SYNOPSIS

Trial Identification

Company:	Janssen Pharmaceutica, LLC			
Finished product:	RISPERDAL® CONSTA®			
Active ingredient:	[Risperidone (R064766)]			
Title:	A 52-week, prospective, randomized, double-blind, multi-center study of relapse following transition from oral antipsychotic medication to two different doses (25 or 50 mg given every two weeks) of risperidone long-acting microspheres (RISPERDAL® CONSTA®) in adults with schizophrenia or schizoaffective disorder	**Trial No:**	RIS-SCH-401	
		Clinical Phase:	IIIb	
Investigator:	Appendix 1.4	**Country:**	4	
Trial Period:	**Start:** 20-Dec-02 (First subject entered)	**No. investigators:**		34
	End: 30-Sep-04 (Last subject out)	**No. subjects entered:**		404
		No. subjects randomized:		324

Protocol Summary

Indication:	Schizophrenia/schizoaffective disorder
Objectives:	**Primary** To explore the efficacy of 25 or 50 mg RISPERDAL® CONSTA® given every two weeks, as measured by the time to relapse over 52 weeks in subjects with schizophrenia or schizoaffective disorder. **Secondary** • To explore the efficacy of RISPERDAL® CONSTA® as assessed by the Clinical Global Impression (CGI) scale, the PANSS total score, as well as PANSS positive, negative, and general psychopathology subscales; and • To explore the safety of RISPERDAL® CONSTA® as assessed by collection of treatment-emergent adverse events (AEs), the Extrapyramidal Symptom Rating Scale (ESRS), the Abnormal Involuntary Movement Scale (AIMS), and the Dickson-Glazer Sexual Functioning Inventory (DGSF), as well as changes in vital signs, laboratory parameters, and ECG measures; and • To explore the effect of RISPERDAL® CONSTA® on cognition, functional outcomes, and subject/caregiver quality of life as measured by a computerized cognitive test battery, the Strauss-Carpenter Level of Functioning Scale (LOF), a resource utilization assessment, the Personal and Social Performance Scale (PSP), and the Schizophrenia Quality of Life Scale (SQLS), a patient attitude/satisfaction summary, and the Experience of Caregiving Inventory (ECI), respectively; and • To investigate dopamine D_2 receptor occupancy in striatal brain regions at trough plasma levels of RISPERDAL® CONSTA® at steady state using Positron Emission Tomography (PET), and to investigate the relationship between D_2 receptor occupancy and plasma levels of risperidone and 9-OH-risperidone.
Trial design:	This prospective, randomized, double-blind, multicenter study consisted of two phases: Screening and Treatment. The Screening phase consisted of the Screening visit (Visit

