SYNOPTIC CLINICAL STUDY REPORT

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Name of Sponsor/Company	Janssen-Ortho Inc. Janssen-Cilag Ltd.
Name of Finished Product	Risperdal® Consta®
Name of Active Ingredient(s)	risperidone

Protocol No.: RIS-SCH-4055

Title of Study: Pragmatic randomized trial of Risperdal® CONSTA® versus oral atypical antipsychotics in poorly adherent subjects with schizophrenia in a routine care setting.

Principal Investigator: not applicable

Publications Based on the Study: none to date

Study Period: January 11, 2006 – April 30, 2009 [date of first study related procedure - date of last observation for last subject]

Phase of Development: IV

INTRODUCTION

This document presents the results of the final analysis for the Phase IV study: RIS-SCH-4005 "Pragmatic randomized trial of Risperdal® Consta® versus oral atypical antipsychotics in poorly adherent subjects with schizophrenia in a routine care setting" ([3]). Due to the low recruitment rate [Appendix 1] and the results of the second interim analysis [4] recruitment was terminated on June 24, 2008. The study was stopped due to futility with a last patient visit of April 30, 2009.

OBJECTIVES

The primary objective of this study was to determine whether Risperdal® Consta® provided improved effectiveness over a 2 year period, measured by the proportion of subjects who experience a clinical exacerbation, compared to oral atypical antipsychotics (risperidone, olanzapine, quetiapine, and where commercially available, aripiprazole and amisulpride) prescribed in a routine care setting for the long term treatment of subjects with schizophrenia

The secondary objectives were to evaluate effectiveness via: Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Severity and Change (CGI-S and CGI-C), Resource Utilization Questionnaire (RUQ), Assessment of Quality of Life (AQOL), Personal and Social Performance Scale (PSP), evaluation of symptomatic remission over time, proportion of clinical exacerbations for the entire

trial period, time to clinical exacerbation and the number of clinical exacerbations calculated at two time points: occurring up to 3 months and then from 3 months to the end of study. Safety and tolerability were also assessed.

METHODS

Approximately 244 subjects with DSM-IV TR diagnosis of schizophrenia currently treated with oral antipsychotic (AP) medication and meeting eligibility criteria were included. Patients must have had a minimum of 2 hospitalizations or 2 clinical exacerbations or 1 of each, over the past 2 years due to suspected deteriorating adherence. Subjects were then randomized to Risperdal® Consta® (CONSTA group) or to oral medication (Oral group) using stratification by PANSS scores of <= 80 and > 80 at randomization. Subjects who were on an existing atypical antipsychotic (AAP) and randomized to the oral medication arm could either a) continue with their existing AAP or b) switch to another atypical agent. Subjects on a conventional neuroleptic and randomized to oral medication had to be switched to an AAP of the investigator's choice.

Subjects on CONSTA were to visit the clinic every 2 weeks throughout the trial in order to receive the injection. To ensure maintenance of an adequate therapeutic level of antipsychotic, subjects switching from their current antipsychotic treatment could continue on their previous oral medication for the first 3 weeks following the initial injection of Risperdal* Consta*. The oral antipsychotic was discontinued or tapered to discontinuation. This 24-month study required a total of 6 assessment visits. The total treatment duration for all subjects was a maximum of 2 years.

The main goal of this study was to investigate whether Risperdal® Consta® (risperidone LAI) provided better efficacy maintenance over 2 years, as measured by the time to clinical exacerbation, in comparison to oral atypical antipsychotic therapy. For this assessment, clinical exacerbation was defined as one of the following:

- Hospitalization due to an exacerbation of subject's schizophrenia
  OR
- Subjects requiring a change from their current antipsychotic to another antipsychotic treatment or initiation of an adjunctive antipsychotic treatment
  OR
- 2-point worsening in CGI-S plus one of the following:
  - Emergency room visit due to a worsening of subject's schizophrenia
  - Utilization of treatment team services (e.g. social worker, case manager, nurse, psychiatrist, family physician)
  - 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
  - Requiring an increase in dose of their existing antipsychotic medication as a result of poor symptom control

If a subject was seen for a visit as part of usual clinical practice, a CGI-S was performed. When assessing clinical exacerbation, the CGI-S score from the most

recent subject visit was to be used as the comparison for determining a 2-point worsening.

