Dexmethylphenidate Extended-Release Capsules in Children With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: This study compared once-daily dexmethylphenidate extended release (D-MPH-ER) 20 mg/day and placebo over 12 hours in children ages 6 to 12 with attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting. **Method:** All of the children were stabilized for ≥2 weeks on a total dose (nearest equivalent) MPH 40 mg/day or immediate-release D-MPH 20 mg/day before screening. After a practice day, they received 6 days of D-MPH-ER 20 mg/day or placebo at home, returning on day 7 for one dose. Subjects were evaluated at predose and postdose hours 0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 and then crossed over to the other treatment arm using the identical protocol. The primary efficacy variable was the change from predose in Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP) combined score from 1 to 12 hours. Secondary efficacy variables included SKAMP combined score at 0.5 hours, SKAMP subscale scores, and math test results over 12 hours. **Results:** Sixty-eight children were randomized, with 67 completing the study. Onset of action was indicated by a significant difference between D-MPH-ER and placebo at 0.5 hour on the SKAMP combined score ($p = .001$). For efficacy measures, differences from placebo were significant at all points between 0.5 and 12 hours ($p < .001$ to $p = .013$). **Conclusions:** D-MPH-ER provided sustained improvement in attention, deportment, and academic productivity throughout the 12-hour laboratory day. *J. Am. Acad. Child Adolesc. Psychiatry,* 2008;47(2):199–208.
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Racemic methylphenidate (MPH) (a 50-50 mixture of the *D-threo-* and *L-threo*-enantiomers) has been shown to be both efficacious and safe in the treatment of attention-deficit/hyperactivity disorder (ADHD).[1–3] Several studies in animals and humans imply that the clinical efficacy of D,L-MPH may reside in the D-enantiomer.[4–6]

Dexmethylphenidate hydrochloride (D-MPH; Focalin, Novartis Pharmaceuticals, East Hanover, NJ) is the chirally pure d-isomer of MPH. Like D,L-MPH, D-MPH is approved for twice-daily administration for the treatment of ADHD. Because it does not racemize after oral administration,[5] doses of D-MPH at half those for the racemic mixture can produce comparable levels of efficacy and tolerability.[4,6,7] However, with immediate-release formulations of MPH (D- or D,L-), the need for two daily doses presents certain challenges. Compliance over the long term can potentially be problematic, and concerns have been raised about noncompliance or drug diversion in the school setting. Hence, a once-daily extended-release formulation of D-MPH (D-MPH-ER) has been developed using the proprietary Spheroidal Oral Drug Absorption System (SODAS) technology. According to the Focalin XR package insert, this

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Study results are posted on the Novartis Clinical Trials Results Database (www.novartis.com) under the number CRIT124EUS09.

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formulation provides an initial release of 50% of the total dose immediately after dosing, followed by a second release approximately 4 hours later.[8] In a previous study,[9] the extended-release formulation demonstrated significant differences from placebo at each time point measured in a 12-hour laboratory classroom setting.

The purpose of this study was to further assess the efficacy, safety, tolerability, time of onset, and duration of effect of D-MPH-ER 20 mg/day versus placebo over 12 hours in pediatric patients with ADHD in a laboratory classroom setting. The laboratory classroom uses trained observers to define the time course of treatment effects based on repeated assessments of attention, deportment, and academic productivity.[7,9–11]

METHOD

Study Design

A randomized, multicenter, double-blind, placebo-controlled, crossover design was used in this investigation. This design allowed each child to be exposed to both treatments (7 days each of D-MPH-ER 20 mg/day and placebo) and act as his or her own control. Subjects were randomly assigned to the D-MPH-ER–placebo or the placebo–D-MPH-ER treatment sequence. Following a practice laboratory classroom testing session, the efficacy of each treatment was assessed on two consecutive Saturdays during a 12-hour laboratory classroom day.

