SYNOPSIS

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

Protocol No.: 42603ATT3004

Title of Study: An Open-Label, Multicentre Study to Evaluate the Long-Term Safety of Prolonged Release (PR) OROS® Methylphenidate (18, 36, 54, 72 and 90 mg/day) in Adults with Attention Deficit/Hyperactivity Disorder.

Coordinating Investigator: Prof. [redacted] M.D. - UMC St.Radboud (966), Nijmegen; The Netherlands

Publication (Reference): None

Study Period: 13 January 2006 (first subject first visit)
10 July 2008 (last subject last visit)

Phase of Development: III

Objectives:

The **primary objective** of the **open-label phase** was to assess long-term safety and tolerability of flexibly dosed (18-90 mg/day) PR OROS methylphenidate (MPH) in adult subjects diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD) who had completed the 7-week open–label phase of the 42603ATT3002 study.

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

- to assess the long-term efficacy of PR OROS MPH expressed as change in the sum of the inattention and hyperactivity/impulsivity subscales of the investigator-rated Conners' adult ADHD rating scale (CAARS);
- to assess the long-term effect on ADHD symptoms expressed as change in CAARS subscale scores;
- to assess the long-term effect on overall functioning, work, family and social functioning, and quality of life (QoL) 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) and CAARS Self-Report: Short Version (CAARS-S:S), respectively.

The study was amended to include a 4-week, double-blind, randomized withdrawal phase (International Amendment 3 [Amendment INT-3]).

The **primary objective** of the **double-blind, randomized, placebo-controlled withdrawal phase** was to evaluate maintenance of treatment effects of PR OROS MPH in adult subjects with ADHD who had received long-term (at least 52 weeks) treatment with PR OROS MPH at the optimal dose.

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

- to evaluate the treatment effect as rated by the investigator on the GAE scale or the subject on the SDS and Q-LES-Q scales;

- to evaluate the subject's self report of ADHD symptoms associated with the use of PR OROS MPH compared to placebo (CAARS-S:S);
- to evaluate the effect of PR OROS MPH compared to placebo based on CGI-S and CGI-C;
- to evaluate the number of subjects showing an increase of < 30%, 30-50%, or > 50% in the investigator-rated CAARS total score and of subjects with CAARS total score 0-17 at double-blind endpoint in the PR OROS MPH group and the placebo group;
- to evaluate safety through AE reporting, vital signs and clinical laboratory tests.

Methods: This was an open-label extension of study 42603ATT3002 followed by a double-blind, randomized, placebo-controlled, withdrawal phase conducted at multiple sites in Europe that evaluated PR OROS MPH in adult subjects with ADHD.

During the open-label phase of study 42603ATT3004, subjects were maintained on a flexible dose (18, 36, 54, 72, or 90 mg/day) of PR OROS MPH. Subjects who entered study 42603ATT3004 immediately after study 42603ATT3002 continued the optimal dose as determined in study 42603ATT3002. Subjects who experienced an interruption of study drug administration after 42603ATT3002 for up to 30 calendar days before entering 42603ATT3004 were titrated to an optimal dosage. Treatment duration was extended from 52 weeks to 72 weeks (International Amendment 2 [INT-2]) or 108 weeks in Germany (GER-4/INT-3) to allow continued treatment with PR OROS MPH until subjects could enter the double-blind phase (International Amendment 3 [INT-3]).

An interim period was allowed for subjects who completed the open-label phase of 42603ATT3004 INT-1 prior to approval of INT-2. Subjects continued open-label PR OROS MPH using commercial drug supply until they could enter the extended (72 weeks) open-label treatment period (INT-2).

The double-blind phase was designed to evaluate maintenance of treatment effects following long-term use of PR OROS MPH (INT-3). To enter the double-blind phase, subjects were required to have received at least 52 weeks of treatment with PR OROS MPH and to provide informed consent. During the double-blind phase, subjects were randomly assigned in a 1:1 ratio to continued treatment with PR OROS MPH at a fixed dose (i.e., the dose received at the end of the open-label phase) or placebo for 4 weeks.

