CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor/Company: **Janssen Ortho Inc. Canada**

Name of Finished Product: **Risperdal* Consta***

Name of Active Ingredient: **risperidone**

Protocol No.: CR005959

Title of Study: An open-label randomized trial comparing Risperdal* Consta* with oral antipsychotic care in the treatment of early psychosis

Principal Investigator: not applicable

Publication (reference): not applicable

Study Period: 2 years
date of first subject enrolment: 26-Oct-2004
date of last completed visit: 23-Dec-2008

Phase of development: IV

Objectives:
This exploratory study will evaluate the effectiveness, safety and tolerability Risperdal* Consta* in subjects with recent onset psychosis. The impact of therapy on positive, negative, and general symptoms of schizophrenia, schizophreniform disorder and schizoaffective disorder, cognitive deficits associated with schizophrenia, comorbid depressive and anxiety symptoms, functional outcome, overall severity of the illness and relapse rates will be explored. The safety and tolerability of Risperdal* Consta* will be assessed.

Methodology:
This was a 24 month, open-label, 2-arm randomized exploratory study. Eighty-five subjects with early onset (≤3 years) DSM-IV diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder were randomized to either risperidone long acting injectable (RLAI) injections every 2 weeks or continuation therapy with the subject's current oral atypical antipsychotic (risperidone, olanzapine or quetiapine).

44 subjects were enrolled in the risperidone LAI arm, and 41 patients were enrolled in the oral antipsychotic arm. However patient 9002 in the Oral group withdrew consent at baseline. Study assessment visits were conducted every 4 weeks from Visit 3 to Visit 8 (Week 22), then one visit after 6 weeks (Visit 9, Week 28), then every 12 weeks until Visit 14 (Week 88) and a final visit at Week 104.

The study began with an 18 week stabilization phase which was followed by an 82 week maintenance phase for both arms. Subjects stable within 18 weeks of baseline were eligible to continue in the trial in the maintenance phase. Subjects not stable at Week 18 were withdrawn from the study. Interim analyses were performed twice, one at the end of the stabilization phase when the last subject had entered the maintenance phase, and one when approximately 40 subjects had completed Year 1. Subjects on Risperdal* Consta* (RLAI) visited the clinic every 2 weeks throughout the trial to receive Risperdal* Consta* injection.

Number of patients (planned and analyzed): 85 patients planned, 85 patients analyzed for safety, and 77 patients analyzed for intent to treat. In this protocol, intent-to-treat is defined as "subjects who had received at least 3 injections of RISPERDAL* CONSTA* or 6 weeks of oral antipsychotic treatment and had at least one post baseline efficacy assessment".

Diagnosis and main criteria for inclusion:
In-patients or outpatients aged 18-30 with a diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder for no longer than 3 years.
Subjects must satisfy the following criteria to be enrolled in the study:

- Male or female inpatients or out-patients
- Age between 18 and 30 years, inclusive

- Primary DSM-IV diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder for no longer than 3 years after diagnosis and treatment of a psychotic illness
- PANSS score of 60-120 at the Visits 1 and 2
- Currently on monotherapy atypical antipsychotic treatment below the maximum daily CPS guidelines (risperidone 6 mg, olanzapine 20 mg, quetiapine 800 mg) or treatment naïve
- Female subjects must be surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; have a negative urine pregnancy test study entry
- Subjects (or their legally acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study
- Able to complete self-assessments in either English or French
- Subjects with a primary DSM-IV diagnosis of schizoaffective disorder are permitted one mood stabilizer (of which lithium is included) provided they have been on a stable dose for at least 4 weeks prior to screening and are expected to continue on the same medication/dose throughout the stabilization period.
- Subjects with a secondary DSM-IV diagnosis of major depressive disorder are permitted entry provided they are on one antidepressant of stable dose for 4 weeks prior to screening and are expected to continue on the same medication/dose throughout the stabilization period.

