SYNOPSIS

Trial Identification

Name of Sponsor/Company: Ortho-McNeil Janssen Scientific Affairs, L.L.C.	
Name of Finished Product: Risperdal	
Name of Active ingredient: Risperidone	
Protocol Number and Title of Study: Protocol number: RIS-OUT-184 Title of Study: Differences in Cognitive Function due to Acute Sedative Effects of Risperidone and Quetiapine in Stable Bipolar I Disorder Outpatients	
Principal Investigator: Steven Glass, M.D., CNS Research Institute, 130 White Horse Pike, Clementon, NJ 08021 USA	
Publication (Reference): None	
Study Initiation/Completion Dates: 29 OCT 2004 to 12 MAY 2005	**Phase of Development:** 4
Objectives: The primary objective of this trial was to compare the treatment effects of risperidone and quetiapine on cognitive function, using measures commonly believed to be affected by sedation, in individuals with stable bipolar I disorder (BID). The secondary objectives were: 1. To compare the treatment effects on the subjective experience of sedation. 2. To assess the association between subjective experience of sedation and cognitive function.	

Methodology:

This was a single-center, randomized, double-blind, two-period, two-treatment crossover study comparing the treatment effect on cognitive function in patients with stable bipolar disorder. Twenty-eight subjects were randomized to 1 of 2 treatment sequences, each consisting of 2 treatment periods, separated by 6-14 days of washout. In one sequence, 14 subjects received 2 mg qHS of risperidone in the first study period and then 100 mg qHS and qAM (total of 200 mg) of quetiapine in the second study period. In the second sequence, 14 subjects received 100 mg qHS and qAM (total of 200 mg) of quetiapine in the first study period and 2 mg qHS of risperidone in the second study period. Endpoints included cognitive tests and subjective assessments of sedation, performed pre- and postdosing over 2 days in each period. Safety evaluations included assessment of adverse events (AEs), clinical laboratory analyses, vital signs, and physical examination. At screening, clinical laboratory tests included BUN, a thyroid panel of TSH and free T4, serum lithium and valproate levels, and urine drug screens. Serum pregnancy tests were also performed on women of childbearing potential. The total duration of the study was 17 days, from screening to last visit.

Number of Subjects (planned and analyzed)

Thirty subjects were randomized to 1 of the 2 treatment sequences. Twenty-eight subjects completed both treatment periods and were included for endpoint analyses, and 30 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:

A history BID in partial or full remission at the start of the study, as defined by Diagnostic & Statistical Manual, 4th edition (DSM-IV) criteria.

Test Product, Dose and Mode of Administration, Lot/Reference No.:

The test product was 2 mg risperidone given orally. The lot number is 03D28/F005.

Reference Therapy, Dose and Mode of Administration, Lot/Reference No.:

The reference therapy was a total of 200 mg quetiapine provided orally. The lot number is 04K19/F271. Additionally, subjects received placebo for blinding. The lot number is 03E20/F092.

Duration of treatment:

A single dose of risperidone or b.i.d. doses of quetiapine were administered per treatment period, for two treatment periods.

Criteria for Evaluation:

Endpoint Analysis: The evaluable population consisted of all randomized subjects who had taken all doses of the study medications and had a baseline and at least one postbaseline Neurocognitive Composite Score (NCS) assessment in each treatment period. This was the primary population for analyzing the drug effect.

Safety Analysis: The safety population consisted of all randomized subjects who received at least 1 dose of study medication. This was the primary population for demographic summaries and safety analysis.

Statistical methods:

Demographic and baseline characteristics of the trial sample were summarized for the safety and evaluable population. Descriptive statistics were calculated for age, weight, height, body mass index, years since diagnosis, Young Mania Rating Scale (YMRS), and Montgomery-Asberg Depression Rating Scale (MADRS). Counts and percentages were displayed for sex, race, DSM-IV diagnosis, and nicotine and caffeine consumption.

The primary study hypothesis, that there is no difference in mean change from baseline NCS between risperidone and quetiapine treatments, was tested in a crossover Analysis of Covariance (ANCOVA) model.