	1), followed by a period of up to 14 days, during which subjects continued on a stable dose of oral antipsychotic medication. Prior to the Screening period, subjects were to have been clinically stable on antipsychotic medications for at least four weeks (total oral antipsychotic maintenance dose must have not been >8 mg/day risperidone equivalents). Subjects who met all selection criteria were enrolled into the Treatment phase, which consisted of 27 visits over a total of 52 weeks, during which RISPERDAL® CONSTA® was administered every two weeks using a fixed dosing regimen (25 or 50 mg). Subjects received their first injection of their randomly assigned dose of RISPERDAL® CONSTA® on Day 1 (Week 0). Two weeks of oral antipsychotic supplementation (continuation of the stable, prescribed dose) followed this first dose. Between Days 15 and 21, oral antipsychotic medication was allowed for treatment of psychotic symptoms as needed. During the Treatment phase, an intervention with either oral lorazepam or RISPERDAL® was initiated for up to one week if worsening of psychiatric status required acute pharmacologic intervention. Following any one-week intervention, subjects had these medications discontinued, with resumption of RISPERDAL® CONSTA® as antipsychotic monotherapy. Subjects requiring more than three, one week-long periods of oral RISPERDAL® therapy within a three-month period were considered unstable, discontinued from the study, and initiated on antipsychotic therapy as clinically indicated. Subjects, who completed all scheduled visits of the Treatment phase, were eligible to enter the Extension phase, which consisted of visits every two weeks in an open-label fashion as deemed clinically appropriate, until commercialization of RISPERDAL® CONSTA® in the respective participating country. Subjects entering the Extension phase started on RISPERDAL® CONSTA® 25 mg. As clinically indicated, dose increases to 50 mg were permitted. Clinical data collected during the Extension phase were limited to monitoring for serious/adverse events and collection of concomitant medication use. A subset of subjects participated in a Positron Emission Tomography (PET) examination study at four participating sites. They had a PET scan performed within five days prior to their next injection of RISPERDAL® CONSTA®, when plasma levels were at their trough. Plasma levels of risperidone and 9-hydroxy-risperidone were measured for assessment of their correlation with D_2 receptor occupancy.
Main selection criteria:	**Inclusion criteria** 1. Subject (and/or a subject's authorized legal representative) had provided written informed consent and agreed to complete all study procedures; 2. Subjects identified a caregiver (a non-paid individual with whom the subject had significant contact at least once per week) with whom contact was made during the study. Subjects participated in the trial if a caregiver was not available or unwilling to complete a survey; 3. Subject was 18 to 70 years of age and, if female, was not of child bearing potential or was using adequate contraception; 4. Subject had a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria; 5. Subject was judged to be symptomatically stable, with regard to his or her psychiatric condition, and medically stable, with no clinically significant or unstable coexistent medical conditions; 6. Subject was on any oral antipsychotic mediation ('typical' or 'atypical', monotherapy or combination therapy) at a stable dose (no change in dose or frequency) for four weeks prior to Baseline. **Exclusion criteria**

	1. Subject was pregnant or breast-feeding; 2. Subject was hospitalized or required acute crisis intervention for symptom exacerbation in the four weeks prior to Baseline; 3. Subject was at imminent risk of injury to self or others; 4. Subject tested positive on urine drug screen conducted at Screening or had any history of abuse in the last six months as defined by DSM-IV criteria; 5. Subject had (i) impaired hepatic or renal function; (ii) a previously defined hypersensitivity to risperidone; (iii) a history of neuroleptic malignant syndrome (NMS); 6. Subject was treated with: (i) depot antipsychotics in the past 6 months of Baseline; (ii) RISPERDAL® CONSTA® in a previous trial; (iii) other investigational agents or devices within the past 30 days; (iv) electroconvulsive therapy (ECT) within 6 months of Baseline; 7. Subject was currently treated with: (i) carbamazepine; (ii) oral antipsychotic maintenance therapy prescribed at a total daily dose >8 mg/day risperidone equivalents; (iii) clozapine or was treatment-resistant in the judgment of the investigator; 8. Subject was an employee of the Investigator or the institution, or was otherwise involved in the conduct of the trial.

Treatment:	
Form – dosing route	RISPERDAL® CONSTA® suspension – intramuscular (gluteal) injection
Medication	RISPERDAL® CONSTA® 25 mg, 50 mg
Batch number	25 mg - 164-0611BA2, 164-0611BA , 164-0611AA 50 mg - 164-2081BA
Dosage	Oral antipsychotic therapy – stable, prescribed dose RISPERDAL® CONSTA® – 25 or 50 mg, i.m., at Baseline and subsequently every two weeks
Duration of treatment	Oral antipsychotic therapy – 2 weeks (Weeks 0 to 2) RISPERDAL® CONSTA® – 52 weeks (Weeks 0 to 52)
Disallowed medication	Dosing with oral antipsychotic medications was not permitted after the first two weeks of the Treatment phase. The only exception was for those subjects receiving higher-than-average doses of maintenance antipsychotics, whose oral antipsychotic medication could be tapered off from Days 15 to 21.

