SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen-Cilag Ltd
Name of Finished Product	Risperdal oral
Name of Active Ingredient(s)	Risperidone

Protocol No: RIS-COD-302 CR005797

Title of Study: Prospective trial of risperidone (Risperdal) following psychological therapy for challenging behaviour in learning disabled children

Principal Investigator: Professor Stephen Read M.D. Huddersfield, UK

Publication (Reference): none (but in progress)

Study Period: 3rd November 2003 - 05 June 2006

Phase of Development: IIIb

Objectives: The primary objective is to effect an assessment of the safety and efficacy of 0.25mg-4mg of oral Risperdal in behaviour disorder in mild, moderate and severe mentally retarded children who have previously been treated with psychological methods for behaviour disorder, which has been judged of insufficient benefit. The primary efficacy parameter is the degree of change versus baseline as measured on the total score of the Aberrant Behaviour Checklist (ABC)
Secondary efficacy parameters were CGI-S, change versus baseline on the subscales of the ABC, change versus baseline on the Hostility Checklist and CQOL change versus baseline to last recorded assessment. Safety assessments include Etrapyramidal Symptom Rating Scale (ESRS) when indicated, adverse event monitoring and ECGS

Methods: This open single center study conducted in the UK. Subjects received 0.25mg –4mg or oral risperidone for a period of six months.

Only the test medication (risperidone) was permitted for the treatment of the challenging behaviour during the study period. Administration of other psychotropic agents was prohibited.

The decision to use morning or evening dosing was made by the clinician. The starting dose was 0.25 mg or 0.5 mg per day, based on clinical judgment, for days 1 and 2: the dose could then be increased to 0.5 mg per day on day 3. At the discretion of the investigator, older subjects with a larger body weight were permitted to use the adult starting dose of 1 mg per day.
After day 3, the dosage could be raised by increments of 0.25 mg or 0.5 mg per day (at weekly intervals), if judged necessary by the clinician and depending on the therapeutic response. The maximum dose permitted was 4 mg per day. Similarly, dose reduction was permitted on the basis of clinical judgment: dose reductions were not limited.
Behaviour disorder was assessed using the ABC, CGI-Severity (CGI-S) Hostility Checklist scales and Child Health Related Quality of Life (CQOL)
Safety assessments included vital signs, physical findings, adverse event (AE) monitoring and electrocardiograms (ECGs). In addition, the Extrapyramidal Symptom Rating Scale (ESRS) was to be used when indicated

Number of Subjects (planned and analyzed): 20 subjects planned for enrollment with 19 randomised. Of the 19 patients randomized, 18 were included in the ITT analysis, 15 included in the PP analysis and 19 included in the safety analysis.

Diagnosis and Main Criteria for Inclusion:

Healthy, subjects between 5 and 16 years old who have been under the supervision of a clinical /educational psychologist for at least a 6-month period prior to study entry, receiving psychological therapy *unless such therapy is not indicated, as in subjects with IQ <50 or demonstrating very severe self-harming behaviour*. Subjects score 8 or more on the Hostility checklist and have a DSM-IV Axis II diagnosis of Mild Mental Retardation (317), Moderate Mental Retardation (318) or Severe Mental Retardation (319): these three diagnoses represent IQs ranging from ≤ 75 to ≥ 20. Subjects must be accompanied by a responsible adult

Test Product, Dose and Mode of Administration, Batch No.:

Product Description	Dose	Batch number	Expiry Date
Risperidone - tablets	0.5 mg	02GL409	Jul-04
Risperidone - tablets	0.5 mg	03JL764	Oct-05
Risperidone - tablets	0.5 mg	04BL350	Feb-06
Risperidone - tablets	0.5 mg	5CL1X00	Feb-07
Risperidone - tablets	1 mg	02FL115	Jun-05
Risperidone - tablets	1 mg	04CL837	Mar-07
Risperidone - tablets	1 mg	4LL0000	Nov-07
Risperidone - liquid	100 ml bottles	02GB458	Jul-05
Risperidone - liquid	100 ml bottles	03LB068	Dec-06
Risperidone - liquid	100 ml bottles	4DB5P00	Apr-07
Risperidone - Quicklet tablets	1 mg	5BG5128	Aug-06
Risperidone - Quicklet tablets	2 mg	4KG3895	Aug-06