One week after a subject's final dose of study medication, a post-study visit for collection of additional safety data was conducted. For subjects not participating in the double-blind phase, this visit was planned one week after last medication intake in the open-label phase. For subjects continuing into the double-blind phase, the post-study visit was planned one week after the last medication intake in the double-blind phase.

The following medications were not allowed during the study (neither in the open-label nor in the double-blind phase): alpha-2 adrenergic receptor agonists, tricyclic antidepressants*, theophylline, coumarin anticoagulants or anticonvulsants, selective serotonin reuptake inhibitors (SSRIs)* (including fluoxetine*), monoamine-oxidase (MAO) inhibitors, herbal and over-the-counter stimulant diet preparations or drugs that contain stimulants, any treatment for ADHD (except MPH-containing medication[a]), and any other medication likely to interfere with safe administration of MPH.

* Unless the subject had been on a stable dosage during the 42603ATT3002 study, in which case treatment could continue as long as dosage remained unchanged for the duration of the study.

[a] According to inclusion criterion 8, subjects were only allowed to take PR OROS MPH for the treatment of ADHD during the study.

Number of Subjects (planned and analyzed): planned in open-label: no formal sample size
analyzed in open-label: 155
planned in double-blind: 80
analyzed in double-blind: 45

Diagnosis and Main Criteria for Inclusion:

- Adult male or female subjects, aged between 18 and 65 years, inclusive;
- Diagnosis of ADHD according to the DSM-IV and confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV;
- Described chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before age 7 years and continuing to meet DSM-IV criteria at the time of assessment. ADHD was not to be 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);
- Completion of the open-label phase in the 42603ATT3002 study according to protocol, or within 30 days of completion of the open-label phase of the 42603ATT3002 study.

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

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

For all countries except Portugal, open-label trial medication was sourced from commercial stock in the respective country and relabeled. Trial medication for Portugal was manufactured by ALZA Corporation in the USA and relabeled/ packaged by Fisher USA, under the responsibility of the sponsor. Batch numbers for trial medication used in Portugal were: 0542670 (36 mg) and 0543557 (54 mg). The 18-mg tablets were not used in Portugal.

Double-blind phase: PR OROS MPH 18, 36, and 54-mg tablets and matching placebo; doses: 18, 36, 54, 72, or 90 mg/day; oral.

Batch numbers for medication used during the double-blind phase were: 0014983 (18 mg), 0014985 (36 mg), 0017210 (54 mg), 0015065 (placebo).

Duration of Treatment:

Subjects were treated for up to 72 weeks in the open-label phase (up to 108 weeks in Germany) and for 4 weeks in the double-blind phase of the study.

Criteria for Evaluation:

Efficacy: CAARS, CGI-S, CGI-C, CAARS-S:S, SDS, Q-LES-Q, GAE

Safety: adverse events, laboratory tests, vital signs and body weight, physical examination, ECG (Germany only)

Statistical Methods: Intent-to-treat analysis, paired t-test, ANCOVA, Wilcoxon's signed rank test, descriptive statistics.

The analysis set for the primary efficacy analysis was the intent-to-treat population. In the double-blind phase, the per protocol population was used as a sensitivity analysis for the primary efficacy parameter. The intent-to-treat population was used for the secondary efficacy analyses.

In the open-label phase, there were two time points of efficacy assessments (at baseline and at the end of the open-label phase [except for the German patients, Amendment GER-1/INT-1]). Depending on the distribution of the scores, a paired t-test was performed or a Wilcoxon's matched pairs signed ranks test. The hypothesis to be tested was that there was no difference between baseline and endpoint.

