parameters changes over time were statistically significantly different in the risperidone LAI arm compared to the quetiapine arm, none of these changes were considered clinically significant, except for changes in prolactin. Mean prolactin values at screening were elevated in all 3 treatment arms. While in the quetiapine and aripiprazole arm, mean prolactin values decreased significantly throughout the treatment period towards normal range values, mean prolactin values in the risperidone LAI arm remained largely unchanged.

In the category of biochemistry parameters, treatment-emergent markedly abnormal values were observed for the following parameters:

Most commonly observed (in more than 15% of subjects in the risperidone LAI or quetiapine arm) treatment-emergent markedly abnormal biochemistry values were abnormal triglycerides, abnormal glucose, bicarbonate, and BUN. Most commonly observed (in more than 15% of subjects in the risperidone LAI or quetiapine arm) treatment-emergent markedly abnormal haematology values were abnormal neutrophil count, reticulocyte count, and lymphocyte count. Incidences in the risperidone LAI and the quetiapine arms were largely comparable.

Treatment-emergent markedly abnormal prolactin values were observed in 28% of females and 28% of males treated with risperidone LAI compared to 9% of females and 15% of males treated with quetiapine. Treatment-emergent markedly abnormal prolactin values in the aripiprazole arm had an incidence of 7% in females and 44% in males.

Treatment-emergent markedly abnormal urinalysis values were frequent in both the risperidone LAI and quetiapine arm.

Most commonly reported AEs related to laboratory abnormalities in the risperidone LAI arm were those linked to prolactin values, i.e., hyperprolactinaemia (reported as AE based on laboratory values).

VITAL SIGNS:

Changes in vital signs parameters over time were generally small. Nevertheless, heart rate had increased statistically significantly from baseline to endpoint in the quetiapine arm. No significant changes from baseline were noted in the other treatment arms. Heart rate at Month 24 and endpoint was moreover significantly higher in the quetiapine arm than in the risperidone arm.

Incidences of vital signs abnormalities were generally low (in at most 6% of subjects in any treatment arm) as were incidences of vital signs abnormalities reported as AE (in at most 3% of subjects in any treatment arm).

BODY WEIGHT:

Relatively small changes in body weight were observed over the 24-month treatment period. The shift in weight in the risperidone LAI arm from baseline to endpoint – an increase of 1.3 kg – was however statistically significant. Between-group comparison of risperidone LAI and quetiapine body weight values revealed that the higher body weight in the risperidone LAI arm compared to the quetiapine arm was statistically significant at endpoint but not at other assessment points. The influence of differences in treatment duration on weight change in this study is unknown.

The changes in body weight were reflected in the BMI, with a small but statistically significant increase in BMI in the risperidone LAI arm from baseline to endpoint of 0.4 kg/m^2.

Weight increased was reported as AE for 7% of subjects treated with risperidone LAI, 6% treated with quetiapine, and 4% treated with aripiprazole. This AE was considered possibly related to study medication for the majority of subjects with weight increased reported as AE.

HIP AND WAIST CIRCUMFERENCE:

Hip circumference remained largely the same in the 3 treatment arms. Changes in waist circumference in the quetiapine and aripiprazole treatment arms were insignificant. In the risperidone LAI arm the change in waist circumference from baseline to endpoint was small but statistically significant (increase of 1.6 cm). Significant increases were present from the second post-baseline assessment point (Month 12) onwards. The endpoint value of waist circumference was significantly higher in the risperidone LAI arm than in the quetiapine arm.

CONCLUSION:

Two-year treatment with risperidone LAI provided better relapse prevention than treatment with the newer oral antipsychotic quetiapine.

Efficacy of risperidone LAI treatment, from early in the study onwards, was apparent from statistically significant changes from baseline in all investigated efficacy parameters. Even more, risperidone LAI treatment provided better improvement in psychopathology than did quetiapine treatment, as evidenced from statistically significantly larger changes from baseline in several efficacy parameters throughout the 2-year treatment period.

IRUB analysis pointed out that resource use for relapsed subjects per relapse and related costs were comparable between treatment arms. The analysis also showed that costs of resource use after relapse are much higher than those of routine care. Therefore, it is the number of subjects relapsing that largely influences the differences in costs of resource use between treatment arms.

Besides the recognised safety pattern of risperidone, no new or additional safety-related information emerged in this study, including quetiapine and aripiprazole.

JANSSEN-CILAG
MEDICAL AFFAIRS EMEA
creating value for patients

Janssen-Cilag Medical Affairs EMEA
Turnhoutseweg 30,
B-2340 Beerse,
Belgium

Errata to Synopsis RIS-SCH-3001; Phase IIIb/IV

CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness

Risperidone long-acting injectable

The following items were found in the Synopsis after the final pubblish and approval of the report were complete:

Page	Section	Description of errata
1	Synopsis: study period	"4 October 2004 – 21 November 2007 [date of first study related procedure - date of last observation for last subject]" should be: "4 October 2004 – 27 November 2007 [date of first study related procedure - date of last observation for last subject]"

Approver:[First Initial, Last Name], [Day Month Year]

A. SCHREINER 09-DEC-2008

A. Schreiner

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