Janssen Research & Development

Clinical Study Report Synopsis
[42603ATT3013; Phase 3]

JNJ-629330-AAC (Methylphenidate HCl)

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SYNOPSIS

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Name of Sponsor/Company	Janssen-Cilag International N.V. Medical Affairs EMEA
Name of Finished Product	CONCERTA®
Name of Active Ingredient(s)	Methylphenidate HCl

Protocol No.: 42603ATT3013

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Efficacy and Safety of Prolonged Release (PR) OROS® Methylphenidate (MPH) (54 and 72 mg/day) in Adults With Attention Deficit/Hyperactivity Disorder (ADHD).

EudraCT Number: 2007-002111-82

Principal Investigator: [redacted] M.D., [redacted] Germany

Publication (Reference): not published

Study Period: 4 February 2008 (first subject first visit)
2 April 2009 (last subject last visit)

Database Lock: 18 May 2009, unlocked on 2 June 2009 and relocked on 3 June 2009

Phase of Development: 3

Objectives:

Primary Objective
The primary objective of this study was to evaluate the efficacy of 2 fixed dosages of PR OROS MPH (54 and 72 mg/day) compared with placebo in adult subjects with ADHD. The primary efficacy endpoint was the change in the ADHD symptoms total score of the investigator-rated Conners' Adult ADHD Rating Scale (CAARS), from start of treatment to the end of the double-blind treatment (end of 13 weeks or last assessment).

Secondary Objectives
The secondary objectives of this study were:

- Assessment of the global improvement in severity of illness associated with the use of PR OROS MPH compared with placebo using the Clinical Global Impression (CGI) score;
- Assessment of subject's self report of reduction of ADHD symptoms associated with the use of PR OROS MPH compared with placebo using the CAARS-Self Report Short Version (CAARS-S:S);
- Assessment of the benefits to work, family and social functioning associated with the use of PR OROS MPH compared with placebo using the Sheehan's Disability Scale (SDS);
- Assessment of dependence and craving and of functional outcome and aspects of quality of life (QoL) using the Drug Use Screening Inventory Revised (DUSI-R) and the ADHD Impact Module - Adult (AIM-A).
- Assessment of investigator's assessment of treatment effectiveness using the investigator-rated CAARS subscales;
- Assessment of safety on the basis of adverse event (AE) reporting, vital signs, electrocardiogram (ECG) and clinical laboratory tests;
- Assessment of depression and anxiety co-morbidities, using the Hamilton Depression Rating Scale (using 17 items; HAM-D17) and the Hamilton Anxiety Rating Scale (HAM-A).

Methods: This was a multicenter, double-blind, randomized, placebo-controlled, parallel group, dose-response study conducted at 42 sites in Europe that evaluated PR OROS MPH in adults with ADHD.

Subjects eligible to enter the study, based on prospectively defined inclusion/exclusion criteria, entered a screening period. The screening period could have lasted for up to 2 weeks to enable safe tapering and discontinuation of any disallowed medication taken at the time of enrollment. If fluoxetine or monoamine oxidase (MAO) inhibitors were to be discontinued, a screening period of 4 weeks was allowed.

Subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups to receive oral dosages of PR OROS MPH 54 or 72 mg, or placebo once daily. Subjects received treatment for 13 weeks. Subjects randomly assigned to PR OROS MPH treatment started at a dosage of 36 mg PR OROS MPH. From Day 8 onwards, these subjects received either 54 or 72 mg/day (per the randomization schedule) for 12 weeks.

One week after a subject's final dose of study drug, a post-study visit was planned for collection of additional efficacy and safety data.

Number of Subjects (planned and analyzed):

Planned: 300 subjects (100 per treatment group)

Analyzed: see table below

		PR OROS MPH		
Number of	**Placebo**	**54 mg/day**	**72 mg/day**	**Total**
Screened subjects				320
Randomized and treated subjects	97	89	92	278
Randomized and not treated subjects	0	1	0	1
Subjects in the ITT analysis set	97	90	92	279
Subjects in the modified ITT analysis set	82	56	59	197
Subjects in the per-protocol analysis set	85	65	63	213
Subjects in the safety analysis set	97	89	92	278

Diagnosis and Main Criteria for Inclusion: Adults with a diagnosis of ADHD according to the criteria described in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), with some symptoms before age 7 years and who continued to meet the DSM-IV criteria at the time of assessment were enrolled in this study. ADHD was not diagnosed if the symptoms were better accounted for by another psychiatric disorder (e.g. mood disorder, anxiety disorder, psychotic disorder, personality disorder). Confirmation of adult diagnosis of ADHD based on Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was required.

