1 SYNOPSIS

Trial Identification

Company:	Janssen Medical Affairs, L.L.C.		
Finished product:	RISPERDAL® CONSTA™		
Active ingredient:	R064766		
Title:	**Schizophrenia Treatment Acceptance Response Trial: A 20-week, open-label, multi-center, randomized study comparing the effect of the GAIN Acceptance Approach with approach-as-usual in supporting patient acceptance of long-acting risperidone (RISPERDAL® CONSTA™) in adults with schizophrenia**	**Trial No:** **Clinical Phase:**	RIS-SCH-404 IV
Investigators:	137 Investigators; see Appendix 16.1.4 for a complete list.	**Country:**	United States
Reference:	N/A		

Trial Period:	**Start:**	05 December 2003	**No. investigators:**	137
	End:	16 October 2004	**No. patients entered the Approach Phase:**	650
			No. patients entered the Treatment Phase:	572

Protocol Summary

Indication / objectives:	The primary objective of this trial was to demonstrate the effectiveness of the GAIN Acceptance Approach as a method for supporting patient acceptance of RISPERDAL® CONSTA™ therapy in patients with schizophrenia transitioned from oral antipsychotics to RISPERDAL® CONSTA™ (25, 37.5, or 50 mg administered every two weeks). Secondary objectives included evaluation of the following: adherence rate of RISPERDAL® CONSTA™ therapy; clinician-rated changes in patient disease severity in individuals treated with RISPERDAL® CONSTA™; clinician attitudes regarding the GAIN Acceptance Approach, including its manual and training; and patient and clinician satisfaction with RISPERDAL® CONSTA™ therapy.
Trial design:	This was a 20-week, prospective, site-randomized, multi-center study to compare the effect of the GAIN Acceptance Approach with Approach-as-Usual (AAU) in supporting patient acceptance of long-acting risperidone (RISPERDAL® CONSTA™) in adults with schizophrenia. Each site participating in this trial was randomized to receive either training on the GAIN Acceptance Approach or to receive no specific training (approach-as-usual [AAU]). The study consisted of a two-week Screening Phase, a six-week Approach Phase, and a 12-week Treatment Phase. During the Screening Phase, patients provided informed consent for the Approach Phase of the study, specifically indicating interest in being approached about a new treatment for psychiatric illness and involved in testing an approach to discuss treatment options with patients. After Informed Consent for Approach was

	signed, scheduled assessments were performed, and patients meeting entry criteria entered the Approach Phase. The Approach Phase consisted of three visits conducted every two weeks, resulting in a patient decision regarding acceptance of RISPERDAL® CONSTA™ therapy. During this phase, patients were exposed to an approach representative of either usual care or the GAIN Acceptance Approach (only at sites randomized to the GAIN Acceptance Approach). Patients in both groups received the same level of care. All patients continued on their current medication regimen, including oral antipsychotics, during this phase. The Treatment Phase consisted of seven visits over a period of 12 weeks, during which RISPERDAL® CONSTA™ was administered every two weeks. Patients received their first dose of RISPERDAL® CONSTA™ at Visit T1 (Week 6), after Informed Consent for Treatment was obtained and inclusion/exclusion criteria were verified, and returned for study drug administration every two weeks thereafter with final administration occurring at Visit T6 (Week 16). All patients continued their oral antipsychotic regimen for the first three weeks of treatment, concurrent with RISPERDAL® CONSTA™ administration. After the third week of treatment, one week following the second RISPERDAL® CONSTA™ injection, oral antipsychotics were discontinued. After 12 weeks of treatment, or upon study drug discontinuation, patients completed treatment attitude and satisfaction questionnaires. Clinician attitudes regarding RISPERDAL® CONSTA™ were also assessed through the use of a Clinician Attitude/Satisfaction Summary administered after all patients at a particular site completed the study. Following study completion, training on the GAIN Acceptance Approach was offered to all sites.
Main selection criteria:	The study population consisted of patients 18 to 70 years of age having schizophrenia (Disorganized, Catatonic, Paranoid, Residual, or Undifferentiated) meeting DSM-IV disease diagnostic criteria (295.10, 295.20, 295.30, 295.60, or 295.90). Patients indicated the long-term use of an oral antipsychotic medication ('typical' or 'atypical', except clozapine) at a stable dose for four weeks prior to Screening (monotherapy or combination therapy). Patients were medically stable with no evidence of clinically significant or unstable cardiovascular, renal, hepatic, gastrointestinal, neurological, endocrine, metabolic, or pulmonary disease over the six months prior to Screening. Female patients of childbearing potential were hysterectomized, had bilateral tubal ligation, were two years post-menopausal, or agreed to use adequate contraception during the study. Patients (or authorized legal representative) were required to understand the nature of the study and provide written informed consent.