Secondary effectiveness evaluations included: Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Severity and Change (CGI-S and CGI-C), Resource Utilization Questionnaire (RUQ), Assessment of Quality of Life (AQOL), Personal and Social Performance Scale (PSP), evaluation of symptomatic remission over time, proportion of clinical exacerbations for the entire trial period, time to clinical exacerbation and the number of clinical exacerbations calculated at 2 time points: occurring up to 3 months and then from 3 months to the end of study.

Number of Subjects (planned and analysed)

In total, 183 of the required 244 subjects were recruited over a period of 30 months (enrolment was anticipated to be completed in 12 months from study start-up), and recruitment was halted on June 24, 2008. The second interim analysis was finalized on March 17, 2009 and resulted in recommendation of trial termination due to futility on March 31, 2009.

The actual number of randomised subjects was 167. The predefined analysis sets consisted of:

- First Interim Analysis occurred November 8, 2006 with 60 pts ongoing
- Second Interim Analysis occurred April 18, 2008 with 179 pts ongoing
- ITT population: 165 subjects (79 treated with risperidone LAI, 86 with oral AAP)
- PP Analysis Set: 128 subjects (63 treated with risperidone LAI, 65 with oral AAP)
- Safety Analysis (all randomized subjects) Set: 167 subjects (81 treated with risperidone LAI, 86 with oral AAP)

Diagnosis and Main Criteria for Inclusion

Inclusion criteria:

Subjects were to satisfy the following criteria to be enrolled in the study:

- Male or female inpatient or outpatient subjects, aged 18 – 65 years inclusive
- Diagnosis of schizophrenia (subtypes include: Paranoid, Catatonic, Disorganized, Residual and Undifferentiated) as per Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text revision (DSM-IV TR)
- 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 sterilisation or abstinence) before entry and throughout the study; and have a negative urine pregnancy test at screening before study entry
- Subjects who have had a minimum of 2 hospitalizations or 2 clinical exacerbations or 1 of each, over the past 2 years due to suspected deteriorating adherence

- Within the last 5 years, patient must have demonstrated a satisfactory response (minimum of 6 weeks) to oral antipsychotics to confirm no treatment resistance. If the patient was previously treated with clozapine, the reason for initiation of clozapine must not be due to treatment resistance.
- On monotherapy antipsychotic treatment as per local product label guidelines, at baseline.
- 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
- Otherwise healthy as confirmed by physical exam, vital signs and laboratory testing.
- Subject has an address and access to a telephone

Exclusion criteria:

Potential subjects who met any of the following criteria were excluded from participation in the study:

- Primary DSM-IV TR Axis I diagnosis other than schizophrenia
- Confirmed hypersensitivity or intolerability to risperidone
- Contraindications for use as listed in the product monographs for risperidone, olanzapine, quetiapine, and where commercially available aripiprazole and amisulpride
- Female subjects who are currently pregnant or breastfeeding or planning a pregnancy within 2 years of trial start
- Long acting formulations of neuroleptic medications within 1 treatment cycle of screening
- 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 local label dose of the monotherapy antipsychotic) or 1 adequate trial with oral risperidone.
- 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
- Evidence of substance dependence (except for nicotine and caffeine dependence) according to DSM-IV TR criteria diagnosed in the last month prior to entry
- Treatment with electroconvulsive therapy (ECT) within 2 years of screening
- Have received an experimental medication or used an experimental medical device within 30 days before screening.
- Employees of the investigator or study centre, 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.

Test Product, Dose and Mode of Administration

Risperdal® Consta®Arm

Risperidone long-acting injectable, an extended release microsphere formulation of risperidone containing 25 mg, 37.5 mg, or 50 mg risperidone was administered by intramuscular gluteal injections every 2 weeks (+/-3 days). Treatment was initiated at 25 mg. Oral supplementation with an atypical antipsychotic was required for the first 3 weeks following the initial injection and for dose increases to 37.5 mg and 50 mg. Dose increases were per product label and usual clinical practice. A test dose of oral risperidone was recommended if the subject had never been treated with risperidone. The dosage was reduced to the next lowest level if there were emergent of safety and/or tolerability problems, and according to the Investigator's judgment.