Assessment Schedule for Screening and Treatment phases

Phase	Screening (Open-Label)	Treatment (Double-blind)												
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Day[b]	**-14**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**
RISPERDAL® CONSTA® administration		X	X	X	X	X	X	X	X	X	X	X	X	X
Oral antipsychotic administration	X	X[c]												
Informed Consent	X													
Psychiatric/Medical History	X													
Demographics, Inclusion/Exclusion Criteria	X													
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X													
ECG	X	X[d]												
AE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X	As needed												
Drug screen	X	As needed												
Laboratories	X	X[d]						X[d]						X[d]
PANSS	X	X		X		X		X			X			X
CGI-Severity	X	X		X		X		X			X			X
CGI-Change				X		X		X			X			X
AIMS[e]		X												X
ESRS		X		X				X						X
LOF scale		X												X
PSP scale		X												X
SQLS[f]		X												X
DGSF[f]		X						X						X
Computerized Cognitive Battery[f]		X						X						X
Patient Attitude/Satisfaction Assessment[f]		X						X						X
Resource Utilization Assessment		X						X						X
ECI[g]		X												X
Relapse Summary and EOT Form		As needed												
Pharmacogenomics	X													

[a] If subject relapses or discontinues prematurely, Visit 28 (Endpoint/EP) evaluations to be completed.

[b] All assessments should be performed on the scheduled visit day (± 3 days).

[c] Continuation of full doses of oral antipsychotic medications is mandatory for the first two weeks after the first RISPERDAL® CONSTA® dose (Day 1 to 14).

[d] If Screening laboratory or ECG assessment is performed within 14 days of the Baseline (Week 0) visit, assessment does not need to be repeated. Week 12 and 24 laboratory assessments will be for prolactin level only.

[e] The AIMS must be completed before the ESRS when these assessments are scheduled during the same visit.

[f] All self-administered assessments must be completed first. Patients should complete assessments in a quiet area, as free from distraction as possible.

[g] The same caregiver should complete this assessment during the study.

Phase	**Treatment (Double-blind)**													
Visit[a]	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**[a] **(EP)**
Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Day[b]	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**
RISPERDAL® CONSTA® administration	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam														X
ECG														X
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	As needed													
Drug screen	As needed													X
Laboratories						X[c]								X
PANSS			X			X			X					X
CGI-Severity			X			X			X					X
CGI-Change			X			X			X					X
AIMS[d]														X
ESRS						X								X
LOF scale														X
PSP scale														X
SQLS[e]														X
DGSF[e]						X								X
Computerized Cognitive Battery[e]														X
Patient Attitude/ Satisfaction Assessment[e]						X								X
Resource Utilization Assessment						X								X
ECI[f]														X
Relapse Summary and EOT Form	As needed													X

[a] If subject relapses or discontinues prematurely, Visit 28 (Endpoint/EP) evaluations to be completed.

[b] All assessments should be performed on the scheduled visit day (± 3 days).

[c] Week 36 laboratory assessment will be for prolactin level only.

[d] The AIMS must be completed before the ESRS when these assessments are scheduled during the same visit.

[e] All self-administered assessments must be completed first. Patients should complete assessments in a quiet area, as free from distraction as possible.

[f] The same caregiver should complete this assessment during the study.