Duration of Treatment: Study drug was administered for 6 months

Criteria for Evaluation:

Baseline and Disease Characteristics

The following baseline parameters were assessed: Informed consent, Vital signs, Weight, Aberrant Behaviour Checklist, Clinical Global Impression of Severity Hostility Checklist, Child Quality of Life Rating Scale (CQOL),] Adverse events, Concomitant therapy

The efficacy of the test medication was evaluated using the following four scales: ABC, CGI-S, Hostility Checklist and CQOL.

The ABC contains 58 items in total, divided into the following subscales:

Subscale I (Irritability)	[15 items, range 0 to 45]
Subscale II (Lethargy)	[16 items, range 0 to 48]
Subscale III (Stereotypy)	[7 items, range 0 to 21]
Subscale IV (Hyperactivity)	[16 items, range 0 to 48]
Subscale V (Inappropriate Speech)	[4 items, range 0 to12]

The ABC was to be scored at all visits by the Investigator or Research Nurse. The CGI-S is the Investigator's assessment of the subject's condition on a 7-point scale. It was to be scored at all visits by the Investigator or Research Nurse.

The Hostility Checklist is a questionnaire consisting of 24 items to be scored absent, moderate or severe, to be completed at each visit. The total hostility score is calculated as the sum of all 24 items. In addition, two subscale scores are calculated for violence and self-injury.

The CQOL questionnaire was to be completed at entry, month 3 (Visit 7) and month 6 (Visit 10). The questionnaire consists of 15 domains – in each domain, the parent or carer of the child is asked to score the performance of the child with respect to the domain, how upset they are by the child's level of performance and how satisfied they are by the child's level of performance.

The secondary parameters included the following:

Change versus baseline to month 3 (Visit 7) and month 6 (Visit 10) of the observed case total ABC score. Change versus baseline to the last recorded assessment of the five ABC sub-scales. Change versus baseline to the last recorded assessment of the CGI-S. Change versus baseline to the last recorded assessment of the Hostility Checklist. Change versus baseline to the last recorded assessment of the CQOL (function total score, satisfaction total score, upset total score and global score).
Standard safety assessments included AE reporting, vital signs, body weight, ECGs and physical examination. The presence and severity of emergent EPS was assessed via the ESRS prior to the administration of anticholinergic medication.

Statistical Methods: All statistical tests were interpreted at the 5% significance level (two-tailed). In case of a substantial number of protocol violators, an additional on-protocol analysis was to be done to determine whether they influenced the conclusions. All statistical summaries, listings and inferential analyses were performed using the software SAS 8.2.
Sample size was determined by using the raw data from two previous double blind studies, a reduction of 15 on the total ABC score was anticipated. To detect this reduction from a one sample study, with a standard deviation of 20, would require a total of 15 evaluable patients (80% power, 5% significance level, 2-sided test). To allow for dropouts, a total of 20 patients were to be recruited.
Analysis performed was an intent-to-treat (ITT) analysis, i.e. all subjects with at least one post baseline assessment visit were included in the analysis
The primary parameter was the change versus baseline at end point of the total ABC score. The change versus baseline at endpoint was evaluated using the paired t-test (Wilcoxon Matched Pairs Signed Ranks test in the case of non-normality).

The secondary parameters included the change versus baseline to month 3 (Visit 7) and month 6 (Visit 10) observed case total ABC score. The data was summarised and evaluated using the paired t-test. (Wilcoxon Matched Pairs Signed Ranks test in the case of non-normality). Secondary parameters also included the change versus baseline to the last recorded assessment of the five ABC sub-scores. These data were summarised and analysed. The secondary parameters change versus baseline to the last recorded assessment of the CGI-S, and the change versus baseline to the last recorded assessment of the Hostility Checklist total score, were summarised and analysed. The CQOL function total score, satisfaction total score, upset total score and global score, change versus baseline to last recorded assessment were summarised and analysed.
Each secondary parameter was analysed using the paired t-test (Wilcoxon Matched Pairs Signed Ranks test in the case of non-normality).

