CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Janssen-Cilag EMEA	
Name of Finished Product	Concerta®	
Name of Active Ingredient(s)	Methylphenidate HCl	

Protocol No.: 42603ATT3002

Title of Study: A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Safety and Efficacy of Prolonged Release (PR) OROS® methylphenidate (18, 36 and 72 mg/day), With Open-Label Extension, in Adults with Attention Deficit/Hyperactivity Disorder.

Principal Investigator: Not applicable

Publication (Reference): None

Study Period: 07 April 2005 – 01 August 2006 | **Phase of Development:** III

Objectives:

The **primary objective** of the **double-blind phase** of this study was to evaluate the efficacy and safety of 3 fixed dosages of Prolonged Release (PR) OROS methylphenidate (18, 36 and 72 mg/day) compared with placebo in adult subjects with attention deficit / hyperactivity disorder (ADHD). The efficacy response was measured by the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated Conners' Adult ADHD Rating Scale (CAARS), from start of treatment to the end of the double-blind phase.

Secondary objectives of the **double-blind phase** were:

- to assess the improvement in severity of illness associated with the use of PR OROS® methylphenidate compared with placebo using a clinical global impression score;
- to assess the subject's self report of reduction of ADHD symptoms associated with the use of PR OROS® methylphenidate compared with placebo;
- to assess the benefits to work, family and social functioning associated with the use of PR OROS® methylphenidate compared with placebo;
- to assess the investigator's assessment of treatment effectiveness;
- to assess the dose-response relationship of PR OROS® methylphenidate;
- to assess safety based on AE reporting, vital signs and clinical laboratory tests.

The **primary objective** of the **open-label extension** was to assess safety and tolerability of PR OROS® methylphenidate in a flexible dose regimen (18-90 mg/day) in adult subjects diagnosed with ADHD.

Secondary objectives of the **open-label phase** were:

- to assess the efficacy of PR OROS® methylphenidate expressed as a function of change in the sum of the inattention and hyperactivity/impulsivity subscales of the investigator-rated CAARS;
- to assess the effect on ADHD symptoms by means of change in total ADHD subscales;
- to assess the effect on overall functioning, work, family and social functioning, and quality of life parameters as measured by the Clinical Global Impression Scale - Severity (CGI-S) and Change (CGI-C), Sheehan Disability Scale (SDS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and Global Assessment of Effectiveness (GAE), respectively;
- to assess the safety based on AE reporting, vital signs and clinical laboratory tests.

Methodology: this was an international, multicentre, double-blind, randomized, placebo-controlled, parallel group, dose-response study (5-week duration) with 3 fixed dose groups (18. 36 and 72 mg) followed by an open-label extension period of 7-week duration with flexible dosing. The study was conducted in Great Britain, Germany, Denmark, Norway, Sweden, Finland, Czech Republic, Greece, France, The Netherlands, Spain, Portugal, and Switzerland.

Number of Subjects (planned and analyzed): planned: 400
analyzed in double-blind: 401
analyzed in open-label: 370

SYNOPSIS (CONTINUED)

Diagnosis and Main Criteria for Inclusion: attention deficit / hyperactivity disorder (ADHD) in adult subjects.

- Adult male or female subjects, aged between 18 and 65 years, inclusive;
- Diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV, Revision 2000) and confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV;
- Reported chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before age 7 years and still meeting DSM-IV criteria at the time of assessment. ADHD was not diagnosed if the symptoms were better accounted for by another psychiatric disorder (e.g. mood disorder (especially bipolar disorder), anxiety disorder, psychotic disorder, personality disorder);
- CAARS score of ≥ 24 as determined by investigator at screening visit.

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

Double-blind phase: PR OROS® methylphenidate 18 and 36 mg tablets; doses: 18, 36 or 72 mg/day; oral;

batch n° 18 mg: 0009478/0410815 – 0009478/0413859
36 mg: 0009477/0413862 – 0009477/0509380

Open-label phase: PR OROS® methylphenidate 18 and 36 mg tablets; doses: 18, 36, 54, 72 or 90 mg/day; oral;

batch n° 18 mg: 0009478/0410815 – 0009478/0509369
36 mg: 0009477/0413862 – 0009477/0415973 – 0009477/0522184
54 mg: 0009989/0412349 – 0014585/0435317 – 0009989/0520664 – 0009989/0533009