The primary endpoint in the double-blind phase was the comparison between the PR OROS methylphenidate group and placebo group for the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated CAARS from double-blind baseline to double-blind endpoint. The change from double-blind baseline score at each time point and at endpoint in the double-blind phase was analyzed using an analysis of covariance (ANCOVA) model. The model included treatment, sex and country as factors and age and baseline sum of inattention and hyperactivity/impulsivity subscale scores as covariates. As there is only one comparison of interest for the primary objective of the double-blind phase, no correction for multiplicity was done. If applicable, secondary endpoints in the double-blind phase were analyzed in a similar fashion as the primary parameter, i.e., using ANCOVA. In case of categorical data, an alternative test was used. In addition to the secondary efficacy endpoints as defined per protocol, two additional endpoints were defined prior to breaking of the study blind to assess the loss of effect: 1) a comparison between treatment groups of the proportion of subjects with an increase in CGI-S score from double-blind baseline of 1 or more and 2) a comparison between treatment groups of the proportion of subjects with either an increase in CGI-S score from double-blind baseline of 2 or more or a discontinuation due to lack of efficacy during the double-blind period.

RESULTS OPEN-LABEL PHASE:

SUBJECT AND TREATMENT INFORMATION:

In total, 156 subjects were screened of which 155 were treated in the open-label phase of this study. Overall, 99 subjects (63.9%) completed and 56 subjects (36.1%) discontinued the open-label phase. Main reasons for discontinuation were the occurrence of adverse events (n=16), withdrawal of consent (n=15), and being lost to follow-up (n=11).

In the "intent-to-treat / open-label" population, most subjects (98.1%) were White, 54.2% were male, and mean (SD) age was 35.0 (10.60) years.

The mean (SD) duration of treatment during the open-label phase in study 42603ATT3004 was 437.1 (206.75) days (approximately 62 weeks). The mean (SD) dose (excluding zero doses) for this period was 54.3 (21.04) mg daily and the most frequently used final dose was 36 mg PR OROS MPH, used by 35.9% of subjects.

EFFICACY:

All efficacy parameters showed an improvement at endpoint compared to baseline. Improvement was statistically significant for the investigator-rated CAARS and CGI-S scales as well as for the self-reported CAARS-S:S and SDS scales, indicating a reduction of ADHD symptoms and their impact on the subjects' daily activities.

ITT / Open-Label	**PR OROS MPH (N=155)**	**p-value**
CAARS Total Score		
Mean Change at Endpoint (SD)	-1.9 (7.82)	0.003
CAARS Hyperactivity/impulsivity subscale		
Mean Change at Endpoint (SD)	-0.9 (4.36)	0.010
CAARS Inattention subscale		
Mean Change at Endpoint (SD)	-1.0 (4.63)	0.008
CAARS-S:S		
Mean Change at Endpoint (SD)	-3.1 (9.63)	<0.001
CGI-S		
Median Change at Endpoint (Range)	0.0 (-4 - 3)	0.007
CGI-C		
Median Endpoint Score (Range)	3.0 (1 - 6)	-
GAE		
Median Endpoint Score (Range)	2.0 (0 - 3)	-
Q-LES-Q		
Mean Change at Endpoint (SD)	1.4 (15.15)	0.275
SDS		
Mean Change at Endpoint (SD)	-1.7 (6.16)	<0.001

SAFETY:

Most subjects (126; 81.3%) experienced one or more treatment-emergent adverse events during the open-label phase. The majority (93.7%) of the adverse events during open-label treatment (occurring in 63.9% of subjects) were mild or moderate in severity. Twenty-seven (17.4%) subjects reported at least one severe adverse event.

There were no deaths during the study. Twelve subjects (7.7%) experienced one or more serious adverse events, none of which were considered related to PR OROS MPH by the investigator. Each SAE with a distinct MedDRA (Medical Dictionary for Regulatory Activities) preferred term occurred in only 1 subject. Fifteen subjects (9.7%) permanently discontinued open-label medication due to at least one adverse event. One additional subject discontinued study 42603ATT3004 for an AE that started during study 42603ATT3002 (i.e., not treatment-emergent in 42603ATT3004). None of the AEs that led to premature discontinuation during the open-label phase were reported in more than two subjects. Sixty-two subjects (40%) experienced one or more adverse events that were considered at least possibly related to study medication by the investigator.