Test Product, Dose and Mode of Administration, Batch No.:
PR OROS MPH 18 and 36-mg capsules; doses: 36, 54 or 72 mg/day; oral;
batch numbers 18 mg: 19616.1 and PD2951
36 mg: 19616.3 and PD2952

Reference Therapy, Dose and Mode of Administration, Batch No.: matching placebo. Placebo and PR OROS MPH were over-encapsulated to look identical; batch number: 19616.2

Duration of Treatment: 13 weeks, excluding screening and the post-study visit

Criteria for Evaluation:

Efficacy was assessed using investigator-rated assessment scales (CAARS, Clinical Global Impression - severity of illness scale [CGI-S] and Clinical Global Impression – global change scale [CGI-C]) and subject-rated assessment scales (CAARS-S:S, SDS, DUSI-R and AIM-A). Efficacy assessments were performed at screening (CAARS only), baseline (all scales except CGI-C), Weeks 1, 3, 7, and 9 (CAARS and AIM-A only), Weeks 5 and 13 (all scales), and the post-study visit (only CAARS, CGI-

S, CGI-C, and AIM-A). On the pre-specified study days, CAARS-S:S was to be performed prior to and approximately 11 hours after the intake of the study medication in the morning.

Safety was assessed by means of AE monitoring, clinical laboratory tests, ECG measurements, vital sign and body weight measurements, HAM-D17 and HAM-A scores, and DSM-IV assessments of substance use disorder. AEs were monitored throughout the study (including at the post-study visit one week after end of treatment) and vital signs were measured at each study visit. An ECG was obtained at screening, baseline and at Week 13. Clinical laboratory results, body weight measurement results and HAM-D17 and HAM-A scores were obtained at screening (laboratory results and body weight measurement results only), baseline, Week 5 and Week 13.

Statistical Methods:

Sample size justification: A sample size of 89 subjects for each treatment group provides at least 90% power to detect a mean difference of 6 units between an active dose group and placebo in change from baseline with respect to the (absolute) change in the ADHD symptoms total score of the investigator-rated CAARS. The sample size calculation was based on a two-sample, two-sided, t-test with $\alpha = 0.025$ and a standard deviation (SD) of 11. Adjusting for approximately 11 subjects per group who might miss either baseline or post-baseline efficacy assessments, the required number of randomized subjects per treatment group was approximately 100. The total number of required subjects across the 3 treatment groups was approximately 300.

Analysis methods: The intent-to-treat (ITT) analysis set, which consisted of all randomized subjects, was considered the primary efficacy analysis set. The modified ITT (i.e., ITT analysis set excluding subjects who discontinued due to reasons other than lack of efficacy, such as AEs, loss to follow-up, etc.) and the per-protocol analysis sets (i.e., ITT analysis set excluding subjects with major protocol deviations) were used for sensitivity analyses on the primary efficacy parameter. The safety analysis set consisted of all randomized subjects who received at least one dose of study medication.

The primary efficacy endpoint was the change in the ADHD symptoms total score of the investigator-rated CAARS from baseline to the last assessment in the double-blind treatment period. The change from baseline score at each time point (observed and last observation carried forward [LOCF] imputed) and at endpoint were analyzed using an analysis of covariance (ANCOVA) model. The model included treatment, gender and country as factors and age and baseline ADHD symptoms total score of the investigator-rated CAARS as covariates. Treatment effects were estimated based on least-squares (LS) means of the difference. Dunnett's procedure was used to adjust for multiple comparisons of the 2 PR OROS MPH dosages versus placebo, and accompanying Dunnett-adjusted 95% confidence intervals were presented for the LS means of each PR OROS MPH dosage group versus placebo. An analysis of observed scores available at each time point was also performed.

For the secondary efficacy endpoints, between-group comparison of changes from baseline in CAARS-S:S, SDS, DUSI-R and AIM-A were analyzed using an ANCOVA model with treatment, gender and country as factors and age and baseline score as covariates or using other applicable statistical tests. Between-group comparisons of CGI-S at each assessment time point and at endpoint were analyzed by means of an ANCOVA on the ranks of changes from baseline including treatment, gender and country as factors and baseline score and age as covariates. For the between-group comparison of CGI-C, an ANCOVA on the ranks of the actual values including treatment, gender and country as factors and age as a covariate was generated.