Oral Antipsychotic Arm

Subjects taking an APP and randomized to the oral arm either remained on their current AAP or were switched to another atypical oral therapy at the discretion of the Investigator. Subjects who were on a conventional neuroleptic were switched to an oral AAP medication of the Investigator's choice. Dose increases were permitted only if the patient was not adequately controlled on their current dosage.

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 clinical exacerbation.

Criteria for Evaluation

Efficacy

- Time to clinical exacerbation: clinical exacerbation was defined as one of the following:
  a. Hospitalization due to an exacerbation of subject's schizophrenia
     OR
  b. Subjects requiring a change from their current antipsychotic to another antipsychotic treatment or initiation of an adjunctive antipsychotic treatment
     OR
  c. 2-point worsening in CGI-S plus one of the following:
     - Emergency room visit due to a worsening of subject's schizophrenia
     - Utilization of treatment team services (e.g. social worker, case manager, nurse, psychiatrist, family physician)
     - 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
     - Requiring an increase in dose of their existing antipsychotic medication as a result of poor symptom control

- Positive and Negative Syndrome Scale
  The PANSS was assessed at:
  - Baseline;
  - Months 6, 12 18 and 24 (endpoint).

- Clinical Global Impression Scale
  The CGI (Severity and Change) was assessed at:
  - Baseline;
  - Months 6, 12 18 and 24 (endpoint).
- Functioning assessment
  The Personal and Social Performance Scale (PSP), was assessed at:
  - Baseline;
  - Months 6, 12, 18, and 24 (endpoint).
- Health status and quality of life assessments
  Assessment of Quality of Life (AQOL) was assessed at:
  - Baseline;
  - Months 6, 12 18 and 24 (endpoint).
- Resource use
  Resource Use Questionnaire (RUQ) was assessed at:
  - Baseline;
  - Months 6, 12 18 and 24 (endpoint);

Safety

- Adverse events: AEs were reported for the duration of the study
- Extra-pyramidal symptoms
  Abnormal Involuntary Movement Scale (AIMS) was assessed at:
  - Baseline;
  - Months 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 6, 12, 18, and 24 (endpoint).
- Other safety parameters:
  Weight was measured at:
  - Baseline;
  - Months 6, 12, 18 and 24 (endpoint).

  Waist and hip circumference was measured at:
  - Baseline;
  - Months 12 and 24 (endpoint).

Statistical Methods

The sample size was determined in order to detect with 95% power a hazard ratio of 2.0 between the Oral and the CONSTA groups, assuming a 40% drop-out rate over 2 years and a mean time to clinical exacerbation of 0.877 years for the oral atypical group. The required sample size was 122 subjects per arm (a total of 244). The

calculation of the sample size also assumed a group sequential trial with 3 interim analyses plus the final analysis with an overall significance level of 5%. The interim analyses were to occur when approximately 50 subjects were been randomized into the trial, when a total of approximately 75 subjects completed 12 months and again at 18 months.

Due to the low recruitment rate enrollment was terminated on June 24, 2008. The study was stopped due to futility on March 31, 2009 per the recommendation of the second interim analysis.

Primary Outcome

The primary objective of the study was to compare the proportion of subjects who experience a clinical exacerbation from 12 weeks post randomization to end of the study. Subjects who discontinued the trial for reasons other than clinical exacerbation or complete the trial without having clinical exacerbation, were considered right-censored observations. Subjects who require a switch in their antipsychotic treatment or the addition of an adjunctive antipsychotic during the trial were considered as having experienced a clinical exacerbation. However, data from these subjects continued to be collected for these subjects and was included in the secondary analyses.

Subjects who required a dose increase that exceeds the total daily maximum dose as per local product label, were considered minor protocol violators, however, data continued to be collected and included in all analyses.

Time to clinical exacerbation was compared using the Kaplan Meir survival curves. Comparisons between the treatment groups were performed using the log-rank test. A Cox proportional hazard model was used to investigate the influence of the stratification factor. The number of clinical exacerbations was calculated over the entire 24-month trial and a treatment comparison will be conducted using a Poisson regression model.

