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ABSTRACT

Objective: In clinical trials, duration of effect of Concerta® (OROS® methylphenidate [MPH]) CII has been established through 12 hours after intake, but the onset of treatment effect has not been precisely measured.^{1,2} The objective of this report is to present the observed time course of treatment effect of OROS MPH in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: This was a double-blind, randomized, placebo-controlled, cross-over, analog classroom study evaluating OROS MPH in children aged 9 to 12 years with ADHD (NCT00799409). Subjects initiated treatment with OROS MPH 18 mg/d with incremental increases until an optimal individualized dose was achieved (to a maximum of 54 mg/d). Subjects continued taking the optimized dose of OROS MPH through the 7-plus days separating the 2 laboratory assessment days. On the 2 laboratory assessment days, subjects were randomized to 1 of 2 treatment sequences (OROS MPH on laboratory day 1/placebo on laboratory day 2 or placebo on laboratory day 1/OROS MPH on laboratory day 2). Permanent Product Math Test number attempted (PERMP-attempted) and correct (PERMP-correct) were measured 0.5 hours before baseline and 1, 2, 4, 8, 10, 11, and 12.5 hours post dose. Onset of treatment effect was defined as the first time point and offset as the last time point where a statistically significant difference versus placebo was observed for PERMP-attempted mean score. A repeated measures mixed model was employed for this analysis.

Results: Before treatment, the LS mean PERMP-attempted score for the ITT population was 75.8 for the OROS MPH condition vs 80.6 for placebo ($P<0.05$). Statistically significant onset of treatment effect was seen at 1 hour post dose (104.4 OROS MPH vs 80.0 placebo; $P<0.0001$). Statistically significant difference between treatments was observed throughout the interim time points from 1 hour post dose through the last measurement 12.5 hours after dose; consequently, neither actual offset nor duration could be determined for this study. Accuracy as measured by PERMP-correct was similar for both treatment groups and consistent across the period of observation (approximately 92% with placebo and 94% with OROS MPH). Adverse events reported by greater than or equal to 5% of patients during the study included decreased appetite, abdominal pain, headache, irritability, initial insomnia, dizziness, nasal congestion, and pyrexia. No subject discontinued because of adverse events, and no serious adverse events or deaths were reported.

Conclusions: Results from this study confirm a robust treatment effect after taking OROS MPH with onset demonstrated at 1 hour and persisting for at least 12.5 hours after dosing.

INTRODUCTION

- Long-term, placebo-controlled trials are not ethically acceptable.
- Concerta® (OROS® methylphenidate [MPH]) CII treatment is associated with improvement in the performance of math problems in children in simulated school settings.¹
- Duration of effect of OROS MPH has been established through 12 hours after intake, but the onset of treatment effect has not been precisely measured previously.^{1,2}
- This study evaluates the time course of effects of treatment in a laboratory school setting within a study design that enhances the precision of earlier studies.

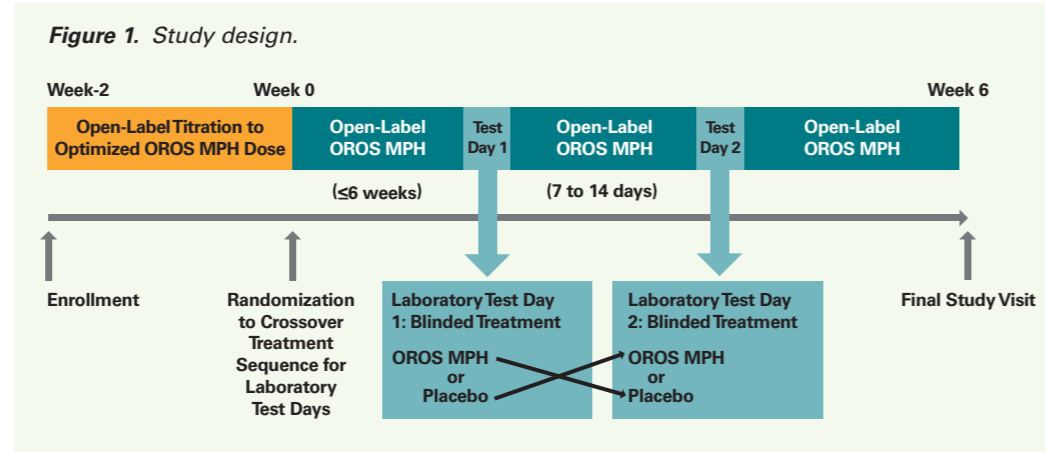
OBJECTIVE

- The objective of this report is to present the observed time course of treatment effect of OROS MPH in children with ADHD.