Study Population. Males and females ages 6 to 12 years and diagnosed with ADHD were eligible for enrollment. Subjects were recruited from the investigators' private practices, child neurology clinics, school referrals, pediatricians' offices, and general psychiatry offices. To be eligible for inclusion into this study, children were required to fulfill the *DSM-IV* criteria for ADHD of any type, as established by the Diagnostic Interview Schedule for Children.[12] Before study participation, all of the subjects had to be clinically and behaviorally stable in the opinion of the referring physician and the site's principal investigator. They also had to have been taking their current dose of medication without adjustment for at least 2 weeks. This was required to be a total daily dose or nearest equivalent of MPH 40 mg or immediate-release D-MPH 20 mg (Concerta 36 mg was allowable) before screening. Concerta 36 mg/day was considered the nearest equivalent of MPH 40 mg/day that is commercially available to prescribers, thus being a comparator with real-world applicability. Only children whose parents and/or guardians provided written informed consent were enrolled. Assent was also obtained from all of the children.

Female subjects were required to be premenarcheal or sexually abstinent, or using an adequate and reliable contraceptive method (e.g., double-barrier method), which was documented in the medical record. Any girls who were sexually active were required to have a negative result on a urine pregnancy screening test. Children were excluded if they or their parents/guardians were unable to understand or follow instructions necessary to participate in the study, if they were deemed by the investigator to have below-normal cognitive capacity, or if they were home schooled, diagnosed with Tourette disorder or a tic disorder, or had a history of, or concurrent, significant medical or psychiatric illness or substance abuse disorder. Children taking an antidepressant medication, those who initiated psychotherapy within the 3 months preceding screening, and those with a positive urine drug screen were ineligible. Also excluded were any children with poor response or intolerance to MPH, currently taking other medications for ADHD, taking or planning to take any other investigational drug within 30 days of study start, or who had previously participated in D-MPH-ER studies.

Study Visit and Treatment Schedule. All of the subjects were scheduled to participate in a total of five visits, which consisted of a screening day (day −14 to −7), a practice day (day 0), a period 1 visit (day 7), a period 2 visit (day 14), and a final visit (day 15). Except for the screening and final visits, all of the visits occurred on three consecutive Saturdays at the participating centers. At screening, all of the prospective subjects underwent a physical examination, an electrocardiogram, blood and urine sampling for routine laboratory tests, urine drug screening, and (for girls) a urine pregnancy test. Informed consent was obtained and documented. A complete medical and psychiatric history was obtained, and the Computerized Diagnostic Interview Schedule for Children-IV was conducted by a trained staff member to confirm an ADHD diagnosis.

One to 2 weeks after screening, subjects participated in a practice visit to familiarize themselves with the laboratory classroom environment and the types of evaluations that would be completed during the study day. Math tests were administered to determine the appropriate level of difficulty for each child. The subjects were instructed to take their last dose of regularly prescribed medication on the Thursday before the practice day.

Subjects remaining eligible for study participation were then randomized to a treatment sequence. The first assigned treatment was dispensed to the parent and consisted of one bottle containing six capsules of blinded study medication. Parents were instructed to dispense the first dose (one capsule) of study medication the following morning (day 1, Sunday). Once-daily dosing in the morning was to continue for days 2 to 6 (Monday–Friday). On the morning of their period 1 visit (day 7), study personnel dispensed blinded study medication to the children. Upon completion of testing on day 7, the next study medication was dispensed to parents. All of the study medications were identical in appearance for blinding purposes. The same dosing schedule was repeated for the second treatment period, with the period 2 visit occurring on study day 14.

SKAMP and Math Test Assessments. Efficacy was measured as the change from predose on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale,[13] as well as performance on a pencil-and-paper math test (the Permanent Product Measure of Performance).[14] The SKAMP scale is a 13-item instrument designed to measure target classroom manifestations of ADHD.[13–16] The scale yields an Attention subscale score, a Deportment subscale score, and a combined score that reflects both parameters.

The ratings are based on the frequency and quality of behaviors as observed by raters. Three independent, blinded raters from each of the research centers were trained on the SKAMP rating instrument at a central location by an independent rater-trainer. These trained raters completed the SKAMP for all of the participants at specific intervals throughout the 12-hour testing period. The primary efficacy variable was the change from predose in the SKAMP combined score with the primary analysis time points being 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours postdose. Changes from predose in SKAMP Attention and SKAMP Deportment scores were among the secondary efficacy measures obtained from 0.5 hour up to 12 hours,