Safety analyses were planned for all subjects who received at least one dose of study medication
Type and incidence of all AEs were tabulated. Special attention was given to those subjects who discontinued the study for an adverse event, who experienced a severe or a serious adverse event.

RESULTS:

Study Completion	**Risperidone (n=19)**
Completed study	16
Withdrew	3
Reasons for withdrawal:	
- Adverse event	1
- Insufficient response	1
- Subject ineligible to continue study	1

Summary of Demographic Details of Intention to Treat Population

	Total (N= 18)
Age (completed years) N	18
Mean (SD)	11.5 (3.1)
95% CI for mean	(10.0, 13.0)
Median	12
Q1-Q3	9-15
Min-Max	6-16
Sex, N	18
Male	16 (88.9%)
Female	2 (11.2%)
Race, N	18
Caucasian	15 (83.3%)
Hispanic	0
Black	0
Asian	2 (11.1%)
Oriental	0
Other	1 (5.6%)
IQ Rating N	18
Missing	2
Mean (SD)	55.9 (12.3%)
95% CI for mean	(49.3, 62.4)
Median	59
Q1-Q3	48-65
Min-Max	26-73

Primary Efficacy Analysis

The primary efficacy parameter for this study, the change versus baseline at endpoint of the total ABC score (i.e. all 58 items in the checklist), showed a significant decrease. This was demonstrated in both ITT and PP populations.

Primary efficacy results – Change versus baseline in Aberrant Behaviour Checklist total score.

	Risperidone	**Risperidone**
Baseline to LOCF final	**Mean (SD)**	**p-value[1]**
Total ABC score[2]	-43.8 (25.7)	<0.0001
Total ABC score[3]	-42.7 (28.0)	<0.0001

LOCF = last observation carried forward, [1] paired t-test, [2] ITT population (n=18)

Secondary Efficacy Analyses :ABC Total Score At Other Visits

The baseline and total score at month 3 (Visit 7) and the baseline and total score at month 6 (Visit 10) both showed a significant decrease

Secondary efficacy results – Aberrant Behaviour Checklist score at other visits.

	Risperidone (n=18)	
Baseline to Visit	**Mean (SD)**	**p-value[1]**
Total ABC score (Visit 7; month 3)	-43.4 (20.9)	<0.0001
Total ABC score (Visit 10; month 6)	-47.5 (20.9)	<0.0001

[1] paired t-test

ABC Sub-scales

The change from baseline to LOCF final visit (Visit 10) in the five ABC subscale scores showed significant decreases, albeit at varying levels

Baseline to LOCF final	**Risperidone (n=18)**	
	Mean (SD)	**p-value[1]**
ABC irritability score	-14.1 (9.0)	<0.0001
ABC lethargy score	-7.8 (8.7)	0.0015
ABC stereotypy score	-2.7 (5.0)	0.0335
ABC hyperactivity score	-17.3 (12.5)	<0.0001
ABC inappropriate speech score	-2.0 (2.3)	0.0020

[1] paired t-test, [2] ITT population (n=18), [3] PP population (n=15)

Hostility Checklist

There were significant decreases for hostility scores and hostility sub-scale scores in the change from baseline to final LOCF visit

Baseline to LOCF final	**Risperidone (n=18)**	
	Mean (SD)	**p-value**
Hostility total score	-25.8 (15.9)	<0.0001[1]
Hostility violence subscale score	-15.9 (9.5)	<0.0001[1]
Hostility self injury subscale score	-9.9 (9.1)	<0.0001[2]

[1] paired t-test[2] , Wilcoxon matched-pairs signed-rank test

Clinical Global Impression of Severity

There was a significant decrease in CGI-S score in the change from baseline to final LOCF visit analysis

Baseline to LOCF final	**Risperidone (n=18)**	
	Mean (SD)	**p-value**
CGI-S score	-2.9 (1.1)	<0.0001[1]

[1] Wilcoxon matched-pairs signed-rank test

Child Health-Related Quality Of Life

There were significant changes in CQOL, except in the CQOL global score. CQOL function total score and CQOL satisfaction total score decreased significantly and CQOL upset total score increased significantly