METHODS

Study Design and Procedures

- The study population included children aged 9 to 12 years with a diagnosis of ADHD.
- This was a double-blind, randomized, placebo-controlled, cross-over, analog classroom study (NCT00799409) (Figure 1).



- Open-label dose titration occurred over a 2-week period.
 - Subjects initiated treatment with OROS MPH 18 mg/d with incremental increases until an optimal individualized dosage was achieved (to a maximum of 54 mg/d).
- Dose titration was followed by a 6-week assessment period.
 - Subjects were eligible to enter the assessment period if they met the following criteria:
 - Titrated to 54 mg/d or their maximum tolerated dose
 - Achieved Clinical Global Impression (CGI) of “very much improved” or “much improved”
 - Achieved a total ADHD Rating Scale-IV score <85th percentile for the subject’s age and gender
 - Subjects continued taking the optimized dose of open-label OROS MPH through the 6-week assessment period, except on the 2 laboratory test days, when they took blinded treatment.
 - Subjects participated in 2 laboratory test days (separated by at least 7 days), during which they performed a variety of tasks, including the math test reported here.
 - Eligible subjects were randomly assigned to 1 of 2 double-blind treatment sequences 1:1 ratio) for laboratory test days:
 - OROS MPH on laboratory day 1 and placebo on laboratory day 2
 - Placebo on laboratory day 1 and OROS MPH on laboratory day 2

Outcome Measures

- Permanent Product Math Test number attempted (PERMP-attempted) and correct (PERMP-correct) were measured 0.5 hours before baseline and 1, 2, 4, 8, 10, 11, and 12.5 hours after dose.
- Treatment-emergent adverse events were also collected.

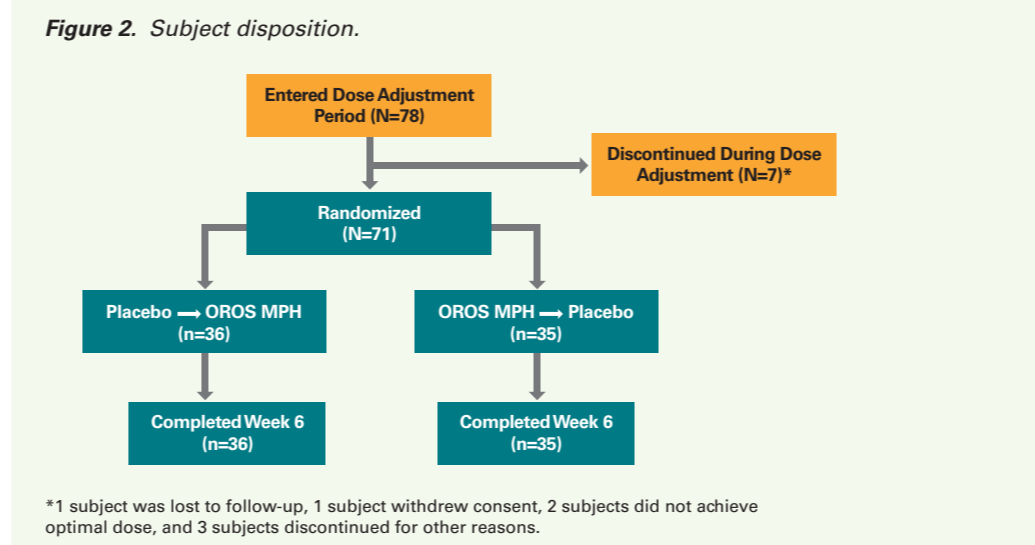
Statistical Analysis

- All randomized subjects were included in efficacy analyses.
- For the analysis of these efficacy parameters, a repeated measures mixed model was used that specified appropriate contrasts with terms for time, treatment, time-by-treatment interaction, subject, sequence, and period. The subject term was considered a random effect nested within sequence.
- Onset and offset of treatment effect were defined as the first time point and last time point, respectively, when a statistically significant difference between treatment conditions occurred for the PERMP-attempted mean score.
- Treatment-emergent adverse events are reported for all patients in this safety analysis set during OROS MPH treatment (either open-label or double-blind) between enrollment, dose titration, and final visit.