Additional analyses were performed to evaluate possible rebound effects after end of PR OROS MPH treatment. The change in ADHD symptoms from baseline of the double-blind treatment period to the post-study visit was evaluated (by evaluating the change in CAARS ADHD symptoms total score, the change in CGI-S score and the CGI-C score at the post-study visit).

RESULTS:

SUBJECT AND TREATMENT INFORMATION:

A total of 279 subjects were randomly assigned to receive a daily dose of PR OROS MPH 54 mg (90 subjects), PR OROS MPH 72 mg (92 subjects) or placebo (97 subjects) during the double-blind treatment period. Overall, 178 subjects (63.8%) completed the study. The main reason for study discontinuation in the PR OROS MPH groups was the occurrence of an AE, while the main reason for study discontinuation in the placebo group was lack of efficacy (see table below).

Study Completion/Withdrawal Information: Intent-to-Treat Analysis Set

	Placebo (N = 97) n (%)	PR OROS MPH 54 mg/day (N = 90) n (%)	PR OROS MPH 72 mg/day (N = 92) n (%)	Total (N = 279) n (%)
Completed	68 (70.1)	55 (61.1)	55 (59.8)	178 (63.8)
Discontinued	29 (29.9)	35 (38.9)	37 (40.2)	101 (36.2)
Adverse event	2 (2.1)	15 (16.7)	19 (20.7)	36 (12.9)
Lack of efficacy	14 (14.4)	1 (1.1)	4 (4.3)	19 (6.8)
Non-compliance	3 (3.1)	5 (5.6)	5 (5.4)	13 (4.7)
Consent withdrawal	4 (4.1)	3 (3.3)	3 (3.3)	10 (3.6)
Loss to follow-up	5 (5.2)	2 (2.2)	0	7 (2.5)
Sponsor's decision	0	2 (2.2)	0	2 (0.7)
Ineligibility to continue the study	0	1 (1.1)	1 (1.1)	2 (0.7)
Other	1 (1.0)	6 (6.7)	5 (5.4)	12 (4.3)

BASELINE CHARACTERISTICS:

Overall, the mean (SD) age at baseline was 35.7 (10.20) years, 52.3% of the subjects were male and 95.7% were white. Mean (SD) body weight at baseline was 77.2 (15.55) kg and mean (SD) BMI was 25.6 (4.39) kg/m^2. Mean (SD) age at initial ADHD diagnosis was 31.7 (13.62) years. Based on the CAADID responses for adulthood diagnosis, 69.9% of the subjects qualified for ADHD combined subtype. Overall, demographic and baseline characteristics were comparable across treatment groups.

EFFICACY RESULTS:

PR OROS MPH dosed at 72 mg/day was superior to placebo in improving ADHD symptoms in adult subjects as shown by the significantly larger decrease from baseline in ADHD symptoms total score of the investigator-rated CAARS at endpoint (primary efficacy measure, adjusted $p = 0.0024$; see table below). The difference in change from baseline between the 54 mg/day PR OROS MPH group and the placebo group was not statistically significant (adjusted $p = 0.1356$). Sensitivity analyses based upon different assumptions concerning causes of missing data confirmed the robustness of the results from the primary efficacy analysis. Analysis of the primary efficacy endpoint using the modified ITT analysis set (i.e., ITT analysis set in which subjects who discontinued due to reasons other than lack of efficacy were excluded) and the per-protocol analysis set (i.e., ITT analysis set in which subjects with major protocol deviations were excluded) showed a significantly larger decrease from baseline in ADHD symptoms total score for both PR OROS MPH treatment groups relative to the placebo group.

PR OROS MPH reduced the severity of both hyperactivity/impulsivity and inattention symptoms as shown by the significantly greater improvement compared to placebo for the CAARS hyperactivity/impulsivity subscale in the 72 mg/day PR OROS MPH group and for the CAARS inattention subscale in both the 72 mg/day and 54 mg/day PR OROS MPH groups.