Secondary Outcomes

Secondary outcomes included:

- The proportion of subjects who experience a clinical exacerbation measured beginning post-randomization to month 24.
- PANSS Positive and Negative Symptom Scale
- CGI-S Clinical Global Impression – Severity
- CGI-C Clinical Global Impression – Change
- RUQ Resource Utilization Questionnaire
- AQOL Assessment of Quality of Life
- PSP Personal and Social Performance Scale

Similar analyses than those described for the primary outcome were used to analyze the proportion of subjects who experience clinical exacerbation measured from beginning of randomization.

Between-group differences in the mean changes, together with 95% confidence intervals, were obtained for continuous variables. Mean changes were calculated from baseline to each visit and at endpoint. Categorical outcomes such as CGI-C, were explored by classifying the data as binary outcomes (e.g. at least minimal improvement vs. no change or worse). Between-group differences in proportions of subjects and 95% confidence intervals were calculated.

Safety

Safety was assessed by physical examination, weight, body mass index (BMI), waist/hip 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 Abnormal Involuntary Movement Scale (AIMS).

RESULTS

STUDY POPULATION

A total of 183 subjects were enrolled in the study in forty two centers from four countries (Australia: 15, Canada: 104, Ireland: 6 and United Kingdom: 58). Of these, 167 subjects were randomized (81 in the CONSTA group and 86 in the Oral group). However, subjects 215004 and 409002 randomized to the CONSTA group did not receive any medication and were not included in the modified ITT population. Therefore, only 165 subjects were included in the ITT population (79 in the CONSTA group and 86 in the Oral group). Only 64 subjects or 38.8% in the modified ITT population completed the study (33 or 41.8% in the CONSTA group and 31 or 36% in the Oral group).Because of protocol violations only 128 subjects (63 in the CONSTA group and 65 in the Oral group) were included in the PP analysis. 49 of these subjects (24 in the CONSTA group and 25 in the Oral group) completed the study per protocol and were included in the PP analysis..

Table 1. Summary of Subject Disposition

	N	CONSTA		Oral	
		n	%	n	%
Enrolled	183				
Randomized	167	81	48.5%	86	51.5%
ITT	165	79	47.9%	86	52.1%
ITT Complete	64	33	41.8%	31	36.0%
PP	128	63	49.2%	65	50.8%
PP Complete	49	24	38.1%	25	38.5%

Note:
Percents for Randomized, ITT and PP based on the values of N
Percents for complete based on the number of subject in group

Table 2 provides a summary of the reasons for discontinuation. The main reason for not completing the study was the decision of the sponsor to terminate the study (36 subjects or 21.8% in the ITT population).

There were four subjects who discontinued due to adverse events and two subjects who died before completing the study. The two subjects who died were subject 219002 a male of 58 years of age receiving CONSTA, who died due to acute coronary syndrome not considered related to medication, and subject 416002, a male of 35 years of age receiving CONSTA, who died due to alcohol poisoning, not related to medication.

Most subjects were from the PANNS ≤ 80 stratum with 57.6% of the subjects in the modified ITT in this stratum.

Table 2. Reasons for Discontinuation

	ITT				PP			
	CONSTA N= 79		Oral N= 86		CONSTA N= 63		Oral N= 65	
	n	%	n	%	n	%	n	%
Completed								
No	46	58.2	55	64	39	61.9	40	61.5
Yes	33	41.8	31	36	24	38.1	25	38.5
Reasons for Termination								
Subject withdrew consent	13	16.5	3	3.5	10	15.9	2	3.1
Lost to follow-up	3	3.8	5	5.8	3	4.8	5	7.7
Adverse event	4	5.1			4	6.3		
Death	2	2.5			2	3.2		
Investigator withdrew subject	2	2.5	1	1.2	2	3.2	1	1.5
Insufficient response	1	1.3	4	4.7	1	1.6	2	3.1
Subject non-compliant	3	3.8	6	7	2	3.2	6	9.2
Protocol violation	1	1.3	4	4.7				
Other	5	6.3	8	9.3	4	6.3	5	7.7
End of study (as per Sponsor)	12	15.2	24	27.9	11	17.5	19	29.2

Demographics

Table 3 provides a summary of demographics. As can be seen from the tale most subjects were male (72.1%), of white race (79.4%), of 38.2 ± 11.7 years of age, with paranoid schizophrenia (87.7%) and with 12.3 ± 10.3 years since onset of symptoms. Subjects reported an average weight of 86.3 ± 20.99 kg, with a waist circumference of 100.3 ± 15.7 cm and a BMI of 29.1 ± 6.54 (kg/m^2). No difference was observed between the treatment groups and the results observed in the PP population were similar to those observed in the ITT population.