Reference Therapy, Dose and Mode of Administration, Batch No.:

Double-blind phase: Placebo 2 tablets / day; oral; batch n° 0015065/12150.1

Open-label phase: no reference

Duration of Treatment:

Double-blind phase: 35 days (5 weeks)

Open-label phase: 49 days (7 weeks)

Criteria for Evaluation:

Efficacy: CAARS; CGI; CAARS-S:S; SDS; Q-LES-Q, GAE, onset of therapeutic effect, responder rate

Safety: adverse events, laboratory tests, vital signs, body weight, physical examination and pregnancy testing

Statistical Methods: Intent-to-treat analysis, Cochran-Mantel-Haenszel-correlation test, Wilcoxon's signed rank test, ANCOVA, t-tests, Kodell-Chen-closed testing procedure, Jonckheere-Terpstra, Cochran-Armitage one-sided monotone trend tests, Dunnett's test, Sidak correction.

SYNOPSIS (CONTINUED)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS DOUBLE-BLIND PHASE:

As shown below, PR OROS methylphenidate administered at doses of 18 mg, 36 mg and 72 mg/day was significantly more effective than placebo in improving CAARS total scores at double-blind end point (primary efficacy end point) in adult subjects with ADHD. No trend towards a dose-response relationship of PR OROS methylphenidate for change from baseline to double-blind end point in CAARS total score was found. However, it should be noted that this study was not powered to detect differences between the PR OROS methylphenidate dose groups. Findings for the primary parameter were consistent with and complemented by the results for the secondary efficacy variables response rate, CGI-S, CGI-C, and subject-rated CAARS-S:S. Quality of life as measured by SDS, Q-LES-Q-SF and GAE also improved during the double-blind treatment period, though statistical superiority over placebo was only demonstrated for SDS results. A more pronounced improvement in CAARS total score in the PR OROS methylphenidate groups compared with placebo was first observed after 1 week of treatment in the double-blind phase; statistical superiority over placebo (unadjusted for multiplicity) was maintained for each PR OROS methylphenidate group for the duration of the 5-week double-blind phase. At the end of the double-blind phase, significantly more subjects who received PR OROS methylphenidate showed a response to treatment (i.e., at least 30% reduction in CAARS total score) compared to subjects who received placebo.

ITT / double-blind analysis set		**PR OROS MPH**		
	Placebo	**18 mg**	**36 mg**	**72 mg**
CAARS total score (primary variable)	**(N=95)**	**(N=99)**	**(N=101)**	**(N=99)**
Mean change[a] (SD)	-7.6 (9.93)	-10.6 (10.34)*	-11.5 (9.97)*	-13.7 (11.11)*
Response rate[b]	**(N=95)**	**(N=99)**	**(N=101)**	**(N=99)**
n (%)	26 (27.4)	50 (50.5)*	49 (48.5)*	59 (59.6)*
CGI-S	**(N=93)**	**(N=97)**	**(N=100)**	**(N=98)**
Median change[d] (Range)	0.0 (-3 - 1)	-1.0 (-4 - 1)*	-1.0 (-4 - 1)*	-1.0 (-4 - 1)*
CGI-C	**(N=93)**	**(N=97)**	**(N=100)**	**(N=98)**
Median[c] (Range)	3.0 (1 - 6)	3.0 (1 - 5)*	3.0 (1 - 6)*	3.0 (1 - 6)*
CAARS-S:S	**(N=91)**	**(N=93)**	**(N=95)**	**(N=92)**
Mean change[d] (SD)	-5.8 (11.26)	-10.4 (12.90)*	-11.3 (12.42)*	-14.4 (15.52)*
SDS	**(N=74)**	**(N=76)**	**(N=79)**	**(N=75)**
Mean change[d] (SD)	-2.2 (3.90)	-4.8 (6.25)*	-4.1 (5.62)*	-5.1 (6.96)*
Q-LES-Q-SF	**(N=78)**	**(N=82)**	**(N=86)**	**(N=78)**
Mean change[d] (SD)	5.0 (14.17)	5.6 (12.30)	4.7 (15.68)	6.7 (18.97)
GAE	**(N=93)**	**(N=97)**	**(N=100)**	**(N=98)**
Median[c] (Range)	0.0 (0 - 3)	1.0 (0 - 3)	1.0 (0 - 3)	1.0 (0 - 3)

* denotes a statistically significant difference with placebo in favor of PR OROS methylphenidate using Dunnett's procedure to adjust for multiple comparisons.