RESULTS

Disposition

- 78 Subjects received ≥ 1 dose of study medication.
- The disposition of subjects is presented in Figure 2.



Demographics

- Demographic and disease characteristics of all subjects who entered the dose adjustment period are in Table 1.

Table 1. Demographic and Disease Characteristics

Characteristic	All Subjects (N=78)
Gender, n %	
Male	55 (70.5)
Female	23 (29.5)
Age (y), mean (SD)	10.1 (1.08)
Race, n %	
White	45 (57.7)
Black	22 (28.2)
Asian	3 (3.8)
Other	8 (10.3)
Ethnicity, n %	
Hispanic or Latino	14 (17.9)
Not Hispanic or Latino	64 (82.1)
Weight, kg	
Mean (SD)	41.13 (13.381)
Minimum, Maximum	23.2, 100.9
ADHD subtype, n %	
Combined	63 (80.8)
Inattentive	15 (19.2)
Hyperactive-Impulsive	0

Efficacy Outcomes

Attempted and Correct Math Scores

- Before treatment on the laboratory days, the least squares (LS) mean PERMP-attempted scores was lower for the OROS MPH condition (75.8) than for the placebo condition (80.6), $P=0.0158$ (Figure 3).
- At every post dose time point that was tested, subjects who received OROS MPH on the laboratory school days had greater PERMP-attempted scores and greater PERMP-correct scores than subjects who received placebo on the laboratory school days (Figure 3 and Figure 4).

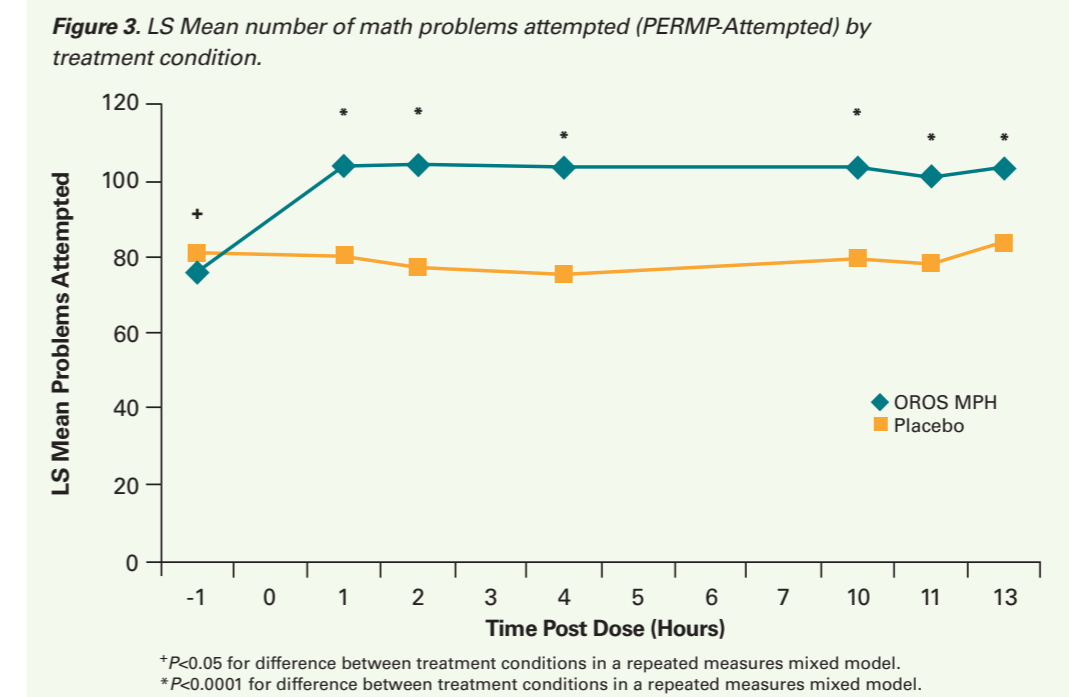
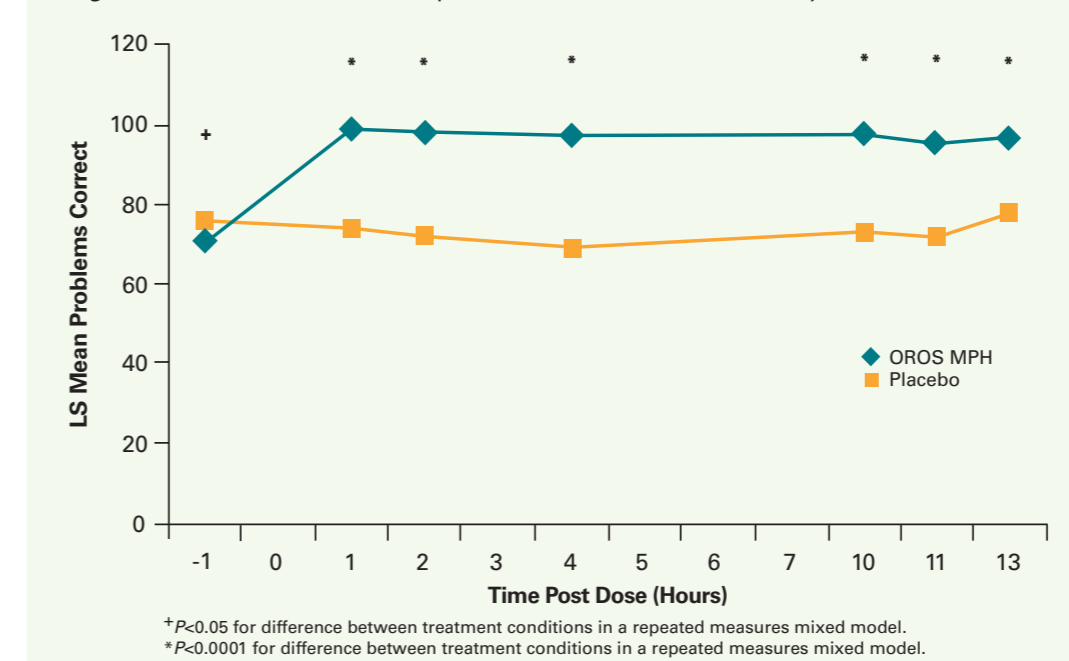