Statistical methods:	*Sample size*: The sample size of 256 subjects (128 in each group) was based on an estimated relapse rate of 25% in the RISPERDAL® CONSTA® 50 mg group and 40% in the RISPERDAL® CONSTA® 25 mg group over a one-year period. Assuming approximately 20% of the subjects would not complete the study due to reasons other than relapse; the total number of subjects needed to be enrolled was estimated to be 320. *Populations*: The following analysis populations were defined: • Safety population: all subjects who received one dose of RISPERDAL® CONSTA®. • Intent-to-treat (ITT) population: prospectively defined population of subjects who received at least one dose of RISPERDAL® CONSTA® (or any portion of dose), and had a relapse or at least one post-baseline efficacy assessment. The efficacy analysis and summaries were provided for the ITT population. The Evaluable population consisted of all ITT subjects without significant post-enrollment protocol violations/deviations. The results of the Evaluable patient analyses are presented in the Appendix tables, but are not discussed in the body of the report. *Efficacy analysis*: The primary efficacy analysis of time-to-relapse was analyzed using standard survival analysis methods, including Kaplan-Meier product-limit survival curve estimates, log-rank tests, and proportional hazard regression models with Week 0 (Visit 2) as Baseline. One-year incidence of relapse was the primary endpoint. In addition, time-to-relapse in the two treatment arms were stratified by prior antipsychotic therapy, and summary statistics, including survival curves were provided with 95% confidence intervals. Relapse rates were also evaluated. The secondary efficacy analyses comprised summary statistics on changes from baseline and observed values for other continuous/ordinal efficacy variables (PANSS, CGI-C, CGI-S, LOF, PSP, SQLS, ECI, Cognitive measures, resource utilization), including sub-domains, at each time of evaluation and at each subject's last efficacy evaluation (Endpoint). A paired t-test was used for within group differences, and analysis of covariance methods with treatment, site, baseline value, and treatment by covariate interaction terms was used for inter group comparisons. Categorical variables were evaluated using the Cochran-Mantel-Haenszel (CMH) test stratifying on site or rank tests as appropriate. Secondary variables were also evaluated using repeated measures analyses, comparing treatment groups over time rather than at each visit. Analysis of covariance (ANCOVA) with treatment, strata group (dose of prior antipsychotic ≤4 or >4 mg/day risperidone equivalents) and site as the main effects, baseline as the covariate, and treatment by covariate and blocking factor interaction terms were used to compare across strata on changes from baseline and observed values for the above secondary efficacy variables. Categorical parameters were examined by means of the CMH test, controlling for site and strata group. Patient preference/attitudes, and caregiver burden were measured by a Likert-type scale and summarized using mean, standard deviation, median, minimum, and maximum, or frequencies and percents, as appropriate. Continuous parameters were assessed by means of ANCOVA and paired t-tests, whereas categorical outcomes were examined using either with the CMH test or Pearson's chi-square statistic, or Wilcoxon rank-sum test, as appropriate. *Safety analysis*: Assessment of safety was based on the frequency of AEs, laboratory values, vital signs, ECGs, physical examination findings, scores on EPS scales (AIMS and ESRS) and sexual function measures (DGSF), and concomitant medications.

Main features of the subject sample and summary of the results

Baseline characteristics – subject disposition		
	RISPERDAL® CONSTA®	
	25 mg	50 mg
No. of subjects randomized (M/F)	163 (109/54)	161 (93/68)
Age: mean (± SD), years	41.7 ± 12.0	40.2 ± 11.9
Age: median (min-max), years	42.0 (18; 68)	40.0 (18; 66)
Discontinuation of treatment (reason)		
All reasons	78 (48%)	80 (50%)
Relapse	38 (23%)	26 (16%)
Withdrawal of consent	18 (11%)	23 (14%)
Adverse Events	9 (6%)	10 (6%)
Lost to follow-up	7 (4%)	8 (5%)
Worsening of schizophrenia, non-relapse	3 (2%)	6 (4%)
Death	1 (<1%)	0
Protocol violation	1 (<1%)	1 (<1%)
Principal Investigator's decision	1 (<1%)	4 (2%)
Other	0	2 (1%)

Pharmacokinetics	Not Performed

Pharmacodynamics	Not Performed

Efficacy

Primary variable

- Time to relapse (Relapse during Days 1-20 considered Censored)

	RISPERDAL® CONSTA® 25 mg N = 162	RISPERDAL® CONSTA® 50 mg N = 161	Total N = 323
Relapsed	35 (22%)	24 (15%)	59 (18%)
Censored	127 (78%)	137 (85%)	264 (82%)
Mean time to relapse (weeks) [95% CI]	42.1 [39.6, 44.6]	46.9 [44.7, 49.1]	45.2 [43.5, 46.9]
Log-rank p-value = 0.131 (unstratified)			

- Time to relapse (Relapse during Days 1-20 considered Relapse)

	RISPERDAL® CONSTA® 25 mg N = 162	RISPERDAL® CONSTA® 50 mg N = 161	Total N = 323
Relapsed	38 (24%)	26 (16%)	64 (20%)
Censored	124 (77%)	135 (84%)	259 (80%)
Mean time to relapse (weeks) [95% CI]	41.3 [38.8, 43.9]	46.3 [44.0, 48.6]	44.5 [42.8, 46.3]
Log-rank p-value = 0.116 (unstratified)			