Treatment

Form – dosing route:	Patients entering the Treatment phase of the study received RISPERDAL® CONSTA™ administered via intramuscular injection.
Batch numbers:	RISPERDAL® CONSTA™ 25 mg: 4DA607 RISPERDAL® CONSTA™ 37.5 mg: 3NA380 RISPERDAL® CONSTA™ 50 mg: 3NA381
Dosage:	Patients entering the Treatment phase of the study initiated RISPERDAL® CONSTA™ at 25 mg; patients on higher-than-average oral antipsychotic doses could be considered for a 37.5 mg starting dose. RISPERDAL® CONSTA™ was subsequently given at this initiation dose every two weeks, with changes in dose to either 37.5 or 50 mg according to clinical need. A minimum of four weeks was required between dose increases. Dose decreases could be instituted as clinically indicated.
Duration of treatment:	The Treatment Phase consisted of seven visits over a 12-week period during which RISPERDAL® CONSTA™ was administered every two weeks for a total of six injections.
Disallowed medication:	Patients treated with depot antipsychotics within six months of Baseline or who were currently being treated with clozapine were not eligible for participation in the study. Patients discontinued their oral antipsychotic medication following the third week of the Treatment Phase.

Assessments

Efficacy • Primary variable	The primary outcome measure was the percentage of patients accepting RISPERDAL® CONSTA™ therapy at sites randomized to use of the GAIN Acceptance Approach compared to sites using an AAU method.
• Secondary variables	Secondary endpoints included adherence rate of RISPERDAL® CONSTA™ therapy, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C), Patient Attitude and Satisfaction Summary (PASS).
Safety • Adverse events • Health assessments	The safety assessments conducted during this study included the regular monitoring and recording of all treatment-emergent adverse events (AEs) and serious adverse events (SAEs), and the performance of health assessments prior to study entry and at the final visit. There were no clinical laboratory assessments performed.

Statistical methods:	Primary and secondary efficacy data were analyzed using Generalized Estimating Equation (GEE) methodology, which was executed using a generalized linear model with an exchangeable correlation structure for patients within a site. The model included factors of group and site within group. The exchangeable correlation structure was employed because it was assumed that each subject within a specific site was exchangeable with all other subjects at that same site. For dichotomous data, a binomial distribution with a logit link function was used. For categorical data, a binomial distribution with a cumulative logit link function was used. For ordered categorical data, a Poisson distribution with a log link function was used. For continuous data, a normal distribution with the identity link function was used. Two different patient populations were utilized for the statistical analyses. The Approach Phase population was defined as all patients who signed informed consent to be enrolled into the Approach Phase and received either the GAIN Acceptance Approach or AAU, whether or not safety data were recorded. The Approach Phase population was used to analyze patient acceptance to RISPERDAL® CONSTA™ therapy. The Intent-to-Treat (ITT) population was defined as all patients who signed informed consent to be enrolled into the Treatment Phase and received at least one injection of RISPERDAL® CONSTA™. The ITT population was used to analyze patient adherence to RISPERDAL® CONSTA™ therapy as well as other secondary endpoints.

Main features of the subject sample and summary of the results

	GAIN Acceptance Approach	Approach-as-Usual
No. of sites randomized	60	77
No. of subjects entering Approach phase	261	389
Age (years), mean (SD)	41.3 (13.06)	42.2 (12.52)
Gender n (%) male	149 (57.3%)	255 (65.9%)
Race n (%)		
Caucasian	162 (62.1%)	209 (54.0%)
Black	70 (26.8%)	135 (34.9%)
Hispanic	17 (6.5%)	29 (7.5%)
Other	12 (4.5%)	14 (3.7%)
Age of initial diagnosis		
Median (Min, Max)	23 (5, 67)	23 (4, 62)
CGI – Severity n (%)		
Normal	1 (0.4%)	3 (0.8%)
Borderline ill	4 (1.5%)	17 (4.4%)
Mildly ill	35 (13.4%)	53 (13.7%)
Moderately ill	114 (43.7%)	166 (43.0%)
Markedly ill	67 (25.7%)	90 (23.3%)
Severely ill	35 (13.4%)	43 (11.1%)
Most severely ill	5 (1.9%)	14 (3.6%)
No. of subjects entering Treatment phase (ITT population)	235	337
No. (%) completing Treatment phase	163 (69.4%)	250 (74.2%)
No. (%) discontinued	72 (30.6%)	87 (25.8%)
Reason for discontinuation of treatment:		
• Lost to follow-up	21 (29.6%)	21 (24.1%)
• Withdrawal of consent	7 (9.9%)	22 (25.3%)
• Other reason	14 (19.7%)	16 (18.4%)
• Adverse event	9 (12.7%)	7 (8.0%)
• Worsening of psychiatric illness	7 (9.9%)	9 (10.3%)
• Patient refused Treatment Phase	6 (8.5%)	9 (10.3%)
• Protocol Violation	4 (5.6%)	1 (1.1%)
• Investigator Decision	3 (4.2%)	2 (2.3%)
• Missing	1	0

The two Approach groups had similar demographic and baseline characteristics. The discontinuation rates were comparable between the Approach groups. Higher percentage of patients in the AAU Approach discontinued treatment due to withdrawal of consent than patients in the GAIN Approach (25.3% versus 9.9%).

