Janssen-Ortho Inc., Canada
MEDICAL AFFAIRS

SYNOPSIS

Name of Sponsor/Company:	Janssen Ortho Inc.	Individual Study Table Referring to Part of the Dossier **n/a**	(for National Authority Use only)
Name of Finished Product:	Concerta	Volume: n/a	
Name of Active Ingredient:	methylphenidate	Page: n/a	
Title of Study:		A double blind, randomized trial to evaluate the safety, tolerability and efficacy of CONCERTA® augmentation of SSRI/SNRI monotherapy in adult patients with Major Depressive Disorder	
Investigators:		A. Ravindran ON;A. Fallu, J.;J. Ali NS;R. Chandrasena ON; P.Chokka AB; M-J Filteau QC;W. Gallarraga ON;S. Girgla ON;D. Koczerginski ON;S. Lessard ON, H. Leung ON;R. Milev ON;A. Moscovitch AB;A. Munshi NS;S. Patry QC;M. Renuka-Prasad SK;P. Turner ON	
Study centre(s):			
Publication (reference)		submitted to Journal of Clinical Psychiatry November 2006	
Studied period (years): over 2 years		Phase of development:	Phase 3
	(date of first enrolment)	8 June 2005	
	(date of last completed)	18 April 2006	
Objectives:		To evaluate the effects of adjunctive CONCERTA® or placebo in outpatients with Major Depressive Disorder (MDD).The safety and tolerability of the CONCERTA® and antidepressant combination will be assessed.	
Methodology:		A multi-center, double-blind, randomized, placebo controlled, parallel group, clinical trial. There are 7 mandated study visits consisting of up to a 2-week screening period and a 5-week treatment period. Male or female outpatients (18 – 65 years of age) meeting diagnostic criteria for current Major Depressive Disorder who have had an inadequate response (refer to inclusion criteria #5) to antidepressant therapy and are currently on a stable dose of SSRI/SNRI therapy (defined in protocol) will be enrolled.	
Number of patients (planned and analyzed):		130 planned	145 analyzed
Diagnosis and main criteria for inclusion:		- male or female outpatients, between 18 and 65 years of age inclusive; -current Major Depressive Episode without psychotic features, per DSM-IV-TR criteria and confirmed by M.I.N.I. at screening; -an inadequate response to at least one but not more than 3 trials of adequate dosage of monotherapy antidepressant (SSRI/SNRI) given for a minimum of 4 weeks (the current antidepressant may be considered a failed course) at screening; -currently on an adequate antidepressant dosage (SSRI/SNRI) for the past 4 weeks at screening (see Attachment 2); -must have the following MADRS scores; a minimum total score of ≥ 20, the lassitude item #7 score of ≥ 2 and suicidal thought item #10 score of <4 at screening and baseline; -a CGI-S ≥ 4 at screening and baseline; -healthy on the basis of ECG, physical and laboratory tests	

Test product, dose and mode of administration, batch number:		18mg CONCERTA® or matching placebo administered orally in the morning was provided by Cardinal Health. The maximum dose would be 54 mg (or 3 x 18 mg tab/day).
Duration of treatment:		5 weeks
Reference therapy, dose and mode of administration, batch number		Matching placebo administered as multiples of 18 mg.
Criteria for evaluation:		
	Efficacy:	Efficacy measures collected include: Montgomery-Asberg Rating Scale (MADRS), 7-atypical items of the Hamilton Depression Scale (HAM-D-31), Clinical Global Impression of Severity and Improvement (CGI-S, CGI-I) Scale, the Sexual Function Scale (SEX FX) and the subject's self reports, Multidimensional Assessment of Fatigue (MAF) and Apathy Evaluation Scale (AES).
	Safety:	Adverse events, fasting laboratory tests, vital signs, physical exam, ECG
Statistical Methods:		The primary variable to be assessed is the MADRS. At present the mean treatment difference (defined as the change from baseline in total MADRS score between the two groups) and the standard deviation (SD) of this difference are unknown. This exploratory trial will estimate a 95% confidence interval for the mean treatment difference of the MADRS score change from baseline. The sample size was calculated by requiring that the size of the 95% confidence interval estimate of the MADRS treatment groups difference be less than or equal to 80% the size of the estimated standard deviation of the difference. Assuming a 30% drop out, a sample of 65 subjects per group, for a total of 130 subjects is required The efficacy analyses will be based on the ITT population, defined as all subjects who receive at least one dose of the investigational medication and have at least one post-baseline efficacy assessment. For each continuous efficacy variable, the change from baseline score at each visit and at endpoint will be analyzed by group and for between-group differences with descriptive statistics. Intergroup differences will also be presented with 95% confidence intervals. For each of the categorical efficacy variables, the frequency distribution will be presented by group for each visit. For binary response variables, intergroup differences will be presented with 95% confidence intervals. The primary population for safety will be all subjects who receive at least one dose of study medication. The percentage of subjects with specific treatment-emergent adverse events during treatment will be summarized for each treatment group. For vital signs, changes from baseline in vital sign measurements will be presented descriptively.
SUMMARY – CONCLUSIONS		