ITT / Open-Label Number of subjects with …, n (%)	**PR OROS MPH (N=155)**
at least one AE	126 (81.3%)
at least one severe AE	27 (17.4%)
at least one SAE	12 (7.7%)
at least one AE for which trial medication was permanently stopped	15 (9.7%)[a]
at least one AE considered at least possibly related to trial medication by the investigator	62 (40.0%)

[a] One additional subject discontinued study 42603ATT3004 for an AE that started during study 42603ATT3002 (i.e., not treatment-emergent in 42603ATT3004).

The proportion of subjects who reported at least one adverse event that was coded to a given system organ class was highest for the system organ classes infections and infestations (39.4%), psychiatric disorders (32.3%), and nervous system disorders (30.3%). The most frequently reported adverse events were headache, nasopharyngitis, restlessness, insomnia, back pain, influenza, hypertension, drug effect decreased, and depressed mood.

MedDRA Preferred term (reported in > 5% of the subjects), n (%)	**PR OROS MPH (N=155)**
Headache	33 (21.3)
Nasopharyngitis	31 (20.0)
Restlessness	12 (7.7)
Insomnia	11 (7.1)
Back pain	11 (7.1)
Influenza	10 (6.5)
Hypertension	9 (5.8)
Drug effect decreased	9 (5.8)
Depressed mood	8(5.2)

Evaluation of selected adverse events of special interest revealed a total of 19 subjects (12.3%) with events that were cardiovascular in nature and 6 subjects (3.9%) with events that were psychiatric in nature. Adverse events of interest led to discontinuation in 5 subjects (3.2%).

The only treatment-emergent laboratory abnormality of potential clinical importance occurring in more than 1 subject at endpoint was low thyroid stimulating hormone, which was observed in 3/132 subjects (2.3%). No clinically relevant mean changes over time were observed for any of the vital signs parameters. The most frequent treatment-emergent vital sign abnormality of potential clinical importance was a high value in standing pulse rate, observed in 39 subjects (26.0%). A high value of potential clinical importance in standing and supine pulse rate was observed concurrently on at least one occasion in 10 subjects (6.6%). A concurrent high standing and supine diastolic or systolic blood pressure of potential clinical importance was observed on at least one occasion in 7-9% of subjects. Hypertension reported as an AE led to treatment discontinuation in 2 subjects (1.3%).

RESULTS DOUBLE-BLIND PHASE:

SUBJECT AND TREATMENT INFORMATION:

Of the 99 subjects who completed the open-label phase of the trial, 45 subjects continued into the double-blind phase. Twenty-three subjects were randomized to PR OROS MPH and 22 subjects to placebo. Major treatment deviations (no compliance with study medication intake) were noted for 7 subjects in the "intent-to-treat / double-blind" population, and these were excluded from the "per protocol / double-blind" population.

Thirty-eight subjects (84.4%) completed the 4-week double-blind phase. The 7 subjects who discontinued the double-blind withdrawal phase, 2 (8.7%) in the PR OROS MPH group and 5 (22.7%) in the placebo group, stopped study medication intake due to lack of efficacy.

All subjects in the "intent-to-treat / double-blind" population were White and the mean (SD) age was 36.3 (10.91) years. In the PR OROS MPH group, 47.8% of the subjects were male compared to 31.8% male subjects in the placebo group. No major differences between the groups were observed for other demographics parameters.