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

- Current primary Axis-1 diagnosis other than schizophrenia, schizophreniform disorder or schizoaffective disorder, according to DSM-IV (with the exception of secondary diagnosis of major depressive disorder as described under inclusion criteria.
- Current drug or alcohol dependence
- Treatment with a depot antipsychotic within 3 months of study start
- Confirmed or suspected history of lack of tolerability, hypersensitivity or allergy to risperidone
- Risperidone non-responders (based on evidence of adequate trial of treatment: minimum of 6 weeks of treatment on a maximum dose of 6 mg)
- Subjects who have failed to respond to 2 or more adequate treatment trials of antipsychotics (an adequate trial is defined as 6 weeks of treatment on the maximum CPS dose of the antipsychotic)
- Laboratory abnormality that is deemed clinically significant by the investigator
- Serious, unstable and untreated medical illnesses: vascular or cardiovascular disease, history of liver or renal insufficiency, significant cardiac, pulmonary, gastrointestinal, endocrine, neurological or metabolic disturbances
- Subjects at significant risk of suicide or violence at study start
- Previous treatment with ECT
- Have received an experimental drug or used an experimental medical device within 30 days before the planned start of treatment.
- Female subject who is pregnant or breastfeeding
- Previous treatment with clozapine
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.
- Current treatment with carbamazepine

Test product, dose and mode of administration:
Risperidone long acting injection, 25-50 mg i.m. injection every 2 weeks. Subjects randomized to Risperdal* Consta* received 3 weeks of supplementation with their current oral medication in addition to the initial 25 mg Risperdal* Consta* injection. During the stabilization phase, the dose of Risperdal* Consta* could be increased by increments of 12.5 mg, after a minimum of 6 weeks (3 injections) at the previous dose, to a maximum dose of 50 mg, if the subject meets the following criteria: has a CGI-S score of > 4 (moderately ill or worse) and a CGI-C score of > 4 (no change or worse). During the maintenance phase, the dosage could be increased by the same increments if the subject experienced a worsening of psychotic symptoms (defined as a 25% increase in the total PANSS score, or a 20% increase in the psychosis subscale of the PANSS) to a maximum dose of 50 mg. Dose reduction was permitted if a previous increase did not result in the anticipated improvement. The minimum dose of Risperdal* Consta* was 25 mg.

Duration of treatment: 24 months

Reference therapy, dose and mode of administration:
Oral antipsychotic (risperidone, quetiapine, olanzapine), as per local label. Medication was administered daily for the duration of the study (24 months). Subjects randomized to the oral antipsychotic arm remained on their current antipsychotic and followed the same CGI parameters in the stabilization phase and PANSS parameters in the maintenance phase as the Risperdal* Consta* group for dose increases or decreases.

Criteria for evaluation:

Efficacy:

This was an exploratory study that was not powered to detect difference either within or between study arms. The protocol specified the following comparisons for each of the continuous efficacy variables: analyses performed on the change from baseline score at each visit and at endpoint. Analysis was also performed on the change from the start of the maintenance period to each following visit and at endpoint.

Primary Evaluations:

- Total symptoms, as assessed by the PANSS
- Time to relapse, defining relapse as per Csernansky (2002)
- Social, occupational and functional outcome

Secondary evaluations:

- Co-morbid depressive symptoms, as measured by the change in CDSS score from baseline to endpoint
- Co-morbid symptoms of mania, as measured by the change in YMRS score from baseline to endpoint
- Co-morbid symptoms of anxiety, as measured by the HAM-A score from baseline to endpoint
- Relapse Rates
- Cognitive assessments, Trails A and B, and the COWAT Verbal Fluency Test
- Drug Attitude Inventory
- SF-36

Safety:
Safety was assessed by physical examination, weight, body mass index, waist circumference, vital sign measurements, clinical laboratory tests (fasting), measurement of prolactin and the monitoring of adverse events. Potential adverse effects related to the medication were monitored using the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS), and the Abnormal Involuntary Movement Scale (AIMS).

Statistical Methods:
This was an exploratory study; no formal sample size calculations were performed. All randomized subjects were included in the analysis of safety, demographic, and baseline characteristic data. For exploratory efficacy outcomes, the main analysis was defined per protocol to include all subjects who had received at least 3 injections of risperidone LAI or 6 weeks of oral antipsychotic treatment and had at least one post baseline efficacy assessment.

For each continuous efficacy variable, the change from the screening/baseline score and the change from the beginning of the maintenance phase were summarized using descriptive statistics by group at each visit and at endpoint. Intergroup mean differences were also presented with the 95% confidence intervals. Between group differences in time from start of maintenance treatment to relapse were analyzed using a Cox proportional hazards model. An estimate of hazard ratio between the treatment groups and its 95% confidence interval were calculated. For each group, Kaplan-Meier estimate of risk (probability) of relapse and 95% confidence interval at the end of the trial were calculated.