A total of 121 ITT subjects (73.8%) were hospitalized for Schizophrenia in the previous 2 years of enrolment with an average of 58 days hospitalized.

A total of 61 ITT subjects (37%) reported problems with substance use or abuse, but only 1 subject reporting alcohol abuse, one reporting stimulant abuse, 7 with cannabinoids abuse, and 1 opiates abuse.

Table 3. Demographics Summary – ITT Population

	CONSTA	Oral	All
Gender (n,%)			
Male	56 (70.9%)	63 (73.3%)	119 (72.1%)
Female	23 (29.1%)	23 (26.7%)	46 (27.9%)
Race (n,%)			
White	61 (77.2%)	70 (81.4%)	131 (79.4%)
Black	9 (11.4%)	6 (7%)	15 (9.1%)
Aboriginal	1 (1.3%)	2 (2.3%)	3 (1.8%)
Asian	5 (6.3%)	6 (7%)	11 (6.7%)
Other	3 (3.8%)	2 (2.3%)	5 (3%)
PANSS (n.%)			
PANSS <= 80	46 (58.2%)	49 (57%)	95 (57.6%)
PANSS > 80	33 (41.8%)	37 (43%)	70 (42.4%)
DSM-IV TR schizophrenia subtype (n.%)			
Paranoid	34 (87.2%)	23 (88.5%)	57 (87.7%)
Disorganized	1 (2.6%)	1 (3.8%)	2 (3.1%)
Undifferentiated	4 (10.3%)	2 (7.7%)	6 (9.2%)
Age (mean, std)	37.4 (12.46)	38.9 (10.9)	38.2 (11.67)
Time since onset of symptom (years) (mean, std)	12.3 (9.25)	12.4 (11.29)	12.3 (10.32)
Weight (Kg) (mean, std)	85.5 (19.66)	87 (22.26)	86.3 (20.99)
Height (cm) (mean, std)	171.1 (10.17)	173.2 (10.04)	172.2 (10.12)
Waist circumference (cm) (mean, std)	100.2 (15.95)	100.3 (15.54)	100.3 (15.69)
Hip circumference (cm) (mean, std)	105.7 (11.6)	108.3 (15.74)	107.1 (13.89)
BMI (kg/m^2) (mean, std)	29.3 (6.74)	28.9 (6.39)	29.1 (6.54)

EFFICACY

Although the study was stopped due to futility, the efficacy analysis calculations were performed on both the intent to treat and the per protocol analysis sets. The PP group consisted of all subjects that received at least one dose of study medication, and that had at least one efficacy assessment after baseline. 128 subjects are included in the per protocol group: 63 in the Consta arm and 65 in the oral AAP arm.

PRIMARY EFFICACY PARAMETER: TIME TO CLIINICAL EXACERBATION

The main goal of this study was to investigate whether Risperdal® Consta® provided better efficacy maintenance over 2 years, as measured by the time to clinical exacerbation, in comparison to oral atypical antipsychotic therapy.

The primary objective of the study was to compare the proportion of subjects who experience a clinical exacerbation from 12 weeks post randomization to end of the study on the risperidone LAI and oral AAP arms. Table 4 provides a summary of these exacerbations for the ITT population. A total of 38 subjects (48.1%) in the CONSTA group reported exacerbations compared to 37 subjects (45.5%) in the Oral group. About 38.8% required a change of antipsychotic medication, 35% of subjects required hospitalization for the exacerbation, 23.6% reported 2 point worsening in the CGI scale plus one of the following:

- Emergency room visit to emergency room due to worsening of subject's schizophrenia.
- Utilization of treatment team services (e.g. social worker, case manager, nurse, psychiatrist, family physician).
- 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.
- Requiring an increase in dose of their existing antipsychotic medication as a result of poor symptom control.