Subject Flow		
	Concerta	**Placebo**
	N (%)	**N (%)**
Randomized	73	72
Completed study	62(84.9)	68(94.4)
Early discontinuation	**11 (15.1)**	**4 (5.6)**
Subject choice (consent withdrawn)	0	1 (1.6%)
Insufficient response	1 (1.4%)	1 (1.4%)
Adverse event	6 (8.2%)	0
Subject non-compliant	2(2.7%)	0
Other reason		
Study drug lost	0	1(1.4%)
Study med stolen	2 (2.7%)	1(1.4%)

All randomized patients were eligible for the intent to treat (ITT) population; 68 Concerta and 66 placebo patients were eligible for the per protocol population. Since the results for the per protocol population were similar to the ITT population, the results presented here are for the ITT population.

Treatment group (AGE)			**N**	**Mean**	**SD**	**Minimum**	**Maximum**
Concerta			73	45.6	10.81	22	65
Placebo			72	41.9	10.90	18	65

EFFICACY RESULTS

Characteristics		**Concerta**	**Placebo**
Gender:	Male	26 (35.6%)	25 (34.7%)
	Female	47(64.4%)	47(65.3%)
Race:	Caucasian	71(97.3%)	71 (98.6%)
	Other	2(2.8%)	1(1.4%)

Trial medication mean dose, all patients.

	N	**Mean**	**SD**	**Minimum**	**Maximum**
Concerta	73	36.4	9.15	8.6	45.8
Placebo	74	40.8	5.21	18.0	45.9

Trial medication mean final dose, completers

	N	**Mean**	**SD**	**Minimum**	**Maximum**
Concerta	62	48.2	10.15	18.00	54.0
Placebo	68	51.6	6.89	18.0	54.0

Final dose frequency:65.8% of patients were on a final Concerta dose of 54mg, 21.9% on 36mg and 12.3% on 18mg.

The primary efficacy variable, the MADRS, improved over time, with a statistically significant improvement in favor of Concerta® observed at day 14 ($p<0.05$). However, this difference was not maintained at other timepoints measured and there was no significant difference in mean MADRS scores between the two groups at endpoint (-10.38 for Concerta®; -10.83 for placebo). None of the secondary efficacy variables (7 atypical items HAM-D, CGI-S and I,SEX-FX) demonstrated a difference at endpoint between the active and placebo group except for the AES and the MAF using mixed model analysis.

The AES was statistically significant in favour of Concerta beginning at Day 5 ($p<0.02$) and at each visit thereafter to Day 35/endpoint ($p<0.01$).

		The MAF demonstrated a statistically significant effect in favor of Concerta at each visit beginning at Day 5(p-0.005) to Day 28($p<0.005$) but not at endpoint($p=0.11$). When the mixed model analysis was performed, a statistically significant difference was found in favor of Concerta® (df=1, F-value 6.82, $p<0.01$). Similar to the MADRS, the mean CGI-I score was statistically significant at day 14 in favor of Concerta® (2.8, $p = 0.0074$) compared to placebo (3.3) and was not maintained. The mean CGI-S score was statistically significant in favour of Concerta only at Day 5 ($p=0.02$) and not at any other visit.
		The Sexual Functioning Questionnaire (SEX FX) is a clinician-rated scale to evaluate function in the domains of desire, arousal, and orgasm among depressed patients, who are either taking antidepressant medication or who are untreated (Kennedy et al, 2000). One component of the scale measures change in the domains of sexual function the other component measures change of overall satisfaction of sexual functioning and enjoyment of sexual romantic life. There were was a statistically significant difference seen in the SEX-FX for function in subjects sexually active at baseline but no difference in the patient's global sexual impression of satisfaction/enjoyment. There was no statistically significant difference between treatment groups for patients who were not sexually active at baseline.

SAFETY RESULTS

Fifty-one patients (69.9%) in the active group and 43 (59.7%) in the placebo group had at least one adverse event. The most frequently occurring treatment emergent adverse events(TEAE) for Concerta were: headache (30%), nausea (15%) and for placebo was: headache (19%).