N = number of subjects with data

[a] change from baseline to double-blind end point

[b] response was defined as a 30% or greater reduction from baseline in CAARS total score (at double-blind end point)

[c] at Week 5 (end of double-blind phase)

[d] change from baseline to Week 5 (end of double-blind phase)

SYNOPSIS (CONTINUED)

SAFETY RESULTS DOUBLE-BLIND PHASE:

Results of this 5-week, double-blind, randomized, placebo-controlled, parallel group study indicate that PR OROS methylphenidate, administered in daily doses of 18 mg, 36 mg and 72 mg, was generally well tolerated by adult subjects with ADHD. There were no deaths during the trial and the incidence of serious adverse events and adverse events leading to study drug discontinuation was low.

All Subjects / double-blind		**PR OROS MPH**			
Number of subjects with … n (%)	**Placebo**	**18 mg**	**36 mg**	**72 mg**	**All**
	N = 96	**N = 101**	**N = 102**	**N = 102**	**N = 305**
at least one TEAE	63 (66)	76 (75)	77 (76)	84 (82)	237 (78)
at least one serious TEAE	0	2 (2)	0	2 (2)	4 (1)
at least one severe TEAE	4 (4)	4 (4)	10 (10)	20 (20)	34 (11)
at least one TEAE leading to permanent stop of trial medication	1 (1)	1 (1)	4 (4)	8 (8)	13 (4)
at least one TEAE at least possible related to trial medication	41 (43)	52 (52)	60 (59)	70 (69)	182 (60)

The most frequently reported adverse events were decreased appetite, headache, insomnia, nausea, dry mouth, dizziness, weight decreased, nasopharyngitis, tachycardia, irritability, anxiety and hyperhidrosis. All these adverse events (except for headache in the highest dose group, weight decreased in the lowest dose group and nasopharyngitis) were reported at a higher incidence in the PR OROS methylphenidate groups than in the placebo group. A trend towards a dose-relatedness for decreased appetite and dry mouth were observed. The same trend was observed for the incidence of adverse events belonging to the following body systems: psychiatric disorders, gastro-intestinal disorders, metabolism and nutrition disorders and cardiac disorders. Incidences were higher in each of the three PR OROS methylphenidate groups than in the placebo group.

Preferred Term (reported by >5% of subject treated with PR OROS MPH) n (%)	**Placebo (N=96)**	**PR OROS MPH**			
		18 mg (N=101)	**36 mg (N=102)**	**72 mg (N=102)**	**All (N=305)**
Decreased appetite	7 (7.3)	20 (19.8)	22 (21.6)	35 (34.3)	77 (25.2)
Headache	17 (17.7)	26 (25.7)	21 (20.6)	17 (16.7)	64 (21.0)
Insomnia	7 (7.3)	12 (11.9)	12 (11.8)	17 (16.7)	41 (13.4)
Nausea	4 (4.2)	8 (7.9)	16 (15.7)	15 (14.7)	39 (12.8)
Dry mouth	2 (2.1)	8 (7.9)	7 (6.9)	21 (20.6)	36 (11.8)
Dizziness	7 (7.3)	6 (5.9)	10 (9.8)	9 (8.8)	25 (8.2)
Weight decreased	5 (5.2)	3 (3.0)	8 (7.8)	11 (10.8)	22 (7.2)
Nasopharyngitis	9 (9.4)	7 (6.9)	8 (7.8)	4 (3.9)	19 (6.2)
Tachycardia	0	4 (4.0)	5 (4.9)	8 (7.8)	17 (5.6)
Irritability	1 (1.0)	4 (4.0)	4 (3.9)	9 (8.8)	17 (5.6)
Anxiety	1 (1.0)	3 (3.0)	5 (4.9)	8 (7.8)	16 (5.2)
Hyperhidrosis	1 (1.0)	5 (5.0)	3 (2.9)	8 (7.8)	16 (5.2)

SYNOPSIS (CONTINUED)

Thirteen subjects discontinued study treatment because of an adverse event that emerged during treatment with PR OROS methylphenidate during the double-blind phase versus 1 subject treated with placebo. One subject in the 36 mg group and the subject treated with placebo discontinued trial medication for these adverse events in the open-label phase. Four subjects who received PR OROS methylphenidate experienced one serious adverse event each.