The initial model included fixed effects for baseline (covariate), sequence, period, treatment, time, treatment-by-time interaction, period-by-time interaction, sequence-by-time interaction, and a random effect for subject. The within-period correlational structure was assumed to be homogenous across periods. The changes from baseline for each of 5 neurocognitive domains were analyzed similarly as were the changes from baseline for each of the 18 individual standardized test scores, as were the changes from baseline for each of the fatigue and vigor subscale scores on the Visual Analog Scale for Fatigue (VAS-F).

Spearman correlation analyses were performed to evaluate the association between the NCS and the VAS-F subscale scores.

The additional secondary endpoint variable, the need to sleep between cognitive testing sessions, was summarized using descriptive statistics. Treatment differences in the need for sleep were assessed by the Mainland-Gart test.

SUMMARY - CONCLUSIONS

Baseline characteristics – subject disposition	**Sequence 1 (R - Q)**	**Sequence 2 (Q - R)**	**Total**
No. of subjects randomized	15	15	30
Subject completion status			
Completed Period 1	14 (93.3)	15 (100.0)	29 (96.7)
Completed Period 2	14 (93.3)	14 (93.3)	28 (93.3)
Discontinued from study	1 (6.7)	1 (6.7)	2 (6.7)
Reasons for Discontinuation			
Withdrew consent	1 (6.7)	0 (0.0)	1 (3.3)
Non-compliant	0 (0.0)	1 (6.7)	1 (3.3)
Age: mean (± SD), years	40.3 (8.34)	40.2 (8.40)	40.2 (8.22)
median (min-max), years	41.0 (19-54)	39.0 (25-53)	40.0 (19-54)
Gender: Male N (%)	11 (73.3)	10 (66.7)	21 (70.0)
Female N (%)	4 (26.7)	5 (33.3)	9 (30.0)
Ethnicity N (%)			
Black	10 (66.7)	8 (53.3)	18 (60.0)
Caucasian	3 (20.0)	7 (46.7)	10 (33.3)
Hispanic	1 (6.7)	0 (0.0)	1 (3.3)
Other	1 (6.7)	0 (0.0)	1 (3.3)

Primary DSM - IV Diagnosis N (%)			
Hypomanic or Manic Episode in PR	0 (0.0)	1 (6.7)	1 (3.3)
Hypomanic or Manic Episode in FR	2 (13.3)	1 (6.7)	3 (10.0)
Major Depressive Episode in PR	1 (6.7)	1 (6.7)	2 (6.7)
Major Depressive Episode in FR	9 (60.0)	10 (66.7)	19 (63.3)
Mixed Episode in FR	2 (13.3)	0 (0.0)	2 (6.7)
Current or Most Recent Episode in FR	1 (6.7)	2 (13.3)	3 (10.0)
Years Since Diagnosis			
N	13	14	27
Mean (SD)	9.8 (5.98)	9.6 (7.95)	9.7 (6.94)

Note: PR = Partial Remission, FR = Full Remission

Endpoint Analyses	**Risperidone (N = 28) Mean (SD)**	**Quetiapine (N = 28) Mean (SD)**	**LS Means (RIS - QUE) (95% CI)**	**P-value**
Primary Variable - NCS				
• Baseline 10:00 a.m.	-0.010 (0.411)	0.002 (0.468)		
• Postdose 10:00 a.m.	0.086 (0.351)	-0.252 (0.510)	0.346 (0.212; 0.481)	<0.0001
• Postdose 12:30 p.m.	0.096 (0.406)	-0.271 (0.555)	0.376 (0.193; 0.558)	0.0003
• Postdose 3:00 p.m.	0.085 (0.333)	-0.029 (0.349)	0.119 0.010; 0.228	0.0333
All Postdose Assessments			0.279 (0.180; 0.377)	<0.0001
Secondary Variable - Processing Speed				
• Baseline 10:00 a.m.	-0.025 (0.659)	-0.021 (0.633)		
• Postdose 10:00 a.m.	0.173 (0.575)	-0.281 (0.664)	0.458 (0.297; 0.618)	<0.0001
• Postdose 12:30 p.m.	0.178 (0.595)	-0.302 (0.854)	0.482 (0.175; 0.790)	0.0034
• Postdose 3:00 p.m.	0.284 (0.597)	0.162 (0.607)	0.125 (-0.049; 0.298)	0.1523
All Postdose Assessments			0.355 (0.199, 0.511)	<0.0001