Baseline to LOCF Final	**Risperidone**	
	Mean (SD)	**p-value**
CQOL function total score	-12.7 (14.3)	0.0015[1]
CQOL upset total score	13.7 (13.2)	0.0004[1]

CQOL satisfaction total score	-13.6 (15.5)	0.0017[1]
CQOL global score	-1.3 (2.3)	0.0557[2]

[1] paired t-test, [2] Wilcoxon matched-pairs signed-rank test

Efficacy Conclusions

There was a significant decrease in ABC total score observed, comparing the baseline and final evaluation. This decrease was present in all the ABC subscales at varying levels and was statistically significant.

There were significant decreases also seen for hostility scores and CGI-S score.

There were significant changes in CQOL, except in the CQOL global score. CQOL function total score and CQOL satisfaction total score decreased significantly and CQOL upset total score increased significantly

SAFETY RESULTS:

Summary of adverse events.

Adverse Events	Risperidone (n=19)	
	N	(%)
All adverse events (AEs)		
Number of mild AEs	65	
Number of moderate AEs	25	
Number of severe AEs	5	
Total number of AEs	95	
Number of subjects with an AE	18	(94.7%)
Serious adverse events (SAEs)		
Number of SAEs	2	
Number of subjects with an SAE	2	(10.5%)
Drug-related* adverse events		
Number of drug-related AEs	37	
Number of subjects with a drug-related* AE	13	(68.4%)
Serious drug-related* adverse events		
Number of SAEs	0	
Number of subjects with a serious drug-related* AE	0	
Adverse events leading to a permanent stop in study medication		
Number of AEs	2	
Number of subjects with an AE leading to a permanent stop in study medication	2	(10.5%)
Number of deaths	0	

*Drug-related adverse events are defined as those with possible, probable or very likely relation to the study medication.

A total of 95 AEs were reported by 18 subjects after receiving study medication. Of these, 65/95 (68.4%) were of mild intensity, 25/95 (26.3%) were of moderate intensity and 5/95 (5.3%) were of severe intensity.
The majority of AEs belonged to the following system organ classes; nervous system disorders (12 subjects; 63.2%), respiratory/thoracic/mediastinal disorders (9 subjects; 47.4%), gastrointestinal disorders (7 subjects; 36.8%), general disorders (7 subjects; 36.8%) and investigations (5 subjects; 26.3%).Of the nervous system disorders, headache was the most commonly reported symptom (8 subjects; 42.1%). Hypotension was reported in four subjects (21.1%): two of these events were considered to be very likely related to study medication.

Thirteen subjects reported a total of 37 drug-related AEs. The most common system organ class affected was nervous system disorders (9 subjects; 47.4%) with 5 subjects reporting headache, 3 subjects reporting somnolence and 2 subjects reporting dizziness.
Adverse events leading to a permanent cessation of study medication were observed in two subjects; breast hypertrophy (1 subject; 5.3%) and epilepsy (1 subject; 5.3%). The AE of breast hypertrophy started on Visit 10 (final visit, month 6), therefore, the subject was shown as completing the study (rather than being withdrawn from it). The subject with epilepsy had a grand mal convulsion after 21 weeks treatment and withdrawn from the study.
Five severe AEs were recorded in four subjects (21.1%); upper abdominal pain (1 subject; 5.3%), salivary hypersecretion (1 subject; 5.3%), limb injury (1 subject; 5.3%), grand mal convulsion (1 subject; 5.3%) and breast hypertrophy (1 subject; 5.3%).