Adverse events were summarized by the type and incidence of adverse events over the entire trial period. For vital signs and clinical laboratory variables, data were summarized. Changes from baseline results for the SAS, BARS and AIMS to each visit were summarized by group with descriptive statistics. Intergroup differences were also presented with 95% confidence intervals.

SUMMARY – CONCLUSIONS

EFFICACY SUMMARY

Primary Evaluations:

- There were no statistically or clinically significant differences in PANSS scores (positive, negative, composite, general, total, positive symptoms factor, negative symptoms factor, disorganized thoughts, uncontrolled hostility/excitement, anxiety/depression), from baseline to endpoint, between the risperidone LAI and oral antipsychotic arms(treatment difference p-value based on ANOVA test with treatment as main factor). The study was not powered to detect differences.

- Statistically significant improvement was seen from baseline to endpoint within both treatment arms for PANSS: positive score, negative score, general score, total score, positive symptoms factor, negative symptoms factor, disorganized thoughts factor, and anxiety depression factor.

- The mean time to relapse for RLAI was 80.5 weeks and for Oral was 79.5 weeks. P-value 0.1125.

- There were no significant differences in social, occupational and functional outcomes between the risperidone LAI and oral antipsychotic treatment groups at baseline or at endpoint.

Secondary evaluations:

- There were no significant differences in CDSS, YMRS HAM-A, Trails A and B, the COWAT, the Drug Attitude Inventory or the SF-36, between the risperidone LAI and oral antipsychotic groups at baseline or at endpoint, or from baseline to endpoint between groups.

SAFETY RESULTS

From twelve Canadian centres, 101 patients were screened and 85 were randomized. Safety was evaluated in all 85 randomized patients: 44 (51.8%) were randomized to risperidone LAI and 41 (48.2%) were randomized to oral antipsychotic therapy.

In the Risperdal* Consta* treatment arm, 39 subjects (89%) experienced at least 1 treatment emergent adverse event (AE). In the oral antipsychotic arm, 35 subjects (85%) experienced at least 1 treatment emergent adverse event (AE). 32 subjects (73%) on risperidone LAI and 21subjects (51%) on oral APs experience AEs that were deemed related to study medication.

Five subjects in the risperidone LAI arm withdrew because of an adverse event. These AEs were: akathisia, alcoholism, erectile dysfunction and insomnia.

In the risperidone LAI treatment arm, 2 subjects (4.5%) experienced a treatment-emergent serious adverse event (SAE). In oral arm, 3 subjects (7.3%) experienced a treatment-emergent SAE. None of the serious AEs in the risperidone LAI or oral arms was related to the study treatment.

Most frequently reported adverse events (in at least 5% of the subjects in either treatment arm) are presented in Table 4.

A total of 6 SAEs were reported and each event was reported once. In the RLAI group 2 subjects experienced an SAE, one was alcoholism; the second showed depression and suicidal ideation. In the oral group, three patients had SAES; skin laceration, thrombocytopenia and nausea/vomiting. No deaths were reported during the study.

Mean body weight was 80.8 and 83.7 kg at baseline, and 83.5 and 87.3 kg at endpoint in the risperidone LAI and oral arm respectively. 20 subjects (47.6%) experienced weight gain >/= 7% on risperidone LAI, and 17(48.6%) experienced weight gain >/= 7% in the oral antipsychotic arm..There were no statistically significant differences between treatment arms in changes in body weight, waist circumference or BMI. Body weight increased 3.9 kg (sd 10.42) in the RLAI arm (from baseline to last visit) and 5.8 kg (sd 10.98) in the oral arm. Waist circumference increased in both arms from baseline to last visit: 4.8 cm (sd 7.46) in the RLAI arm and 6.1 cm (sd 8.00 cm) in the oral arm.

There were no statistically significant differences between or within treatment arms for Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) or Simpson–Angus Scale (SAS).

The study was not powered to detect differences in adverse event profile.

EFFICACY RESULTS

101 patients were screened at 12 Canadian centers; 85 of these subjects were randomized. The primary efficacy analysis included 77 patients who received at least three doses of risperidone LAI (n = 42; 54.5%) or six weeks of oral antipsychotic therapy (n = 35; 45.4 %), in addition to having at least one post-baseline efficacy assessment. The risperidone LAI and oral antipsychotic groups had similar baseline demographics and clinical characteristics as shown in Table 1. All patients, except one, received antipsychotic monotherapy prior to being randomized. Eight patients with active drug or alcohol abuse (2 in the LAI arm and 6 in the oral arm) were included in the ITT group.