Endpoint Analyses	Risperidone (N = 28) Mean (SD)	Quetiapine (N = 28) Mean (SD)	LS Means (RIS - QUE) (95% CI)	P-value
Secondary Variable - Attention				
• Baseline 10:00 a.m.	-0.020 (0.667)	0.029 (0.665)		
• Postdose 10:00 a.m.	0.152 (0.505)	-0.389 (0.816)	0.579 (0.331; 0.826)	<0.0001
• Postdose 12:30 p.m.	0.072 (0.585)	-0.563 (1.034)	0.675 (0.309; 1.041)	0.0008
• Postdose 3:00 p.m.	0.134 (0.576)	-0.026 (0.639)	0.187 (-0.020; 0.394)	0.0750
All Postdose Assessments			0475 (0.259; 0.692)	<0.0001
Secondary Variable - Working Memory				
• Baseline 10:00 a.m.	-0.162 (0.907)	0.131 (0.770)		
• Postdose 10:00 a.m.	0.147 (0.983)	-0.079 (0.892)	0.429 (0.091; 0.767)	0.0150
• Postdose 12:30 p.m.	0.180 (1.111)	0.074 (1.103)	0.285 (-0.073; 0.643)	0.1139
• Postdose 3:00 p.m.	0.261 (1.055)	0.148 (0.853)	0.215 (-0.105; 0.535)	0.1791
All Postdose Assessments			0.323 (0.070; 0.576)	0.0128
Secondary Variable - Declarative Memory				
• Baseline 10:00 a.m.	0.038 (0.762)	-0.034 (0.920)		
• Postdose 10:00 a.m.	-0.016 (0.825)	-0.366 (0.881)	0.308 (-0.006; 0.622)	0.0542
• Postdose 12:30 p.m.	0.079 (0.670)	-0.206 (0.798)	0.245 (0.022; 0.469)	0.0327
• Postdose 3:00 p.m.	-0.050 (0.722)	-0.350 (0.847)	0.263 (-0.034; 0.561)	0.0805
All Postdose Assessments			0.270 (0.100; 0.439)	0.0021

Endpoint Analyses	Risperidone (N = 28) Mean (SD)	Quetiapine (N = 28) Mean (SD)	LS Means (RIS - QUE) (95% CI)	P-value
Secondary Variable - Executive Function				
• Baseline 10:00 a.m.	0.039 (0.467)	-0.042 (0.371)		
• Postdose 10:00 a.m.	0.005 (0.394)	-0.097 (0.534)	0.069 (-0.091; 0.228)	0.3827
• Postdose 12:30 p.m.	0.047 (0.439)	-0.136 (0.486)	0.151 (-0.075; 0.378)	0.1809
• Postdose 3:00 p.m.	-0.075 (0.351)	-0.024 (0.405)	-0.067 (-0.214; 0.081)	0.3611
All Postdose Assessments			0.038 (-0.042; 0.118)	0.3473
Secondary Variable - VAS-Fatigue				
• Baseline 10:00 a.m.	3.187 1.862	3.607 2.086		
• Postdose 10:00 a.m.	4.101 2.464	5.707 2.361	-1.416 (-2.431, -0.401)	0.0082
• Postdose 12:30 p.m.	3.819 2.545	5.977 2.279	-1.944 (-3.136, -0.751)	0.0025
• Postdose 3:00 p.m.	3.769 2.481	4.385 2.276	-0.333 (-1.144, 0.477)	0.4053
All Postdose Assessments			-1.215 (-2.014, -0.415)	0.0032
Secondary Variable - VAS-Vigor				
• Baseline 10:00 a.m.	5.279 2.037	5.229 2.099		
• Postdose 10:00 a.m.	4.586 2.465	3.307 2.199	1.263 (0.228; 2.299)	0.0188
• Postdose 12:30 p.m.	4.614 2.397	3.607 2.106	0.985 (0.057; 1.913)	0.0384
• Postdose 3:00 p.m.	4.763 2.362	4.221 2.268	0.529 (-0.177; 1.234)	0.1352
All Postdose Assessments			0.851 (0.273; 1.429)	0.0042
Need for Sleep: Fewer subjects reported sleeping between the morning dose and the postdose 10:00 a.m. assessment or between postdose assessments following risperidone dosing. The comparison between treatments was not statistically significant for the Postdose 10:00 a.m. assessment (P=0.0720), but was statistically significant for the Postdose 12:30 p.m. (P=0.0079) and the Postdose 3:00 p.m. assessments (P=0.0009) using the Mainland-Gart test.				