Two serious adverse events (SAEs) were reported in two subjects (10.5%); system organ class nervous system disorders (grand mal convulsion, 1 subject; 5.3%) and investigations (investigation, 1 subject; 5.3%)
SAE Narratives
Subject #14 (CN):
This 8 year-old male was receiving risperidone at 1.75 mg per day (medication start date 14/03/2005) and had a SAE, which occurred on 08/08/2005 (dose of study medication at this time was 1.80 mg). This subject had a prolonged epileptic seizure and was admitted to hospital for treatment. The subject made an uneventful recovery and was discharged from hospital two days later (10/08/2005). Study medication was temporarily stopped. The Investigator indicated the relationship of the SAE to the study medication was doubtful

Subject #15 (MR):
This 12 year-old male was receiving risperidone at 1 mg per day and had a SAE, which occurred on 14/04/2005. This subject was found with a large amount of study medication on the floor. It was not possible to qualify the amounts taken, if any so the subject was admitted to hospital for observation. All parameters were normal and the subject was discharged later the same day. The investigator provided an assessment of causality as not related.

There were no important clinical changes in vital signs or physical findings during the study period. There were no statistically significant changes in systolic blood pressure from baseline to final LOCF. For diastolic blood pressure, the change from baseline to all visits and the LOCF final value was negative, indicating a decrease from baseline .In 3/10 subjects this decrease was significant ($p<0.05$) – at Visits 2 (week 1), 5 (week 4) and 8 (month 4

Safety results - Change in blood pressure.

Baseline to LOCF Final	**Risperidone (n=19)**	
	Mean (SD)	**p-value**
Systolic BP (mmHg)	-0.8 (17.2)	0.8566[1]
Diastolic BP (mmHg)	-1.6 (11.7)	0.5706[1]

[1] paired t-test; Source: PTT 17.3.2

There were no clinically important changes in ECG recordings during the study period

Three subjects dropped out of the study: one of these withdrew due to an AE. There was a high incidence of nervous system disorders, most commonly due to headache. There were two AEs that lead to a permanent cessation in study medication. The AE of hypotension was reported in four subjects. There were no statistically significant changes in systolic blood pressure. A small number of subjects (3/10) experienced a statistically significant decrease in diastolic blood pressure. However, given the small sample size, further investigation would be advised before extrapolating this trend to the population in general. Two subjects experienced two SAEs. There were no deaths.

CONCLUSION:

This was an open, single centre study in which subjects received 0.25 mg - 4 mg of oral risperidone for a period of six months. During this study, 10 visits were made; baseline (entry), at weeks 1, 2, 3 and 4, and at months 2, 3, 4 and 6.

The primary objective of this study was to assess the safety and efficacy of risperidone (oral dose of 0.25 mg – 4 mg) in treating behaviour disorder in mild, moderate and severe mentally retarded children who had previously been treated with psychological methods. Only the study medication (risperidone) was permitted for the treatment of challenging behaviour during the study period.

Behaviour disorder was assessed using the ABC, Hostility Checklist and CGI-S scale. Safety assessments included AE reporting, vital signs, body weight, ECGs and physical examination. In addition, emergent EPS were assessed via the ESRS prior to the administration of anticholinergic medication.

The primary parameter of efficacy was the change versus baseline at end point of the total ABC score.

A total of 19 subjects were included in the study from a single centre in the UK. Eighteen of these subjects were included in the ITT population, of these 16 completed the study.

A significant decrease in ABC total score was observed, comparing the baseline and final evaluation. This decrease was present in all the ABC subscales at varying levels and was statistically significant.

There were significant decreases also seen for hostility scores and CGI-S score. There were significant changes in CQOL, except in the CQOL global score. CQOL function total score and CQOL satisfaction total score decreased significantly and CQOL upset total score increased significantly.

Regarding safety, the AEs reported in this study were those commonly observed in previous studies with risperidone. No new clinically relevant, unexpected AE was detected in this study. A total of 95 AEs were reported by 18 subjects (94.7%) after receiving study medication. Thirteen subjects (68.4%) reported a total of 37 drug-related AEs. The majority of these were nervous system disorders (9 subjects; 47.4%; 14 drug-related AEs) including 5 subjects reporting headache, 3 subjects reporting somnolence and 2 subjects reporting dizziness. One AE led to subject withdrawal. There were two subjects reporting an AE leading to a permanent stop in study medication.

In conclusion, treatment with oral risperidone at a dose of 0.25 mg to 4 mg per day was associated with improvements in various measures of behaviour disorder in the study population. The tolerability profile of risperidone was similar to that observed in the adult population.

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