The dose for each subject in the double-blind phase was determined by the investigator prior to randomization, based on the stable dose taken by the subject during the last 4 weeks of the open-label phase. For the 45 subjects who received double-blind treatment, the mean (SD) open-label treatment duration (including days with missed intakes) in the 42603ATT3004 study was 647.1 days (88.30) and the range was 504 to 747 days. During the last 4 weeks of the open-label phase, 4 subjects (8.9%) had a dose change. The mean (SD) daily dose during the double-blind period was 43.0 (16.94) mg/day in the PR OROS MPH group and the equivalent of 54.8 (23.88) mg/day in the placebo group.

EFFICACY:

At double-blind baseline, i.e., after a mean (SD) open-label treatment duration with PR OROS MPH in study 42603ATT3004 of 647.1 (88.30) days (including days with missed doses), there was a difference

in baseline disease characteristics of subjects randomized to continued PR OROS MPH and subjects randomized to placebo. All efficacy assessments (i.e., CAARS, CAARS-S:S, CGI-S, Q-LES-Q, and SDS) indicated a better symptom control at double-blind baseline for subjects randomized to continued PR OROS MPH group than for subjects randomized to placebo. The mean (SD) baseline score for the primary efficacy parameter, the CAARS total score, was 12.1 (5.34) in the group randomized to PR OROS MPH and 16.5 (7.49) in the group randomized to placebo. CAARS total score increased (i.e., worsened) in both groups during the double-blind withdrawal phase, with a mean change from baseline to endpoint of 4.0 in the PR OROS MPH group and 6.5 in the placebo group. This difference between the treatment groups was not statistically significant (p = 0.2586).

Sensitivity analyses yielded similar results. In the "per protocol / double-blind" population, the change from baseline at double-blind endpoint was 4.6 and 7.3 in the PR OROS MPH group and the placebo group, respectively. The difference between the treatment groups was not statistically significant (p = 0.1901). In the subpopulation of subjects with a double-blind baseline CAARS score of less than 24, the mean (SD) scores at double-blind baseline were 12.1 (5.34) and 13.4 (5.18) in the PR OROS MPH group and the placebo group, respectively, and the mean changes from baseline were 4.0 and 6.8, respectively. Again no statistically significant difference between the 2 groups was observed (p = 0.2191).

ITT / Double-Blind	**Placebo (N=22)**	**PR OROS MPH (N=23)**	**p value (difference between groups)**
CAARS Total Score			
Mean Value at DB Baseline (SD)	16.5 (7.49)	12.1 (5.34)	
Mean Value at DB Endpoint (SD)	23.0 (10.41)	16.2 (9.42)	
Mean Change at DB Endpoint (SD)	6.5 (7.82)	4.0 (7.61)	0.2586
> 50% Increase at DB Endpoint, n (%)	8 (36.4)	6 (26.1)	
CAARS Hyperactivity/impulsivity subscale			
Mean Change at DB Endpoint (SD)	3.4 (4.62)	2.5 (3.82)	0.4010
CAARS Inattention subscale			
Mean Change at DB Endpoint (SD)	3.1 (5.26)	1.6 (4.64)	0.1734
CAARS-S:S			
Mean Change at DB Endpoint (SD)	4.0 (11.98)	4.4 (11.90)	0.5458
CGI-S			
Median Change at DB Endpoint (Range)	1.0 (-1 - 4)	0.0 (-1 - 3)	0.2616
CGI-C			
Median DB Endpoint Score (Range)	5.0 (1 - 6)	4.0 (2 - 7)	0.0422
GAE			
Median DB Endpoint Score (Range)	0.5 (0 - 3)	2.0 (0 - 3)	0.0254
Q-LES-Q			
Mean Change at DB Endpoint (SD)	-2.7 (12.36)	-6.5 (11.37)	0.6665
SDS			
Mean Change at DB Endpoint (SD)	1.6 (8.26)	2.2 (6.05)	0.2926