Table 4. Summary of Exacerbations after Week 12

	CONSTA	Oral	All
Exacerbation Post Week 12?			
No	41 (51.9%)	49 (57%)	90 (54.5%)
Yes	38 (48.1%)	37 (43%)	75 (45.5%)
Number of Exacerbations	72	68	140
Reasons for Exacerbation			
Hospitalization due to an exacerbation of subject's schizophrenia	25 (34.7%)	24 (35.3%)	49 (35%)
Requires a change from current antipsychotic to another Atypical antipsychotic treatment	28 (38.9%)	26 (38.2%)	54 (38.6%)
2-point worsening in CGI-S plus ...	16 (22.2%)	17 (25%)	33 (23.6%)
Hospitalization + 2-point worsening in CGI-S plus ...	2 (2.8%)		2 (1.4%)
Requires a change from current antipsychotic + 2-point worsening in CGI-S plus ...	1 (1.4%)	1 (1.5%)	2 (1.4%)

Figure 1 provides a Kaplan-Meier plot for the time to post week 12 exacerbations. The mean time to the first post week 12 exacerbation in the CONSTA group was estimated to be 11.7 ± 0.73 months and for the Oral group 13.6 ± 0.84 months. As can be seen from the plot no differences are observed between the two group a fact confirmed by the p-value = 0.5605 of the log-rank test. This result does not change after adjusting by the stratification faction (p-value = 0.8979 for the treatment group in the Cox proportional hazard model after adjusting for PANSS stratification).

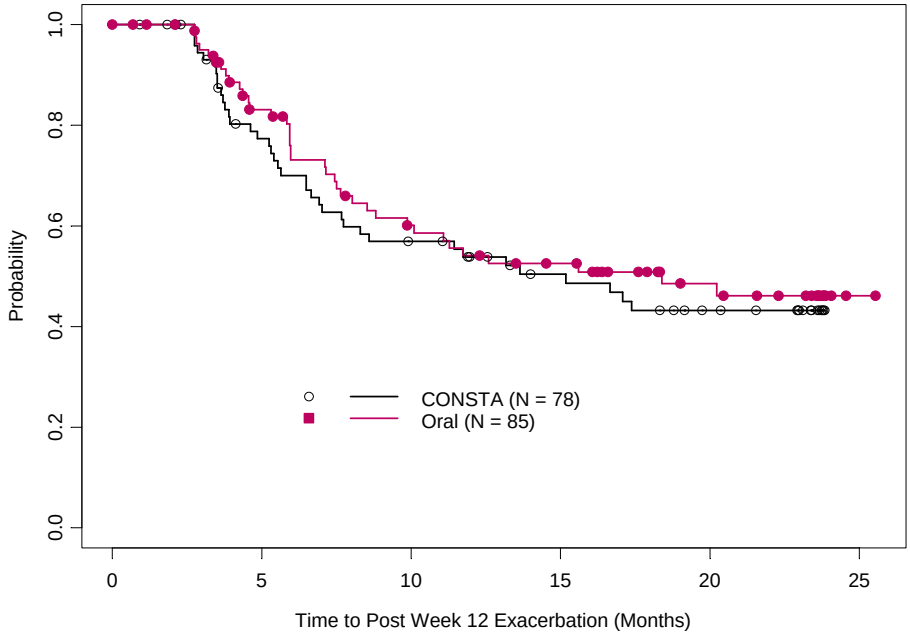

Figure 1. Kaplan Meier Plot for Post Week 12 Exacerbations

Subjects in the CONSTA group reported a total of 72 exacerbations during 93.9 years of exposure for an average of 0.77 exacerbations per years of exposure. Subjects in the Oral group reported a total of 68 exacerbations during 102.3 years of exposure for an average of 0.66 exacerbations per year of exposure. These differences were not considered significant based on the results of a Poisson model analysis including the stratification group as an adjusting variable (p-value = 0.5961).

Similar results were observed when the analysis was carried out using the PP population.