Table of adverse events ≥ 5%

Event	Concerta® % (N)	Placebo % (N)
Headache	30.14 (22)	19.44 (14)
Nausea	15.07 (11)	9.72 (7)
Appetite Decreased Nos	8.22 (6)	
Common Cold	8.22 (6)	
Abdominal Cramps	5.48 (4)	
Dry Mouth	5.48 (4)	
Fatigue Aggravated	5.48 (4)	
Anxiety	5.48 (4)	
Insomnia	5.48 (4)	6.94 (5)

Six patients on Concerta discontinued due to adverse events (increased fatigue(n=1), anxiety(n=1,causality is doubtful), sleepiness(n=1),elevated blood pressure(n=1), dizziness, mood lability, nausea (n=1, for all events causality is doubtful), diarrhea, GI upset (n=1). One patient on placebo discontinued for migraine.

Five patients on Concerta experienced adverse events rated as severe of which 2 were rated as "doubtful" causality by the investigator and 1 other was rated "unlikely". Three placebo patients experienced adverse events rated as severe of which 1 was considered "doubtful" causality and 1 was "unlikely".
A serious adverse event was reported for a patient who had discontinued Concerta and was later involved in an accident, receiving multiple bone fractures.

Heart rate in the Concerta group increased a mean of 1.3 (SD 9.03) beats per minute at endpoint in comparison to a mean 1.7 beat (SD 12.1) per minute decrease in heart rate in the placebo group. Mean systolic blood pressure changes were similar between the 2 groups with a 1.1mm Hg (SD 10.2- increase in the Concerta® group compared to a 0.8 decrease (SD 11.2)in the placebo group. A similar effect was seen in diastolic blood pressure.

Vital Signs

		Concerta N= 73			Placebo N= 72		
		n	Mean	SD	n	Mean	SD
Observed Values	Screened	73	73.3	10.07	71	73.8	10.12
	Baseline	73	76.2	10.16	72	76.7	12.04
Change from Baseline to	Day 5	72	1.1	8.35	72	-0.7	8.15
	Day 14	66	3.0	9.46	71	-1.1	10.55
	Day 21	64	1.6	9.19	69	0.5	9.76
	Day 28	62	4.2	9.28	68	-0.4	9.73
	Day 35 - Final Visit	72	1.3	9.03	71	-1.7	12.07

Systolic BP

		Concerta			Placebo		
		n	Mean	SD	n	Mean	SD
Observed Values	Screened	73	122.0	15.66	71	120.9	13.90
	Baseline	73	124.0	14.77	72	121.1	14.03
Change from Baseline to	Day 5	72	-0.5	7.80	72	-0.8	9.20
	Day 14	66	0.2	10.07	71	-1.3	10.08
	Day 21	64	1.4	10.22	69	-0.8	8.63
	Day 28	62	0.3	10.25	68	-0.6	8.79
	Day 35 - Final Visit	72	1.1	10.15	71	-0.8	11.19

Diastolic BP

		Concerta			Placebo		
		n	Mean	SD	n	Mean	SD
Observed Values	Screened	73	78.6	9.66	71	76.8	8.71
	Baseline	73	78.0	10.45	72	76.1	8.48
Change from Baseline to	Day 5	72	0.2	7.88	72	1.1	9.41
	Day 14	66	1.1	8.77	71	0.4	8.80
	Day 21	64	2.1	8.85	69	0.3	9.04
	Day 28	62	1.2	8.64	68	1.0	8.66

Four subjects, all in the placebo group, developed clinically-significant laboratory test results (elevated cholesterol and/or triglycerides were common to all) over the course of the study. There were no clinically significant ECG changes in either group. A mean decrease of 1.1kg (SD 1.8 was noted in the Concerta® group compared to a mean weight gain of.1kg (SD 1.9)in the placebo group.

CONCLUSION:

This is the first large, multicentre randomized, placebo controlled study to examine the efficacy of Concerta augmentation of antidepressants in treatment resistant depression. An early effect was seen on depressive symptoms as assessed by MADRS and CGI-S/I which disappeared by endpoint. However, the symptoms of fatigue and apathy showed early and sustained improvement over the 5week treatment period in favor of Concerta. Both the Concerta and placebo groups experienced a response rate of 40%. It is possible that the ongoing effect of previously prescribed antidepressants, spontaneous remissions and the supportive therapeutic environment may be contributory to the lack of differentiation between the groups.Patients in the Concerta group did not demonstrate any clinically significant effects on ECG, heart rate or blood pressure. Adverse events were mild to moderate in the majority of Concerta patients and Concerta appeared to be well tolerated based on the small number of discontinuations due to adverse events.

Date of this report:	December 13, 2006

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