Findings of the secondary efficacy parameters CGI-S, CGI-C and CAARS-S:S confirmed the superior efficacy of 72 mg/day PR OROS MPH over placebo in adult subjects with ADHD. The investigator-rated CGI-S and CGI-C scales and the subject-rated CAARS-S:S scale revealed a statistically greater effect of 72 mg/day PR OROS MPH relative to placebo in reducing the severity of ADHD symptoms. The

CAARS-S:S scale also revealed a statistically greater effect of 54 mg/day PR OROS MPH relative to placebo.

The subjects' functional outcome was assessed using the SDS scale to evaluate the degree of impairment in work, social life and family life and by using the AIM-A questionnaire to evaluate ADHD-specific overall functional outcome and aspects of QoL. These functional outcome and QoL measures showed improvement from baseline to endpoint for all three treatment groups. Four of the 6 ADHD-specific AIM-A subscales indicated a significantly greater improvement in the 72 mg/day PR OROS MPH group than in the placebo group and 3 of the 6 ADHD-specific AIM-A subscales indicated a significantly greater improvement in the 54 mg/day PR OROS MPH group than in the placebo group.

The results of the DUSI-R showed that the use of alcohol or any of the other substances in the past year remained largely unchanged during the study across all treatment groups.
A substance use disorder according to the DSM-IV criteria has been reported for 1 subject at Week 5 (72 mg/day PR OROS MPH group) and for 6 subjects at Week 13 (3 subjects from the 72 mg/day PR OROS MPH group, 2 subjects from the 54 mg/day PR OROS MPH group and 1 subject from the placebo group). One subject from the placebo group had a substance use disorder at baseline. The type of substance use disorder has not been captured in the CRF/database for none of the subjects for whom a substance use disorder has been reported.

ITT Analysis Set		PR OROS MPH	
	Placebo (N = 97)	**54 mg/day (N = 90)**	**72 mg/day (N = 92)**
CAARS ADHD symptoms total score			
Mean Value at Baseline (SD)	36.5 (6.05)	35.6 (6.75)	37.3 (6.35)
Mean Value at Endpoint (SD)	26.1 (10.59)	23.0 (11.07)	21.6 (10.21)
Mean Change at Endpoint (SD)	-10.4 (11.03)	-12.5 (10.38)	-15.7 (10.80)
Adjusted p-value		0.1356	0.0024
CAARS hyperactivity/impulsivity subscale			
Mean Change at Endpoint (SD)	-4.9 (5.84)	-5.6 (5.19)	-6.8 (5.67)
p-value		0.2914	0.0220
CAARS inattention subscale			
Mean Change at Endpoint (SD)	-5.5 (6.35)	-7.0 (6.14)	-8.9 (6.37)
p-value		0.0303	0.0003
CAARS-S:S			
Mean Change at Endpoint (SD)	-8.5 (11.64)	-12.8 (13.42)	-12.6 (13.84)
p-value		0.0230	0.0160
CGI-S			
Median Change at Endpoint (Range)	0.0 (-6 - 1)	-1.0 (-4 - 1)	-1.0 (-4 - 1)
p-value		0.2161	0.0006
CGI-C			
Median Endpoint Score (Range)	3.0 (1 - 6)	2.5 (1 - 5)	2.0 (1 - 6)
p-value		0.0518	0.0018
SDS			
Mean Change at Endpoint (SD)	-3.6 (5.33)	-4.4 (6.35)	-4.6 (6.58)
p-value		0.1726	0.1109
DUSI-R: overall problem density score			
Mean Change at Endpoint (SD)	-2.7 (7.87)	-2.6 (8.28)	-3.3 (9.31)
p-value		0.6500	0.3641
Overall AIM-A quality of life			
Mean Change at Endpoint (SD)	0.4 (1.93)	1.1 (2.16)	0.7 (2.15)
p-value		-	-
AIM-A : living with ADHD			
Mean Change at Endpoint (SD)	2.0 (11.91)	4.3 (13.24)	5.9 (12.11)
p-value		0.1527	0.0162
AIM-A : work, home and school - performance and daily functioning			
Mean Change at Endpoint (SD)	10.3 (18.95)	16.4 (22.95)	19.8 (22.47)
p-value		0.0072	0.0009
AIM-A : impact of symptoms on daily life: bother/concern scale			
Mean Change at Endpoint (SD)	13.4 (19.53)	16.8 (21.28)	16.6 (24.62)
p-value		0.0522	0.0834
AIM-A : impact of symptoms on daily life: daily interference scale			
Mean Change at Endpoint (SD)	12.7 (19.37)	17.5 (22.57)	17.6 (21.63)
p-value		0.0370	0.0261
AIM-A : general well-being			
Mean Change at Endpoint (SD)	4.7 (14.95)	9.5 (16.69)	8.7 (16.48)
p-value		0.0356	0.0970
AIM-A : relationships/communication			
Mean Change at Endpoint (SD)	5.7 (20.96)	9.5 (18.88)	13.5 (21.17)
p-value		0.1662	0.0052