SECONDARY EFFICACY PARAMETERS

Secondary effectiveness evaluations include: Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Severity and Change (CGI-S and CGI-C), Resource Utilization Questionnaire (RUQ), Assessment of Quality of Life (AQOL), Personal and Social Performance Scale (PSP), evaluation of symptomatic remission over time, proportion of clinical exacerbations for the entire trial period, time to clinical exacerbation and the number of clinical exacerbations calculated at 2 time points: occurring up to 3 months and then from 3 months to the end of study.

No difference was observed between the treatment arms in any of the secondary efficacy parameters, with the exception of some of the Assessment of Quality of Life (AQOL) subsections (activities of daily living and physical scale) but these were not robust due to the limitations of the study.

SAFETY

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 167 subjects, 81 randomised to Risperdal® Consta®, 86 subjects randomised to oral antipsychotic treatment.

In the Risperdal* Consta* treatment arm, 71 subjects (87.7%) experienced at least 1 treatment emergent adverse event (AE). In the oral antipsychotic arm, 71 subjects (82.6%) experienced at least 1 treatment emergent adverse event (AE). 52 subjects (64.2%) on Consta and 44 subjects (51.2%) on oral APs experienced AEs that were deemed related to study medication.

Four subjects in the Consta® arm withdrew because of an adverse event. These AEs were: akathisia/dystonia, myocardial infarction, psychotic disorder, and anorexia.

In the Risperdal® Consta® treatment arm, 14 subjects (17.3%) experienced a treatment-emergent serious adverse event (SAE), three of which (hostility, anorexia and syncope) were marked as possibly related to study drug. In the oral arm, 6 subjects (7.0%) experienced a treatment-emergent SAE, none of which were 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 5.

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

		CONSTA N= 81			Oral N= 86		
MedDRA System Organ Class Term	**MedDRA Preferred Term**	**n**	**%**	**# of Events**	**n**	**%**	**# of Events**
GASTROINTESTINAL DISORDERS	NAUSEA	8	9.88	9	5	5.81	6
	VOMITING	7	8.64	10	5	5.81	6
	DIARRHOEA	5	6.17	5	4	4.65	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	CHEST PAIN	5	6.17	5	4	4.65	4
	FATIGUE	5	6.17	5	5	5.81	5
INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	7	8.64	8	7	8.14	11
INVESTIGATIONS	BLOOD GLUCOSE INCREASED	2	2.47	2	5	5.81	5
	WEIGHT GAIN	13	16.05	13	10	11.63	10
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	6	7.41	9	5	5.81	6
	BACK PAIN	4	4.94	4	7	8.14	11
	MUSCULOSKELETAL PAIN	5	6.17	11	1	1.16	1
	PAIN IN EXTREMITY	7	8.64	10	6	6.98	6
NERVOUS SYSTEM DISORDERS	AKATHISIA	5	6.17	5	4	4.35	5
	DIZZINESS	11	13.58	13	10	11.63	11
	HEADACHE	21	25.93	27	7	8.14	11
	SEDATION	1	1.23	1	6	6.98	6
	SOMNOLENCE	5	6.17	5	5	5.81	5
	TREMOR	5	6.17	5	3	3.49	3
PSYCHYATRIC DISORDERS	AGITATION	12	14.81	20	11	12.79	17
	ANXIETY	18	22.22	37	14	16.28	16
	DEPRESSION	10	12.35	11	4	4.65	5
	HALLUCINATION, AUDITORY	5	6.17	6	1	1.16	1
	INSOMNIA	21	25.93	34	12	13.95	15
	PSYCHOTIC DISORDER	4	4.94	4	6	6.98	7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	6	7.41	9	2	2.33	2

Two deaths were reported on the Risperdal® Consta® arm, one from acute coronary syndrome, and the other from alcohol poisoning; both events were not related to study medication.

Potentially prolactin-related treatment-emergent adverse events were observed in 10 (12.3 %) of the subjects in the Risperdal® Consta® arm and in 9 (10.5%) of the subjects in the oral antipyschotic arm. In the Consta® arm 4 patients had increased blood prolactin levels, 1 galactorrhea, 1 lactation, 1 painful erection, 2 period pains, and 1 sexual dysfunction. In the oral AP arm, 1 subject experienced reduced libido, 2 had abnormal orgasm, 1 breast size increase, 1 ejaculation decrease, 1 erectile dysfunction, 1 increased prolactin level, and 2 reported sexual dysfunction.