Discussion: The NCS is a composite of 18 scores on tests from a sample of domains of cognitive functioning, including the domains of Processing Speed, Attention, Working Memory, Declarative Memory, and Executive Function. In this study, subjects after dosing with risperidone differed significantly on NCS compared to subjects after dosing with quetiapine. Specifically, quetiapine was associated with significant impairment of cognitive function relative to risperidone. In reviewing the scores computed to measure the above 5 individual domains, scores for four of the domains supported the conclusions for the NCS. These domains were Processing Speed, Attention, Working Memory, and Declarative Memory.

There were statistically significant differences favoring risperidone over quetiapine as reported on the VAS-F fatigue subscale in the Postdose 10:00 a.m. and Postdose 12:30 p.m. assessments, but not in the Postdose 3:00 p.m. assessment. The overall treatment difference on the VAS-F Vigor subscale was statistically significant for risperidone over quetiapine.

Fewer subjects reported sleeping between the morning dose and the Postdose 10:00 a.m., Postdose 12:30 p.m., and Postdose 3:00 p.m. assessments following risperidone dosing compared to quetiapine dosing. The comparison between treatments was not statistically significant for the Postdose 10:00 a.m. assessment, but was statistically significant for the Postdose 12:30 p.m. and the Postdose 3:00 p.m. assessments using the Mainland-Gart test.

Safety	Risperidone N=29	Quetiapine N=29
Number (%) of treatment-emergent adverse events (TEAE)	18	36
Number (%) of most frequently reported TEAEs		
• Somnolence	9 (31.0)	24 (82.8)
• Fatigue	4 (13.8)	6 (20.7)
No. (%) with 1 or more TEAE	14 (48.3)	25 (86.2)
No. (%) of deaths	0 (0.0)	0 (0.0)
No. (%) with 1 or more serious TEAE	0 (0.0)	0 (0.0)
No. (%) treatment stopped due to TEAE	0 (0.0)	0 (0.0)

The most commonly reported AEs were somnolence and fatigue. The incidence of somnolence and fatigue was less after treatment with risperidone compared to quetiapine. There were no SAEs or deaths reported in this study, and no subjects discontinued due to an AE.

Conclusions

There were significant statistical differences between the two treatments on postdose NCS. The treatment differences were robust at the two earlier postdose time points and less marked at the final postdose assessment. The overall pattern of scores suggest that NCS remained relatively unchanged after a single risperidone dose, while the NCS appeared to worsen at early postdose time points after quetiapine dosing.

There were significant differences between treatments in the Processing Speed domain. The numeric changes within treatment revealed a trend for increased processing speed at all time points after dosing with risperidone, while processing speed deteriorated in the earlier time points following quetiapine dosing and returned to the baseline level by the second p.m. time point. There were significant differences between treatments in the Attention domain with a similar pattern of change over time as found on the Processing Speed domain. There were significant overall between-treatment differences in the Working Memory and Declarative Memory domains. There were no statistically significant between-treatment differences for the Executive Function domain.

VAS Fatigue subscale scores were significantly different between treatments at earlier postdose time points. Subjects experienced more fatigue following quetiapine dosing than after risperidone dosing at the first and second postdose time points. There were significant between-treatment differences on VAS Vigor subscale scores at the earlier postdose time points. VAS Vigor subscale scores were reduced to a greater degree following quetiapine dosing at the earlier time points.

Cross-sectional correlations between cognitive and subjective measures were inconsistent. Change score correlations showed decreases in cognitive scores being occasionally related to expected increases in fatigue and decreases in vigor.

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