Secondary variables	
• PANSS	No statistically significant differences between the 25 and 50 mg treatment groups in the mean change from baseline were noted for the PANSS total scores at any timepoint. Compared to the baseline total PANSS score (66.8 ± 16.4 for 25 mg group; 66.1 ± 16.5 for 50 mg group), mean changes showed statistically significant improvement at Week 4 (mean change ± SD: -2.9 ± 9.6 for 25 mg group; -4.5 ± 11.0 for 50 mg group) and for each of the subsequent visits within both the 25 mg and 50 mg treatment groups. The Positive, Negative and General Psychopathology subscales, and the Positive, Negative, Disorganization, and Anxiety/Depression Factor Scales showed a similar pattern of change, with statistically significant mean improvements from baseline being observed at most timepoints, but no significant differences between treatment groups being noted. Analysis of the PANSS data stratified by dose of prior antipsychotic yielded results similar to those of the total population, with consistent improvements being noted in Total PANSS, and PANSS subscales and Factor scores; only a few sporadic statistically significant between group differences were observed.
• CGI	A statistically significant difference between the 25 mg and 50 mg treatment groups was noted on the mean change from baseline in the CGI-S only at Week 8 (-0.3 ± 0.6 vs. -0.1 ± 0.6, respectively). Statistically significant mean decreases (improvements) from baseline (3.5 ± 0.8 for 25 mg and 50 mg groups) in the CGI-S rating were seen at Week 4 (mean change ± SD: -0.1 ± 0.6) and subsequent visits in the 25 mg treatment group and at Week 8 (-0.1 ± 0.6) and subsequent visits in the 50 mg group. The proportion of subjects rated as “moderately ill,” “markedly ill,” or “severely ill” at baseline was 50%, 6%, and 1%, respectively, in the 25 mg group, and 44%, 8%, and 1%, respectively, in the 50 mg group. At endpoint, one subject in the 25 mg group remained “severely ill,” however, the proportion of subjects rated as “moderately ill” or “markedly ill” was increased to 28% and 11%, respectively. At endpoint, the proportion of subjects rated as “moderately ill” in the 50 mg group was further reduced to 27%, however, the proportion of subjects rated as “markedly ill” or “severely ill” was increased to 8% and 1%, respectively. No statistically significant difference was noted on the CGI-S ratings at any timepoint between the 25 and 50 mg treatment groups. The mean CGI-C ratings were below 4 (no change) at each visit for both the 25 and 50 mg groups, indicating that, on average, clinicians rated subjects’ improved from their baseline status at all visits. The proportion of subjects who improved (CGI-C ratings of 1, 2, or 3) at endpoint was 60% for the 25 mg group and 59% for the 50 mg group. The proportion of subjects who worsened (CGI-C ratings of 5, 6, or 7) was 20% for the 25 mg group and 22% for the 50 mg group. No significant differences in the mean CGI-C scores or the distribution of the CGI-C ratings were observed between the 25 and 50 mg treatment groups. Results for the CGI-S and CGI-C from the analysis of data stratified by dose of prior antipsychotic were similar to those of the total population, with the exception of a significant difference at endpoint between the 25 and 50 mg groups in the distribution of categorical ratings of the CGI-C in the >4 mg/day subgroup.