SAFETY RESULTS:

At least one treatment-emergent AE was experienced during the double-blind treatment period by 91.3% of the subjects in the 72 mg/day PR OROS MPH group, 86.5% in the 54 mg/day PR OROS MPH group and 78.4% in the placebo group.

No deaths were reported during the study. The incidence of serious treatment-emergent AEs was low (reported for 2 subjects each in the 72 mg/day PR OROS MPH and placebo groups and 3 subjects in the 54 mg/day PR OROS MPH group during the treatment period and for one subject each in the 72 and 54 mg/day PR OROS MPH groups during the post-study period). Study medication was permanently discontinued due to at least one AE in 20.7% of the subjects in the 72 mg/day PR OROS MPH group, 16.9% of the subjects in the 54 mg/day PR OROS MPH group and 1.0% of the subjects in the placebo group.

Safety Analysis Set Number of subjects with … during the treatment period, n (%)	**Placebo (N = 97)**	**PR OROS MPH**		
		54 mg/day (N = 89)	**72 mg/day (N = 92)**	**All (both doses) (N = 181)**
At least one TEAE	76 (78.4)	77 (86.5)	84 (91.3)	161 (89.0)
At least one serious TEAE	2 (2.1)	3 (3.4)	2 (2.2)	5 (2.8)
At least one severe TEAE	10 (10.3)	10 (11.2)	13 (14.1)	23 (12.7)
At least one TEAE for which study medication was permanently stopped	1 (1.0)	15 (16.9)	19 (20.7)	34 (18.8)
At least one TEAE considered at least possibly related to study medication by the investigator	53 (54.6)	63 (70.8)	74 (80.4)	137 (75.7)

N = number of subjects with data; TEAE = treatment-emergent AE

The incidence of distinct treatment-emergent AEs was generally higher in the PR OROS MPH groups than in the placebo group (see table below). A larger proportion of subjects in the 72 mg/day compared to the 54 mg/day PR OROS MPH group experienced decreased appetite (28.3% versus 19.1%), dry mouth (21.7% versus 13.5%), weight decreased (18.5% versus 10.1%), anorexia (13.0% versus 6.7%), dizziness (12.0% versus 5.6%), hyperhidrosis (10.9% versus 3.4%), fatigue (9.8% versus 3.4%) and agitation (8.7% versus 2.2%). Restlessness was observed less frequently in the 72 mg/day PR OROS MPH group than in the 54 mg/day PR OROS MPH group (3.3% versus 9.0%). The difference in incidence of the other AEs between the 72 mg/day and 54 mg/day PR OROS MPH groups was smaller than 5%.

Safety Analysis Set MedDRA preferred term (reported in > 10% of the subjects in any group), n (%)	**Placebo (N = 97)**	**PR OROS MPH**		
		54 mg/day (N = 89)	**72 mg/day (N = 92)**	**All (both doses) (N = 181)**
Headache	25 (25.8)	25 (28.1)	27 (29.3)	52 (28.7)
Decreased appetite	5 (5.2)	17 (19.1)	26 (28.3)	43 (23.8)
Dry mouth	3 (3.1)	12 (13.5)	20 (21.7)	32 (17.7)
Nausea	8 (8.2)	16 (18.0)	16 (17.4)	32 (17.7)
Insomnia	11 (11.3)	13 (14.6)	15 (16.3)	28 (15.5)
Weight decreased	4 (4.1)	9 (10.1)	17 (18.5)	26 (14.4)
Nasopharyngitis	14 (14.4)	13 (14.6)	11 (12.0)	24 (13.3)

N = number of subjects with data; n = number of subjects with at least one treatment-emergent AE