Assessments of laboratory parameters during this double-blind phase of the study did not reveal noteworthy mean changes from baseline. No obvious trends in number of subjects with shifts of laboratory parameters from within to below or above laboratory normal ranges were observed. There was a low incidence of laboratory-related adverse events.

No clinically relevant changes in mean diastolic and systolic blood pressure were noted in any of the treatment groups. Pulse showed small but statistically significant increases from baseline at all time points in the three active treatment groups. A dose-response in the mean increase was observed with increasing PR OROS methylphenidate dose. Incidences of tachycardia and palpitations were higher in the PR OROS methylphenidate groups than in the placebo group.

Mean statistically but not clinically significant decreases versus baseline in body weight and BMI were observed in the three active treatment groups. These changes showed a dose-related tendency. Decreased appetite and decreased weight were more frequently reported in subjects treated with PR OROS methylphenidate than in those treated with placebo. As mentioned above, a tendency towards a dose-relation was observed for the incidence of 'decreased appetite'. A similar tendency was seen for the adverse event 'decreased weight'.

EFFICACY RESULTS OPEN-LABEL PHASE:

During the open-label phase, when all subjects received an individually optimized PR OROS methylphenidate dose between 18 mg and 90 mg per day, CAARS total scores continued to improve in both the placebo / PR OROS methylphenidate and PR OROS methylphenidate / PR OROS methylphenidate groups (see below), with a more pronounced improvement in subjects who received placebo during the double-blind phase. At open-label end point, a statistically significant improvement relative to double-blind end point was observed for CAARS total score in both groups. The results of the other assessed scales (CGI-S, CGI-C, subject-rated CAARS-S:S, GAE) were consistent with those of the CAARS. The results of the SDS and Q-LES-Q-SF scales indicated a statistically significant improvement of the subjects' quality of life during the open-label phase.

At the post-study visit, when the subjects had been untreated for a week, CAARS total score had worsened statistically significantly relative to open-label end point. As during the double-blind and open-label phases, the results of the other assessed scales (CGI-S and CGI-C) were consistent with those of the CAARS.

ITT / open-label analysis set	Placebo / PR OROS MPH	PR OROS MPH / PR OROS MPH
CAARS total score	**(N=93)**	**(N=276)**
Mean change[a] (SD)	-8.4 (9.42)*	-6.1 (9.30)*
CGI-S	**(N=89)**	**(N=265)**
Median change[b] (Range)	-1.0 (-4 – 1)*	-1.0 (-4 – 2)*
CGI-C	**(N=89)**	**(N=264)**
Median[c] (Range)	2.0 (1 – 4)	2.0 (1 – 5)
CAARS-S:S	**(N=89)**	**(N=259)**
Mean change[b] (SD)	-11.1 (12.92)*	-7.2 (11.90)*
SDS	**(N=68)**	**(N=202)**
Mean change[b] (SD)	-4.6 (5.77)*	-2.8 (5.95)*
Q-LES-Q-SF	**(N=75)**	**(N=230)**
Mean change[b] (SD)	5.6 (16.09)*	4.7 (14.77)*
GAE	**(N=89)**	**(N=264)**
Median[c] (Range)	2.0 (0 – 3)	2.0 (0 – 3)

* denotes a statistically significant change from double-blind end point (CAARS) or Week 5 (other parameters).
N = number of subjects with data
[a] change from Week 5 (end of double-blind phase) at open-label end point
[b] change from Week 5 (end of double-blind phase) at Week 12 (end of open-label phase)
[c] at Week 12 (end of open-label phase)

SYNOPSIS (CONTINUED)

SAFETY RESULTS OPEN-LABEL PHASE:

Results of this 7-week, open-label study indicate that flexible dosed PR OROS methylphenidate 18 mg to 90 mg daily was generally well tolerated by subjects with ADHD. There were no deaths during the trial and the incidence of serious adverse events and adverse events leading to study drug discontinuation was low.