Analysis of the secondary efficacy parameters showed similar results. For the CAARS hyperactivity / impulsivity and inattention subscales and CGI-S the change from baseline was smaller in the PR OROS MPH group than in the placebo group. However, the difference between the treatment groups in change from baseline was not statistically significant for these scales. Fewer subjects in the PR OROS MPH group than in the placebo group had an increase in CAARS total score at double-blind endpoint of > 50%. The scores of the investigator-rated scales CGI-C and GAE at endpoint were better (i.e., lower and higher, respectively) in the PR OROS MPH group than in the placebo group and the difference between the groups was statistically significant (p = 0.0422 and 0.0254, respectively). For the subject self-reported scales CAARS-S:S, Q-LES-Q, and SDS there was a difference between the treatment groups at double-blind baseline, with better scores (i.e., lower scores for CAARS-S:S and SDS; higher score for Q-LES-Q) in the group randomized to PR OROS MPH than in the group randomized to placebo. Change from baseline was similar in the two treatment groups for CAARS-S:S

and SDS, while it was larger in the PR OROS MPH group than in the placebo group for Q-LES-Q. There was no statistically significant difference between the treatment groups in change from double-blind baseline to endpoint for any of these scales.

The proportion of subjects with an increase from double-blind baseline to endpoint of 1 or more units in CGI-S score (i.e., with loss of treatment effect) was smaller in the PR OROS MPH group than in the placebo group (39.1% compared to 63.6%). Similarly, the proportion of subjects who either had an increase in CGI-S score of 2 or more units relative to baseline or who discontinued due to lack of efficacy was 26.1% in the PR OROS MPH group and 40.9% in the placebo group. These differences between the treatment groups were not statistically significant for either definition of loss of effect ($p = 0.1018$ and 0.2833 for the first and second definition, respectively).

SAFETY:

The incidence of AEs during the double-blind withdrawal phase was comparable in the PR OROS MPH and placebo groups. There were no deaths. One subject in the placebo group experienced an SAE (not considered drug-related by the investigator) during the double-blind phase compared to none of the subjects in the PR OROS MPH group. No subjects prematurely discontinued double-blind medication due to AEs.

ITT / Open-Label Number of subjects with …, n (%)	**Placebo (N=22)**	**PR OROS MPH (N=23)**	**All Subjects (N=45)**
at least one AE	8 (36.4)	7 (30.4)	15 (33.3)
at least one severe AE	3 (13.6)	0	3 (6.7)
at least one SAE	1 (4.5)	0	1 (2.2)
at least one AE for which trial medication was permanently stopped	0	0	0
at least one AE considered at least possibly related to trial medication by the investigator	5 (22.7)	3 (13.0)	8 (17.8)

The most frequently reported AE during the double-blind phase was hypertension, reported in 2 subjects (8.7%) in the PR OROS MPH group. All other AEs were reported in no more than 1 subject each per treatment group. Except for hypertension in the 2 subjects of the PR OROS MPH group, no other adverse events of special interest were reported that were cardiovascular in nature. No adverse events of interest that were psychiatric in nature occurred during the double-blind withdrawal phase.

The only treatment-emergent laboratory abnormality of potential clinical importance occurring at double-blind endpoint was low hematocrit, which was observed in 1 subject (4.8%) in the placebo group. Small changes in mean diastolic and systolic blood pressure, pulse rate, weight or BMI were noted from double-blind baseline to endpoint across the two treatment groups. Numerically greater decreases in mean values for standing and supine diastolic and systolic blood pressure were observed in the placebo group than in the PR OROS MPH group. The most frequent vital signs abnormality of potential clinical importance was a high value in standing diastolic blood pressure, observed in 7 subjects (31.8%) in the PR OROS MPH group and 2 subjects (9.1%) in the placebo group. There were no subjects with a concurrent, treatment-emergent high value of potential clinical importance in standing and supine diastolic or systolic blood pressure during the double-blind phase.

STUDY LIMITATIONS:

Limitations concerning the double-blind phase of the study were:

- the sample size assumptions. At the time of sample size calculation, no relevant clinical data from a randomized withdrawal study in adult subjects with ADHD were published. Therefore the sample size assumptions were solely based on clinical judgment.