Figure 4. LS Mean number of math problems correct (PERMP-Correct) by treatment condition.



– Accuracy, as measured by percentage of problems correct, was similar for both treatment groups and was consistent across the period of observation (placebo range= 92.1%–93.5% and OROS MPH range=94.0%–94.3%).

Onset, Offset, and Duration of Treatment Effect

- Statistically significant onset of treatment effect was seen at 1 hour post dose (PERMP-attempted scores were 104.4 for OROS MPH vs 80.0 for placebo; $P<0.0001$).
- Because a significant treatment effect occurred at all time points tested (from 1 hour to 12.5 hours post dose), offset and duration of effect could not be determined.

Adverse Events

- All adverse events reported by $\geq 5\%$ of patients during the study are presented in Table 2.

Table 2. Treatment-Emergent Adverse Events Experienced by $\geq 5\%$ of Subjects During Open-Label and Double-Blind Treatment With OROS MPH

Treatment-Emergent Adverse Events*	Subjects (N=78) n (%)
Decreased appetite	20 (25.6)
Abdominal pain upper	13 (16.7)
Headache	13 (16.7)
Irritability	12 (15.4)
Initial insomnia	6 (7.7)
Dizziness	4 (5.1)
Nasal congestion	4 (5.1)
Pyrexia	4 (5.1)

*Excludes events during the laboratory school test days for subjects who received placebo.

- Adverse events reported in more than 10% of subjects were decreased appetite, abdominal pain, headache, and irritability.
- No unexpected adverse events were observed.
- No subject discontinued because of adverse events, and no serious adverse events or deaths were reported.

LIMITATIONS

- Only subjects demonstrating the required decrease in symptoms during OROS MPH dose titration were randomized; 2 subjects had total and/or subscale ADHD-Rating Scale IV scores that did not decrease below the 85th percentile for age and gender after titration and therefore were not eligible for randomization.
- The offset duration of the treatment effect could not be determined because the effect of OROS MPH was still robust at the longest duration tested (12.5 hours).
- The results were observed in a simulated school setting and therefore might not generalize to real-world school settings.

CONCLUSIONS

- Results from this study confirm a robust treatment effect after taking OROS MPH with onset demonstrated at 1 hour and persisting for at least 12.5 hours after dosing as measured by the PERMP-attempted and -correct scores.
- No unexpected adverse events were observed.

REFERENCES

- Swanson J, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. *Arch Gen Psych*. 2003;60:204-211.
- Pelham WE, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics*. 2001;107:e105.