All Subjects / open-label

Number of subjects with … n (%)	**Placebo / PR OROS MPH**	**PR OROS MPH / PR OROS MPH**	**Total**
	N = 93	**N = 277**	**N = 370**
at least one TEAE	70 (75)	183 (66)	253 (68)
at least one serious TEAE	1 (1)	1 (<1)	2 (<1)
at least one severe TEAE	11 (12)	22 (8)	33 (9)
at least one TEAE leading to permanent stop of trial medication	4 (4)	13 (5)	17 (5)
at least one TEAE at least possible related to trial medication	54 (58)	141 (51)	195 (53)

More subjects in the placebo / PR OROS methylphenidate group than in the PR OROS methylphenidate / PR OROS methylphenidate group (75% versus 66%) experienced an adverse event.

The most frequently reported adverse events in the open-label phase were headache, decreased appetite, insomnia, nausea, nasopharyngitis and restlessness which was in line with the adverse events reported during double-blind phase. Incidence of headache was comparable between the placebo / PR OROS methylphenidate group and the PR OROS methylphenidate / PR OROS methylphenidate group. The other adverse events were reported more frequently in the group of subjects who had been treated with placebo during the double-blind phase.

Preferred Term (reported by >5% of subject) n (%)	**Placebo / PR OROS MPH (N=93)**	**PR OROS MPH / PR OROS MPH (N=277)**	**Total (N=370)**
Headache	16 (17.2)	46 (16.6)	62 (16.8)
Decreased appetite	21 (22.6)	26 (9.4)	47 (12.7)
Insomnia	16 (17.2)	25 (9.0)	41 (11.1)
Nausea	10 (10.8)	16 (5.8)	26 (7.0)
Nasopharyngitis	8 (8.6)	13 (4.7)	21 (5.7)
Restlessness	7 (7.5)	12 (4.3)	19 (5.1)

Two subjects experienced a serious adverse event during open-label period and 2 subjects had a serious adverse event during the post-study period. Seventeen subjects discontinued study medication due to at least one adverse event emerging in the open-label phase. The numbers of discontinuations due of adverse events were similar between the placebo / PR OROS methylphenidate group and the PR OROS methylphenidate / PR OROS methylphenidate group.

Assessments of laboratory parameters did not reveal noteworthy mean changes from baseline. No obvious trends in number of subjects with shifts of laboratory parameters from within to below or above laboratory normal ranges were observed. There was a low incidence of laboratory-related adverse events.

No clinically relevant changes in mean diastolic and systolic blood pressure were noted. Pulse showed small but statistically significant changes from baseline at all time points. Changes were similar to those observed in the highest treatment group during double-blind treatment.

A mean statistically but not clinically significant decrease versus baseline in body weight and BMI was observed after the open-label treatment.

SYNOPSIS (CONTINUED)

CONCLUSION:

PR OROS methylphenidate administered at doses of 18 mg, 36 mg and 72 mg/day was significantly more effective than placebo in improving CAARS total scores at double-blind end point (primary efficacy end point) in adult subjects with ADHD. No trend towards a dose-response relationship of PR OROS methylphenidate for change from baseline to double-blind end point in CAARS total score was found.

Findings for the primary parameter were consistent with and complemented by the results for the secondary efficacy variables response rate, CGI-S, CGI-C, and subject-rated CAARS-S:S. Quality of life as measured by SDS, Q-LES-Q-SF and GAE also improved during the double-blind treatment period, though statistical superiority over placebo was only demonstrated for SDS results.

During the open-label phase, when all subjects received an individually optimized PR OROS methylphenidate dose between 18 mg and 90 mg per day, ADHD symptoms continued to improve in both the placebo / PR OROS methylphenidate and PR OROS methylphenidate / PR OROS methylphenidate groups.

PR OROS methylphenidate administered at a fixed daily dose of 18 mg, 36 mg and 72 mg for a period of 5 weeks was generally safe and well tolerated by adults with ADHD. The same safety profile was demonstrated in a flexible dose regimen between 18 mg and 90 mg daily for a period of 7 weeks. The safety profile during both phases was in line with that reported in other ADHD studies with methylphenidate in pediatric and adult subjects and no unexpected adverse events were reported during any of the phases.

PR OROS methylphenidate administered at doses of 18 mg, 36 mg or 72 mg per day demonstrated efficacy and tolerability in the treatment of attention deficit hyperactivity disorder in adults.

Issue Date of the Clinical Study Report: 26 April 2007

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