- the small sample size. The planned sample size for the double-blind withdrawal phase was 80 subjects. However, of the 99 subjects who completed the open-label phase only 45 subjects consented to participate in the double-blind phase.
- No prespecified cutoffs for key assessments of efficacy were included as part of the criteria for entering the double-blind withdrawal phase.

CONCLUSION:

Flexibly dosed PR OROS MPH was generally safe and well tolerated by adults with ADHD when administered for a period of at least 52 weeks. The safety profile was in line with that reported in other ADHD studies with methylphenidate in adult subjects.

The therapeutic effect as measured by the change from baseline in CAARS total score was maintained over the open-label treatment period of at least 52 weeks. This finding was consistent with and complemented by the results for the secondary efficacy variables, the investigator-rated CGI-S, CGI-C, and GAE scales as well as for the self-reported CAARS-S:S, Q-LES-Q SF, and SDS scales, indicating a sustained reduction of ADHD symptoms and a positive impact on the subjects' daily activities. The change from baseline was statistically significant for all efficacy parameters except Q-LES-Q SF.

The primary efficacy endpoint for the double-blind withdrawal phase failed to show a statistically significant difference between the treatment groups. Nevertheless, two of the secondary endpoints (GAE and CGI-C) showed a significant difference in favor of PR OROS MPH. All other secondary endpoints were numerically in favor of PR OROS MPH, with the exception of Q-LES-Q SF, but did not reach statistical significance. The safety results indicate that PR OROS MPH tablets were well tolerated by adult subjects with ADHD during the 4-week double-blind withdrawal phase.

Note:
EudraCT-Nr: 2005-004037-18

Protocol ID	Region	Investigational site
42603ATT3004	France	Hopital Pitié -Salpetriere 47-83, Bd de l'hopital Paris 75013 France
42603ATT3004	Germany	Zentralinstitut für Medizinische Gesundheit J5 68159 Mannheim Germany
42603ATT3004	Germany	Prosona GmbH Wulfsdorfer Weg 127 22926 Ahrensburg Germany
42603ATT3004	Germany	Facharztpraxis für Psychosomatische Medizin und Psychotherapie 855xx Ottobrunn Germany
42603ATT3004	Germany	MVZ Saar-West, Psychotherapie Berliner Promenade 7 66111 Saarbrücken Germany
42603ATT3004	Germany	Diagnostik- und Therapiezentrum Augustinerstr 15 97070 Würzburg Germany
42603ATT3004	Germany	Universitätsklinikum Freiburg Klinik für Psychiatrie Hauptstr. 5 79104 Freiburg Germany
42603ATT3004	Germany	Facharztpraxis für Kinder- und Jugendpsychiatrie 637xx Aschaffenburg Germany
42603ATT3004	Germany	Universitätklinik Köln Klinik für Psychiatrie und Psychotherapie Kerpener Str. 26 50924 Köln Germany
42603ATT3004	Germany	Rheinische Kliniken Essen Virchowstr 174 45147 Essen Germany
42603ATT3004	Germany	Universität des Saarlandes Institut für gerichtliche Psychologie und Psychiatrie Kirrbergerstr 100 Homburg 66424 Germany