There were no statistically differences in mean PANSS scores between the risperidone LAI and oral antipsychotic group at stabilization or last reported visit. Similar proportions of patients achieved stabilization in the risperidone LAI and the antipsychotic group 76.27% (32/42) versus 88.6% (31/44) oral antipsychotic group, p=0.1607). The number of weeks to stabilization was 11.7 in both the risperidone LAI and oral antipsychotic groups, (p=0.7870). Of the 63 patients who entered the maintenance phase of the study, 34.4% (11/32) risperidone LAI and 16.1% (5/31) oral antipsychotic patients relapsed, although the study was not powered to show a difference between these values. The mean time to relapse for risperidone LAI was 80.5 weeks and 79.5 weeks for the orals (p-value 0.1125).

The most common reason for relapse in both groups was psychiatric hospitalization. There were no differences in mean CGI-S Severity of Illness or mean Social and Functioning Assessment (SOFA) score between the risperidone LAI and oral antipsychotic groups at stabilization visit or last reported visit. Similarly, there were no statistically significant differences between the two groups at stabilization or last reported visit for CGI-S, CDSS, YMRS, HAM-A, SF-36, DAI-10, and the other cognitive assessment scores. This exploratory study collected the number of emergency room, hospital, and GP/walk-in clinic visits during the past month and found no differences in total number of visits reported during the study period for each group. Similar proportions of stabilized risperidone LAI versus oral antipsychotic patients did not complete the study 17/32 (53.1%) versus 16/31(51.6%), respectively. However, non-compliance contributed to the discontinuation of 17.6% (3/17) of stabilized risperidone LAI patients versus 50.0% (8/16) of stabilized oral antipsychotic patients.

CONCLUSION:
This 24-month Canadian study explored the effectiveness, safety, tolerability, and resource utilization between risperidone LAI and oral antipsychotics in recent onset psychosis. No new or additional safety signals were observed in this study.

Date of this report: 4 April 2011

Table 1

Demographic and Clinical Characteristics at Baseline
ITT Population

	RISPERDAL CONSTA (N=42)	**Oral anti-psychotic (N=35)**	**P value**
Gender, N (%) Male Female	 33 (78.6) 9 (21.4)	 32 (91.4) 3(8.6)	
Race, N (%) White Black Asian Aboriginal Other	 34 (81.0) 4 (9.5) 1 (2.4) 1 (2.4) 2 (4.8)	 26 (74.3) 4 (11.4) 2 (5.7) 1 (2.9) 2 (5.7)	
Age, mean (SD), years	22.5 (3.12)	23.0 (2.93)	P=0.4090
Years since onset of symptoms, mean (SD)	2.1 (2.07)	2.2 (1.71)	P=0.7357
Years since beginning of treatment, mean (SD)	1.3 (1.02)	1.5 (1.52)	P=0.4578
Years since diagnosis	0.8 (0.79)	1.0 (0.97)	P=0.2570
DSM-IV Diagnosis, N (%) Schizophrenia Schizoaffective Schizophreniform	 36 (85.7) 4 (9.5) 2 (4.8)	 33 (94.3) 1 (2.9) 1 (2.9)	
Patients with other psychiatric history, N (%)	23 (54.8)	25 (71.4)	
PANSS positive score, mean (SD)	18.1 (4.52)	18.1 (4.06)	P=0.9885
PANSS negative score, mean (SD)	22.5 (6.40)	22.6 (6.33)	P=0.9558
PANSS composite score, mean (SD)	-4.5 (8.41)	-4.5 (8.38)	P=0.9724
PANSS general score, mean (SD)	40.0 (6.23)	39.0 (6.88)	P=0.5260
PANSS total score, mean (SD)	80.6 (12.22)	79.7 (12.47)	P=0.7622
PANSS positive symptoms factor, mean (SD)	23.4 (5.56)	22.9 (5.02)	P=0.6684
PANSS negative symptoms factor, mean (SD)	22.5 (6.27)	22.1 (5.61)	P=0.7762
PANSS disorganized thoughts factor, mean (SD)	18.3 (3.90)	18.7 (5.58)	P=0.7297
PANSS uncontrolled hostility/excitement, mean (SD)	6.5 (2.15)	6.5 (1.90)	P=0.9919
PANSS anxiety/depression factor, mean (SD)	10.0 (3.23)	9.6 (2.46)	P=0.6280
CGI-Severity, N (%) Mild Moderate Marked Severe	 5.0 (11.9) 22.0 (52.4) 13.0 (31.0) 2.0 (4.8)	 7.0 (20.0) 17.0 (48.6) 7.0 (20.0) 4.0 (11.4)	
Hamilton Anxiety Total Score, mean (SD)	7.2 (5.94)	7.3 (4.66)	P=0.9235
Social and Functioning Assessment Score, mean (SD)	53.4 (11.23)	49.5 (12.93)	P=0.1643
Number on long term disability	11 (26.2%)	9 (25.7%)	
Number on short term disability	3 (7.1%)	3 (8.6%)	