Efficacy	GAIN Acceptance Approach	Approach-as-Usual
Primary Variable		
The acceptance rate of RISPERDAL® CONSTA™ therapy (95% CI)	88.5% (82.8%, 92.5%)	85.0% (78.8%, 89.7%)
Secondary Variables		
The adherence rate of RISPERDAL® CONSTA™ therapy (95% CI)	68.7% (61.5%, 75.1%)	73.9% (66.9%, 79.9%)
CGI – Severity, mean (95% CI) Baseline Endpoint	 4.4 (4.22, 4.56) 3.4 (3.15, 3.59)	 4.4 (4.19, 4.59) 3.6 (3.40, 3.87)
CGI – Change, mean (95% CI)	2.6 (2.37, 2.81)	2.8 (2.62, 3.00)
Patient Satisfaction, mean (95% CI) Oral antipsychotic RISPERDAL® CONSTA™	 4.2 (3.91, 4.46) 5.0 (4.77, 5.22)	 4.4 (4.19, 4.59) 5.1 (4.90, 5.33)

There was no statistical difference in the acceptance rates between patients assigned to the GAIN Approach and the AAU Approach. Both Approach groups exhibited much higher acceptance rates than what is typically seen for this indication in this patient population.

Of patients who accepted and were treated with RISPERDAL® CONSTA™, similar adherence rates were seen between the Approach groups. The adherence rates were much higher than the rates typically reported for oral antipsychotic medications in the same patient population.

Among the other secondary measures, patients in both Approach groups showed significant improvement in CGI-S and CGI-C scores relative to their baseline scores, and reported higher degree of satisfaction with RISPERDAL® CONSTA™, compared with previous oral antipsychotic treatment.

Adverse Events

System Organ Class – Preferred Term	GAIN Approach (N=235)	Approach-as-Usual (N=337)
Number of Patients with Adverse Events, n (%)	51 (21.7%)	83 (24.6%)
Gastrointestinal Disorders, n (%)	1 (0.4%)	7 (2.1%)
General Disorders and Administration Site Conditions, n (%) Injection site pain	5 (2.1%) 3 (1.3%)	12 (3.6%) 5 (1.5%)
Musculoskeletal and Connective Tissue Disorders, n (%)	2 (0.9%)	5 (1.5%)
Nervous System Disorders, n (%) Akathisia Extrapyramidal disorder Headache	11 (4.7%) 0 (0.0%) 3 (1.3%) 2 (0.9%)	21 (6.2%) 5 (1.5%) 2 (0.6%) 7 (2.1%)

Psychiatric Disorders, n (%)	27 (11.5%)	52 (15.4%)
Agitation	1 (0.4%)	4 (1.2%)
Anxiety	1 (0.4%)	7 (2.1%)
Depressed mood	5 (2.1%)	0 (0.0%)
Hallucination, auditory	2 (0.9%)	7 (2.1%)
Insomnia	1 (0.4%)	9 (2.7%)
Paranoia	1 (0.4%)	5 (1.5%)
Schizophrenia	14 (6.0%)	15 (4.5%)
Suicidal Ideation	1 (0.4%)	6 (1.8%)
Reproductive System and Breast Disorders, n (%)	2 (0.9%)	4 (1.2%)
Respiratory, Thoracic and Mediastinal Disorders, n (%)	5 (2.1%)	7 (2.1%)
Skin and Subcutaneous Tissue Disorders, n (%)	5 (2.1%)	3 (0.9%)

Note: Includes adverse events reported by >1% of patients which occurred between the date of first injection and the date of the last injection plus 49 days.

Clinical laboratory parameters	No clinical laboratory testing was performed.
Vital signs and physical findings	Vital signs measurements, physical examination findings, and ECG results were not collected during the study.

The incidence of AE was very low in this study, which is consistent with previous safety data suggesting that RISPERDAL® CONSTA™ was safe and well-tolerated with a very low incidence of AE.

Conclusions

The results of the present trial demonstrate that the GAIN Approach to treatment was well accepted by patients with schizophrenia. Patients who started treatment with RISPERDAL® CONSTA™ were likely to remain in treatment. Patients showed clinical improvement in CGI scores after treatment with RISPERDAL® CONSTA™, and reported higher degree of satisfaction with RISPERDAL® CONSTA™, compared with previous oral antipsychotic treatment. The difference seen in reason for discontinuation between the AAU and GAIN Approach groups in the percentage of patients withdrawing of consent may indicate that clinicians employing the GAIN Approach achieved a more enduring alliance with the patient, making it less likely for patients to withdrawal their consent during participation in the trial. The GAIN Approach was also very well accepted by clinicians, with over 90% of sites randomized to the GAIN Approach indicating that they would employ the GAIN method with current and future patients. In addition, the known safety profile of RISPERDAL® CONSTA™ was confirmed, and there were no new safety concerns identified during the study.

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