• LOF	No significant differences between the 25 and 50 mg groups were observed at any timepoint for either the 9-item or 4-item Total LOF scores, for any of the individual item scores or sums of items, or for the distribution of subjects among the different rating categories for each item. Statistically significant changes from baseline observed at endpoint included improvements in social contacts/ relations in the 50 mg group, and improvement in overall functioning in the 25 mg group.
• PSP	No significant differences between the 25 and 50 mg groups were noted at any timepoint for the mean changes from baseline in total PSP scores or the distribution of the subjects among the deciles of PSP categories. Significant mean improvements from baseline in the total PSP score were noted at Week 24 and endpoint for both treatment groups.
• ECI	No significant difference between the 25 and 50 mg groups was observed at endpoint for the mean change from baseline in either total Negative or Positive ECI scale. Statistically significant differences between the 25 and 50 mg groups, indicating a better caregiving experience for the 50 mg group, were note for the Stigma, Effects on Family and Loss items of the Negative ECI subscale. Significant differences between treatment groups at endpoint for these same items were noted for the >4 mg/day subgroup, but not for the ≤4 mg/day subgroup, with significant improvement, compared to the 25 mg group, also being observed in the Total Negative Scale score and Problems with Services item.
• Cognition	Data from the cognitive test battery will be discussed in a separate report.
• Patient attitude and satisfaction	No significant difference between the 25 and 50 mg groups was observed at endpoint on the mean ratings for the patient attitude toward and satisfaction with RISPERDAL® CONSTA®, indicating a general preference for RISPERDAL® CONSTA® over oral antipsychotics (endpoint: 3.8 ± 1.1 vs. 3.7 ± 1.2, respectively), limited concern about pain from the injection (endpoint: 1.2 ± 1.4 vs. 1.6 ± 1.5, respectively), and overall satisfaction with the medication (endpoint: 5.2 ± 1.5 vs. 5.1 ± 1.6, respectively). No significant difference between the 25 and 50 mg groups was observed at endpoint for the categorical ratings on the medication assessment and patient satisfaction items. However, a statistically significant difference between the 25 and 50 mg groups was observed at endpoint on the categorical ratings on the medication decision (easier than taking medication daily: 27% vs. 19%, respectively; family or doctor doesn't bother: 3% vs. 13%, respectively) and concern about pain items (none: 43% vs. 30%, respectively).
• Resource utilization	No statistically significant difference between the 25 and 50 mg treatment groups was noted in the mean number of emergency room visits without hospitalization per subject, mean days hospitalized, or accommodations/ housing status. However, a statistically significant difference was observed in the mean number of hospitalizations per subject between the 25 and 50 mg groups (0.2 ± 0.5 vs. 0.1 ± 0.4, respectively). In addition, a statistically significant difference in the distribution of the categories for the number of hospitalizations was observed between the two treatment groups, indicating fewer hospitalizations for the 50 mg group.

• Correlational analysis	Highly significant negative correlations (r = 0.43 – 0.69; p<0.001) were found between scores on all key secondary efficacy measures (i.e., Total PANSS, PANSS Positive Factor Scale, PANSS Negative Factor Scale, PANSS Disorganized Factor Scale, and CGI-S) and the LOF and PSP total scores for both 25 and 50 mg treatment groups. These results indicate that improvement (i.e., a decrease in score) on the Total PANSS, PANSS Factor scores, and CGI-S was associated with a better level of functioning for the subjects (i.e., an increase in score on the LOF and PSP). For the SQLS scale, reductions in the symptom domains of schizophrenia assessed by the PANSS and CGI-S were associated with a positive effect on the subjects' quality of life, with the association being somewhat stronger in subjects receiving the higher dose (50 mg) of RISPERDAL® CONSTA®.
• SQLS	No statistically significant differences between the 25 and 50 mg groups were observed in any of the SQLS subscales or the total score (Version 4) at baseline, or in the changes from baseline at endpoint.
Efficacy data stratified by dose of prior antipsychotic (≤4 vs. >4 mg/day risperidone equivalent)	▪ A significantly higher proportion of subjects who improved on the CGI-C (categorical CGI-C ratings of 1, 2, or 3) at endpoint was observed in the 50 mg treatment group, compared to the 25 mg group, for the >4 mg/day subgroup. ▪ A significantly greater mean improvement (decrease in score) from baseline on the total ECI Negative scale score at endpoint was noted in the 50 mg treatment group, compared to the 25 mg group, for the >4 mg/day subgroup. ▪ A significantly greater concern about pain, on the assessment of patients' attitude/satisfaction with their medication, was observed at endpoint in the 50 mg treatment group, compared to the 25 mg group, for the >4 mg/day subgroup. ▪ A significantly higher mean number of hospitalizations per subject, on the resource utilization assessment, was observed in the 25 mg treatment group, compared to the 50 mg group, for the >4 mg/day subgroup.