42603ATT3004	Germany	Facharztpraxis für Neurologie und Psychiatrie 107xx Berlin Germany
42603ATT3004	Germany	Charité Universitätsmedizin Berlin - Campus Mitte Klinik für Psychiatrie und Psychotherapie Schumannstr. 20-21 10117 Berlin Germany
42603ATT3004	Netherlands	UMC St. Radboud (966) Afdeling Psychiatrie Reinier Postlaan 10 Nijmegen 6525 GC Netherlands
42603ATT3004	Netherlands	PsyQ Psycho-Medische Programma Carel Reinierszkade 1972, Den Haag, 2593 HR Netherlands
42603ATT3004	Norway	Innlandet Hospital Sanderud Peter Skredders vei 34 Ottestad 2312 Norway
42603ATT3004	Norway	Drammen Psykiatriske Senter Dronninggaten 28 Drammen 3004 Norway
42603ATT3004	Portugal	Centro de Apoio ao Desenvolvimento Infantil Edifico Cadin Estrada da Malveira Cascais 2750-782 Portugal
42603ATT3004	Portugal	Hopital Magalhães Lemos Rua Prof. Álvaro Rodrigues Porto 4100-040 Portugal
42603ATT3004	Spain	Hospital Universitari Vall d´Hebrón Servicio de Psiquiatria Paseo Del Vall Hebron 119-129 Barcelona 8035 Spain
42603ATT3004	Switzerland	Psychiatrische Universitätsklinik Selnautrasse 9 Zürich 8001 Switzerland
42603ATT3004	Switzerland	Facharztpraxis für Psychiatrie und Psychotherapie Basel 40xx Switzerland

Changes in Conduct

The original final protocol, dated 16 August 2005, was amended 3 times (14 September 2005, 31 October 2006 and 26 March 2007). In addition, 1 local (country-specific) amendment was created for France, 3 for The Netherlands, 4 for Portugal, and 6 for Germany. All of these amendments were substantial.

General Amendments

The first international amendment (dated 14 September 2005, substantial) included clarification that assessments were done at Visit 8 of the 42603ATT3002 study (e.g., diagnostic and statistical manual [of mental disorders] 4th edition [DSM-IV] diagnosis), and could as such serve as baseline assessment if a subject continued immediately in this study. Physical assessment was added at baseline to determine eligibility in this study. Physical examinations at Visits 5 and 8 in this study were no longer performed, since this was not considered relevant. Theophylline was added as disallowed medication.

The second international amendment (dated 31 October 2006, substantial) included addition of Visits 5 and 6, and duration of study was changed from 52 to 72 weeks. A clarification that data from Visit 8 in the previous 42603ATT3002 study could be used for subjects who enter this study within 30 days following the last dosing of open-label study medication was added. A statement regarding dosage of PR OROS MPH during last 4 weeks was added (criterion in the new forthcoming phase).

The third international amendment (dated 26 March 2007, substantial) included addition of a double-blind, randomized, placebo-controlled withdrawal phase after the open-label phase of the study.

Country Specific Amendments

The first country (Germany) specific amendment (dated 9 February 2006, substantial) included additional assessment of electrocardiogram (ECG) at screening (after signing of the IC Form and no more than 7 days before the screening visit), and clinical laboratory tests at Visit 3. It also included assessment of CAARS, CGI-C, CGI-S, and CAARS-S:S at visit 3. An extra withdrawal criterion (i.e., subjects were withdrawn in case they had clear symptoms of depression or suicidal tendencies) was added.

The second country (Germany) specific amendment (dated 8 December 2006, substantial) included changes described in International Amendment 2.

In the third country (Germany) specific amendment (dated 29 March 2007, substantial) possible tablet combinations to arrive at 72 mg were changed to allow sites to use medication delivered to German sites to its full potential and an additional ECG assessment was added at Visit 7 was added.

In the fourth country (Germany) specific amendment (dated 1 May 2007, substantial) an ECG assessment at Visit 6 was added at the request of BfArM.

In the fifth country (Germany) specific amendment (dated 12 June 2007, substantial) the previously added ECG assessment at Visit 7 was removed.

In the sixth country (Germany) specific amendment (dated 31 August 2007, substantial) the open-label treatment period was extended up to 108 weeks for German subjects and changes were made in possible tablet combinations to arrive at the different dosages of medication, to allow the German sites to use the delivered medication to its full potential.

List of Publications

1. J Buitelaar, GE Trott, M Hofecker, S Waechter, J Berwaerts, J Dejonkheere et al; Long-term efficacy and safety outcomes with OROS MPH in adults with ADHD; Int J Neuropsychopharmacol. 2011 Jul 29:1-13.

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