Table 2

Study Completion/Discontinuation Information
ITT Population

	RLAI N= 42		Oral N= 35		ALL N= 77*	
	n	%	n	%	n	%
Randomized?						
Yes	42	100.0	35	100.0	77	100.0
Completed if Randomized?						
No	26	61.9	20	57.1	46	59.7
Yes	16	38.1	15	42.9	31	40.3
Reasons for Termination if Randomized						
Subject withdrew consent	5	19.2	1	5.0	6	13.0
Lost to follow-up	3	11.5	4	20.0	7	15.2
Adverse event	5	19.2			5	10.9
Investigator withdrew subject	2	7.7			2	4.3
Lack of efficacy	2	7.7	2	10.0	4	8.7
Subject non-compliant	4	15.4	9	45.0	13	28.3
Not stable by Week 18	2	7.7	1	5.0	3	6.5
Other reason	3	11.5	3	15.0	6	13.0
Mood Stabilisation?						
No	10	23.8	4	11.4	14	18.2
Yes	32	76.2	31	88.6	63	81.8

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

* 85 subjects were randomized. 77 patients met the pre-determined ITT definition.

TABLE 3
PANSS scores change from baseline to last reported visit

Change from Baseline to Last Reported Visit		n	missing	Mean	SD	pvalue within	Diff	Low 95% CL	Upp 95% CL	pvalue between
PANSS Positive Score	**CONSTA**	42	0	-5.0	5.32	<.0001	-0.5	-2.7	1.6	0.6369
	Oral	34	1	-4.5	4.32	<.0001				
PANSS Negative Score	**RLAI**	42	0	-5.3	7.63	<.0001	-0.0	-3.0	2.9	0.9829
	Oral	34	1	-5.4	6.51	<.0001				
PANSS Composite Score	**RLAI**	42	0	0.3	7.15	0.7641	-0.5	-2.8	1.8	0.6796
	Oral	34	1	0.9	6.45	0.4012				
PANSS General Score	**RLAI**	42	0	-7.9	12.49	0.0002	0.3	-4.5	5.1	0.8917
	Oral	34	1	-7.9	8.27	<.0001				
PANSS Total Score	**RLAI**	42	0	-18.1	22.48	<.0001	-0.3	-9.3	8.8	0.9549
	Oral	34	1	-17.7	16.45	<.0001				
PANSS Positive Symptoms Factor	**RLAI**	42	0	-6.1	7.17	<.0001	-0.6	-3.5	2.2	0.6608
	Oral	34	1	-5.4	5.49	<.0001				
PANSS Negative Symptoms Factor	**RLAI**	42	0	-6.2	8.42	<.0001	-0.3	-3.4	2.7	0.8314
	Oral	34	1	-5.7	6.60	<.0001				
PANSS Disorganized Thoughts Factor	**RLAI**	42	0	-3.8	5.70	<.0001	0.4	-2.0	2.8	0.7490
	Oral	34	1	-4.3	4.76	<.0001				
PANSS Positive Uncontrolled Hostility/Excitement Factor	**RLAI**	42	0	-0.5	2.68	0.2124	0.3	-0.8	1.4	0.5391
	Oral	34	1	-0.9	2.68	0.0555				
PANSS Anxiety/Depression Factor	**RLAI**	42	0	-1.5	3.70	0.0149	0.2	-1.1	1.5	0.7982
	Oral	34	1	-1.4	2.50	0.0020				

Table 4

Adverse Events (>5% in any treatment group)
by System Organ Class and Preferred Term
All Randomized Subjects