Safety		
Adverse events (AE)	RISPERDAL® CONSTA®	
Most frequently reported AE (≥5% of subjects):	25 mg (N = 163) n (%)	50 mg (N = 161) n (%)
Insomnia	41 (25)	48 (30)
Psychotic Disorder NOS	37 (23)	29 (18)
Headache	34 (21)	26 (16)
Anxiety	29 (18)	24 (15)
Influenza	16 (10)	4 (2)
Nasopharyngitis	15 (9)	15 (9)
Depressed Mood	14 (9)	10 (6)
Schizophrenia NOS	13 (8)	12 (7)
Weight Increased	12 (7)	14 (9)
Akathisia	11 (7)	12 (7)
Dizziness	12 (7)	9 (6)
Diarrhea NOS	9 (6)	8 (5)
Tremor	10 (6)	8 (5)
Somnolence	10 (6)	7 (4)
Dry Mouth	10 (6)	5 (3)
Hallucination, Auditory	10 (6)	4 (2)
Upper Respiratory Tract Infection	8 (5)	12 (7)
Fatigue	8 (5)	9 (6)
Paranoia	8 (5)	7 (4)
Vomiting	8 (5)	5 (3)
Nausea	7 (4)	9 (6)
Agitation	7 (4)	9 (6)
Toothache	3 (2)	10 (6)
Arthralgia	4 (2)	11 (7)
Back Pain	3 (2)	10 (6)
Nasal Congestion	3 (2)	10 (6)
No. (%) with one or more AE	148 (91)	141 (88)
No. (%) of deaths	1 (<1)	0
No. (%) with one or more serious AE	30 (18)	22 (14)
No. (%) treatment stopped due to AE	50 (31)	42 (26)
Clinical laboratory parameters		
• Clinical chemistry	No statistically significant difference in mean change from baseline at endpoint between the 25 and 50 mg treatment groups was observed in any biochemistry parameters, except for prolactin. No clinically relevant changes from baseline at endpoint in any of the biochemistry parameters, except prolactin, were noted in either of the treatment groups. A statistically significant increase from baseline in mean prolactin values was observed at endpoint in both the 25 and 50 mg groups, with significantly higher mean prolactin values being noted in the 50 mg treatment group, compared to the 25 mg group, at all visits except baseline.	

• Hematology	No statistically significant difference in mean change from baseline between the 25 and 50 mg treatment groups was observed in any hematology parameters at endpoint, with the exception of platelet count, (1.2 ± 39.9 vs. -8.8 ± 44.2, respectively; $p<0.05$). No clinically relevant changes from baseline in any of the hematology parameters at endpoint were noted with either of the two treatment groups.
• Urinalysis	No statistically significant difference in mean change from baseline between the 25 and 50 mg treatment groups was observed in any urinalysis parameters at endpoint. No clinically relevant changes from baseline in any of the urinalysis parameters at endpoint were noted in either of the two treatment groups.
Vital signs and physical findings	No statistically significant difference in mean change from baseline between the 25 and 50 mg treatment groups was noted in any of the vital signs parameters at endpoint. No clinically relevant changes from baseline in any of the vital signs parameters at endpoint were noted in either of the two treatment groups, except for body weight. Clinically notable weight increase at endpoint was observed in 18% of the subjects in the 25 mg group, compared to 22% of the subjects in the 50 mg group. The incidence of clinically notable weight decrease at endpoint was comparable in the 25 mg (13%) and 50 mg (10%) groups. There were no meaningful differences in the physical examination between the two treatment groups at endpoint.
ECGs	No statistically significant difference in mean change from baseline between the 25 and 50 mg treatment groups was noted in any of the ECG parameters at endpoint. No clinically meaningful changes from baseline in any of the ECG parameters at endpoint were observed in either of the two treatment groups.
Movement Disorder Measures • AIMS	No statistically significant difference between the 25 and 50 mg treatment groups in total AIMS or non-global total AIMS score was observed at endpoint. Although not statistically significant, an overall improvement on the total AIMS score from baseline was observed for both the 25 and 50 mg groups at endpoint (mean change ± SD: -0.3 ± 3.2 vs. -0.5 ± 3.7, respectively). Similarly, although not statistically significant, an improvement on non-global total AIMS score from baseline was observed for both the 25 and 50 mg groups at endpoint (mean change ± SD: -0.3 ± 2.5 vs. -0.4 ± 2.6, respectively).
• ESRS	No statistically significant difference in mean change from baseline between the 25 and 50 mg treatment groups in any of the ESRS subscales was observed at endpoint. Improvement or no change from baseline on all of the ESRS subscales was observed for both the 25 and 50 mg treatment groups at endpoint. The distribution of the categorical ratings for the CGI Akathisia subscale indicated that the 50 mg treatment group was associated with a statistically significant improvement, compared to the 25 mg group at endpoint. A statistically significant difference in shifts from baseline at endpoint between the two treatment groups, indicating greater improvement in the 50 mg group, was observed for each of the CGI assessments for Dyskinesia, Parkinsonism, Dystonia and Akathisia, and the Stage of Parkinsonism.