Evaluation of selected AEs of special interest revealed a total of 20.5% of subjects with any event that was cardiovascular in nature and 10.4% of subjects with any event that was psychiatric in nature. The incidence of cardiovascular and psychiatric AEs of interest was low in the placebo group (3.1% and 6.2%, respectively). The incidence of cardiovascular and psychiatric AEs of interest was higher in the 72 mg/day PR OROS MPH group (35.9% and 15.2%, respectively) than in the 54 mg/day PR OROS MPH group (23.6% and 10.1%, respectively). The most frequently reported distinct cardiovascular AEs of interest (reported by ≥ 4.5% of subjects in each of the PR OROS MPH groups) were tachycardia, palpitations and

heart rate increased. These AEs were only observed in the PR OROS MPH treatment groups, with small differences in incidence between the 72 mg/day and 54 mg/day PR OROS MPH groups. The most frequently reported distinct psychiatric AEs of interest (reported by > 1 subject in any treatment group) were anxiety and panic attack. These AEs were more frequently reported in the PR OROS MPH groups than in the placebo group, with similar incidence in the 72 mg/day and 54 mg/day PR OROS MPH groups.

The number of laboratory-related AEs was low, which indicates that out-of-range laboratory values were generally not considered clinically relevant by the investigator.

The mean changes from baseline to endpoint in diastolic and systolic blood pressure, and pulse rate were small in all treatment groups. No relevant differences in incidence of potentially clinically important treatment-emergent supine vital sign abnormalities were observed between the treatment groups.

A small mean weight decrease, which was most pronounced in the first weeks of treatment was observed in subjects receiving PR OROS MPH, while a small mean weight increase was observed in the placebo group.

ECG values outside normal limits were considered not clinically significant by the investigator, except for 1 subject from the placebo group for whom the AE "ECG QT prolonged" was reported and 1 subject from the 72 mg/day PR OROS MPH group for whom the AE "ECG abnormal" was reported.

Assessment of symptoms of depression and anxiety using the HAM-D17 and HAM-A scales revealed that the majority of subjects had no symptoms of depression and mild or no anxiety symptoms at both baseline and endpoint.

Discontinuation of treatment with PR OROS MPH was not associated with an increase from baseline in CGI-S score of 1 point or more in the majority of subjects (≥ 93.7% in any treatment group) and the CGI-C score at the post-study visit was less than 5 for most subjects (≥ 91.0% in any treatment group), suggesting that abrupt discontinuation of treatment is not likely to result in rebound.

In the post-study period, none of the AE terms was reported in more than 3 subjects per treatment group, which indicates that after discontinuation of treatment there were no dominant AEs that would be indicative of a withdrawal phenomenon.

STUDY LIMITATIONS:

- This study evaluated doses of 54 mg/day and 72 mg/day PR OROS MPH. Lower doses that have also shown efficacy in previous studies (i.e., 18 and 36 mg/day) were not evaluated.
- The study was not designed to statistically compare the 54 mg/day dose with the 72 mg/day dose.
- Study medication was not titrated to the assigned dose as it would be done in clinical practice (i.e., 18-mg increments weekly). This could have differentially affected treatment emergence of AEs as well as patient retention across treatment groups.

CONCLUSION:

PR OROS MPH dosed at 72 mg/day effectively reduced ADHD symptoms in adult subjects over a treatment period of 13 weeks (including one week of titration). Subjects treated with 72 mg/day PR OROS MPH showed global improvement in severity of illness and reduction of subject's self-reported ADHD symptoms.
In the analysis of the primary efficacy endpoint, the 72 mg/day dose was superior to placebo. Findings of the secondary assessments (such as assessments of the CAARS hyperactivity/impulsivity and inattention subscale scores, the CGI-C score, the CGI-S score, the CAARS-S:S total score and some of the ADHD-specific AIM-A subscale scores) were in line with findings from the primary efficacy analysis.

The efficacy of the 72 mg/day dose was more pronounced than the findings of the 54 mg/day dose. In the analysis of the primary efficacy endpoint, the 54 mg/day dose was not superior to placebo. However, superiority of the 54 mg/day dose to placebo was observed when the primary efficacy analysis was repeated using the modified ITT analysis set and the per-protocol analysis set. Statistically significant

greater effect of the 54 mg/day dose relative to placebo was also observed for some of the secondary efficacy parameters (such as the CAARS inattention subscale score, the CAARS-S:S total score and some of the ADHD-specific AIM-A subscale scores).

PR OROS MPH doses of 54 and 72 mg/day were generally safe and well tolerated. The safety profile was similar to that reported in other studies of PR OROS MPH in adult subjects with ADHD.