The following table presents a summary of adverse events that resulted in drug being permanently discontinued:

	CONSTA N= 81		**Oral N= 86**	
MedDRA Preferred Term	**n**	**%**	**n**	**%**
ACUTE CORONARY SYNDROME	1	1.23		
AGGRESSION	1	1.23		
AGITATION	1	1.23		
AKATHISIA	1	1.23	1	1.16
ALCOHOL POISONING	1	1.23		
ANGINA PECTORIS	1	1.23		
ANOREXIA	1	1.23		
CHEST PAIN	1	1.23		
DELUSION	1	1.23		
DIZZINESS	1	1.23		
DYSTONIA	1	1.23		
EJACULATION FAILURE			1	1.16
EMOTIONAL DISTRESS	1	1.23		
HAEMATURIA	1	1.23		
HALLUCINATION, AUDITORY	1	1.23		
INSOMNIA	1	1.23		
MYOCARDIAL INFARCTION	1	1.23		
ORGASM ABNORMAL			1	1.16

	CONSTA N= 81		Oral N= 86	
MedDRA Preferred Term	**n**	**%**	**n**	**%**
PARANOIA	1	1.23		
PERSECUTORY DELUSION	1	1.23		
PSYCHOTIC DISORDER	1	1.23	1	1.16
SCHIZOPHRENIA	1	1.23		
WEIGHT INCREASED	1	1.23		

The following table presents a summary of observed extrapyramidal symptoms (EPS)-related treatment-emergent adverse events (TEAE):

EPS RELATED TEAEs MedDRA Preferred Term	**CONSTA N= 81**		**Oral N= 86**	
	n	**%**	**n**	**%**
AKATHISIA	5	6.17	4	4.65
BRADYKINESIA	1	1.23		
COORDINATION ABNORMAL	1	1.23		
DYSKINESIA	2	2.47		
DYSTONIA	1	1.23		
EXTRAPYRAMIDAL DISORDER	1	1.23	3	3.49
HYPOKINESIA	1	1.23		
RESTLESS LEGS SYNDROME	4	4.94		
SPEECH DISORDER	1	1.23		
TARDIVE DYSKINESIA			1	1.16
TREMOR	5	6.17	3	3.49
TOTALS	**18***	**22.2%**	**11**	**12.8%**

*total actual number of pt was 18, some subjects reported more than one EPS AE

Mean body weight was 86.0 and 87.0 kg at baseline, and 88.1 and 90.7 kg at endpoint in the Consta® and oral arms respectively. Overall, 28 subjects (34.6%) experienced weight gain of >/= 7% on Risperdal® Consta®, and 22 (26.2%) experienced weight gain of >/= 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 2.4 kg (sd 9.66) in the Consta arm (from baseline to last visit) and 2.5 kg (sd 10.18) in the oral arm. Waist circumference increased in both arms from baseline to last visit: 1.8 cm (sd 11.15) in the Consta arm and 3.0 cm (sd 9.17) in the oral arm.

There were no statistically significant differences between or within treatment arms for Abnormal Involuntary Movement Scale (AIMS).

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

CONCLUSION

This pragmatic randomized trial of Risperdal® CONSTA® versus oral atypical antipsychotics in poorly adherent subjects with schizophrenia in a routine care setting began in November of 2005 with a scheduled enrollment period of 12 months. While study was progressing more slowly than anticipated, new data (Keks et al., Br. J Psychiatry, 2007; Medori et al. poster at American Psychiatric Association, 2008) were published which varied from those used in the initial statistical planning and sample size calculations. Based upon the recruitment issues, and this additional information; a futility analysis was conducted which confirmed it very unlikely that the study would provide any meaningful data to the medical community. A total of 550 pts would be required to achieve a reasonable level (80% power) to detect difference between treatment arms. With the slow recruitment into the study (approx 5.5 pts/month), it was estimated that it would take an additional 5.9 years (70.7 months) to recruit the required 390 patients The study was stopped due to futility on April 30, 2009.

Although underpowered, the PP and ITT data sets were analyzed and are presented in this report.

No significant difference between the two treatment groups was observed in any of the primary or secondary efficacy parameters. No new or additional safety signals were observed in this study.

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