		RLAI N= 44			Oral N= 41*		
MedDRA System Organ Class Term	**MedDRA Preferred Term**	**N**	**%**	**# of Events**	**n**	**%**	**# of Events**
CARDIAC DISORDERS	PALPITATIONS	2	4.55	2	1	2.44	1
EYE DISORDERS	VISION BLURRED	1	2.27	1	2	4.88	2
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	1	2.27	1	3	7.32	4
	ABDOMINAL PAIN UPPER	1	2.27	1	2	4.88	
	DYSPEPSIA	2	4.55	2	1	2.44	1
	NAUSEA	6	13.64	9	3	7.32	3
	STOMACH DISCOMFORT	2	4.55	2			
	VOMITING	3	6.82	9	3	7.32	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	11	25.00	17	5	12.20	5
INFECTIONS AND INFESTATIONS	BRONCHITIS	2	4.55	2	3	7.32	3
	EAR INFECTION				2	4.88	2
	GASTROENTERITIS VIRAL	2	4.55	2	1	2.44	3
	INFLUENZA	2	4.55	4	2	4.88	2
	NASOPHARYNGITIS	9	20.45	12	7	17.07	10
	SINUSITIS	2	4.55	2	2	4.88	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	HAND FRACTURE	1	2.27	2	2	4.88	2
INVESTIGATIONS	BLOOD CHOLESTEROL INCREASED	1	2.27	1	2	4.88	2
	BLOOD PROLACTIN INCREASED	5	11.36	5			
	BLOOD TRIGLYCERIDES INCREASED	2	4.55	2	3	7.32	3
	WEIGHT DECREASED				2	4.88	2
	WEIGHT INCREASED	10	22.73	12	7	17.07	7
METABOLISM AND NUTRITION DISORDERS	INCREASED APPETITE	2	4.55	2	1	2.44	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	4	9.09	5			
	BACK PAIN	3	6.82	6	4	9.76	5
	MUSCLE SPASMS	5	11.36	5			
	MYALGIA	3	6.82	4	1	2.44	1
	NECK PAIN	1	2.27	1	2	4.88	2
	PAIN IN EXTREMITY	1	2.27	1	2	4.88	2

		RLAI N= 44			Oral N= 41*		
MedDRA System Organ Class Term	**MedDRA Preferred Term**	**n**	**%**	**# of Events**	**n**	**%**	**# of Events**
	PAIN IN JAW				1	2.44	1
NERVOUS SYSTEM DISORDERS	AKATHISIA	2	4.55	3	3	7.32	3
	DIZZINESS	8	18.18	12	5	12.20	5
	DYSKINESIA	1	2.27	1	3	7.32	3
	HEADACHE	15	34.09	21	5	12.20	9
	LETHARGY	2	4.55	2			
	PARAESTHESIA	2	4.55	2			
	SOMNOLENCE	3	6.82	3	3	7.32	4
	TREMOR	3	6.82	3	1	2.44	1
PSYCHIATRIC DISORDERS	AGGRESSION				2	4.88	2
	AGITATION	3	6.82	4			
	ANXIETY	6	13.64	10	4	9.76	8
	DEPRESSION	4	9.09	5	3	7.32	3
	DEPRESSIVE SYMPTOM	2	4.55	3			
	HALLUCINATION	2	4.55	2	1	2.44	1
	INSOMNIA	13	29.55	29	7	17.07	7
	PSYCHOTIC DISORDER	4	9.09	9	4	9.76	9
	RESTLESSNESS	1	2.27	1	2	4.88	2
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	AMENORRHOEA	5	11.36	5			
	ERECTILE DYSFUNCTION	2	4.55	2	1	2.44	1
	GALACTORRHOEA	2	4.55	2	1	2.44	1
	GYNAECOMASTIA	2	4.55	2	2	4.88	2
	SEXUAL DYSFUNCTION	2	4.55	2			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	3	6.82	4	2	4.88	2
	NASAL CONGESTION	3	6.82	4	2	4.88	2
	RHINORRHOEA	2	4.55	2	1	2.44	1
	UPPER RESPIRATORY TRACT CONGESTION	2	4.55	3			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ACNE	2	4.55	2	3	7.32	4
	PRURITUS	2	4.55	2			
	RASH	1	2.27	1	2	4.88	2

* This number (N=41) represents entire study population including the subject who was randomized but withdrew consent prior to receiving study.

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