• DGSF	No statistically significant differences between the 25 and 50 mg treatment groups were observed in the total DGSF score at any timepoint for either male or female subjects. No statistically significant changes from baseline in the total DGSF score were observed for the 25 or 50 mg treatment groups at any timepoint for either gender. In general, most items of the DGSF showed little change in the pattern of response between baseline and endpoint, and there were few meaningful differences between the two treatment groups. In addition, correlational analysis showed no meaningful relationship between plasma prolactin levels and sexual functioning as assessed by the DGSF.
Safety data stratified by dose of prior antipsychotic (≤4 vs. >4 mg/day risperidone equivalent)	▪ A significantly higher mean prolactin value was observed in the 50 mg treatment group, compared to the 25 mg group, for both the ≤4 and >4 mg/day subgroups at endpoint. ▪ A statistically significant increase from baseline in body weight was observed in the 25 mg treatment group for the ≤4 mg/day subgroup at endpoint. ▪ A statistically significant difference in mean weight change from baseline at endpoint was observed in the 25 mg treatment group (-1.6 ± 8.5), compared to the 50 mg group (1.0 ± 7.0), for the >4 mg/day subgroup. ▪ A significant improvement on the CGI-Parkinsonism and Stage of Parkinsonism subscales of the ESRS was observed in the 50 mg treatment group, compared to the 25 mg group, for the ≤4 mg/day subgroup at endpoint. ▪ A statistically significant improvement on the CGI Akathisia rating of the ESRS was observed in the 50 mg treatment group, compared to the 25 mg group, for the >4 mg/day subgroup at endpoint. ▪ A statistically significant difference in shifts from baseline between the 25 and 50 mg treatment groups was observed for the ESRS CGI assessments for Dyskinesia, Parkinsonism, Dystonia and Akathisia, and the Stage of Parkinsonism in both the ≤4 and >4 mg/day subgroups at endpoint.

Outcomes Research	Pharmacoeconomic evaluations were not performed. Data on resource utilization is discussed in the efficacy section above.

Overall Conclusions	The primary endpoint of the study, relapse rate, was numerically but not statistically different between 25mg and 50mg doses of RISPERDAL CONSTA. This result is consistent with the appropriateness of 25mg for many patients; however, various important secondary measures, such as time to relapse and number of hospitalizations, were systematically and statistically better for patients receiving the 50mg dose. This advantage may suggest a reason to use higher doses to try to produce superior efficacy in some patients, for example, those at higher risk of relapse. Pre-planned analyses of this study suggest the advantage of the 50mg dose was particularly pronounced among patients receiving higher doses of antipsychotic medication prior to starting RISPERDAL CONSTA. Most measures of safety and tolerability were not substantially different between dose groups, suggesting that concerns over dose-related tolerability between 25mg and 50mg should not prevent dose escalation when clinically indicated.

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