Serdexmethylphenidate/d-Methylphenidate Capsules for Children With ADHD: Effects on SKAMP-C and WREMB-R as Evaluated in a Randomized, Double-blind, Placebo-controlled Laboratory Classroom Study

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BACKGROUND

- Serdexmethylphenidate (SDX)/dexmethylphenidate (d-MPH) is a central nervous system (CNS) stimulant indicated for the treatment of ADHD in patients 6 years of age and older[1]
- SDX/d-MPH capsules contain a fixed molar ratio of 70% SDX, a novel prodrug of d-MPH[1], and 30% d-MPH
- SDX/d-MPH is a once-daily capsule offering both rapid onset and extended duration of efficacy for the treatment of ADHD
- Children with ADHD may experience severe symptoms of ADHD, especially during the early morning routine and evening homework times of the day[2]
- Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) scale is an instrument that allows for the assessment of ADHD-related difficulties over the day[3]
- The objective of this study was to evaluate the efficacy, safety, and tolerability of SDX/d-MPH capsules in children 6 to 12 years of age with ADHD

METHODS

Study Design and Subjects

- This was a multicenter, randomized, double-blind, placebo-controlled, parallel, efficacy laboratory classroom study
- The study was comprised of a Screening Period, a 3-week open-label Dose-Optimization Phase, and a 1-week double-blind Treatment Phase (Figure 1)
- Eligible subjects were children 6 to 12 years of age in good health who met DSM-5 criteria for a primary diagnosis of ADHD[4] per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
- Eligible subjects must have had scores of ≥3 (mildly ill) on the Clinician-administered Global Impressions–Severity (CGI-S) scale, as well as scores of ≥25 on the ADHD-Rating Scale-5 total score on Visit 2 (Day 0)[5]
- Subjects must have washed out ADHD medications 5 days prior to Visit 2, the start of the Dose-Optimization Phase (Day 0)

Figure 1. Study Design

- Following open-label dose optimization, subjects were randomized on a 1:1 basis to receive single daily doses of their optimized dose of SDX/d-MPH (**Table 1**) or placebo for 7 days

Table 1. SDX/d-MPH Dosage Strengths

SDX/d-MPH dosage strength	Total d-MPH HCl equivalence
26.1/5.2 mg	20 mg
39.2/7.8 mg	30 mg
52.3/10.4 mg	40 mg

- Safety assessments were conducted at each visit, which included monitoring of treatment-emergent adverse events (TEAEs), physical exams, vital signs, ECG parameters, clinical laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Analyses

- The primary efficacy endpoint was the mean change from predose SKAMP-C scores collected at Visit 5, the baseline measurement, to SKAMP-C scores collected postdose over the classroom day during Visit 6, with assessments conducted at 0.5, 1, 2, 4, 8, 10, 12, and 13 hours postdose
- Though the SKAMP questionnaire uses the Likert scale, the SKAMP-C, which aggregates the scores from all the domains, was treated as a continuous measure
- A repeated measures analysis using the Mixed-Effect Model Repeated Measure (MMRM) model was performed to estimate the difference between SDX/d-MPH and placebo
- An additional secondary endpoint included mean change from baseline (Visit 2) in WREMB-R scores (total score, and morning and evening subscores) at Visit 5 and Visit 6
- WREMB-R Scale is an 11-item, parent-rated questionnaire that was developed to assess behaviors for their severity during the morning hours and evening hours[6]
- WREMB-R scores were analyzed as continuous measures using paired and 2-sample t-tests during the Dose Optimization and Treatment Phases, respectively

RESULTS

Subject Disposition and Demographics

- A total of 155 subjects were enrolled in the Dose-Optimization Phase, of which 150 were randomized into the Treatment Phase: 74 and 76 subjects in the SDX/d-MPH and Placebo groups, respectively
- All subjects completed the study through the follow-up visit except for one subject in the placebo group who was lost to follow-up
- In the intention-to-treat (ITT) population (N=150), the mean age was 9.6 years, and a majority of subjects were white (50.7%) and male (61.3%)

Efficacy Assessments

- The mean change from baseline (Visit 5) in the SKAMP-C scores, averaged across the test day (Visit 6), was statistically significantly lower (indicating improvement) with SDX/d-MPH compared to placebo (P<0.001; **Table 2**)[1]

Table 2. Primary Efficacy Measure: SKAMP-C Scores Averaged Over Classroom Day in Subjects 6–12 Years With ADHD (Visit 5 as Baseline)

Treatment Group	N	Mean Baseline Score† (SD)	LS Mean Change From Baseline‡ (SE)	Placebo-Subtracted Difference§ (95% CI)
SDX/d-MPH (26.1/5.2, 39.2/7.8, 52.3/10.4 mg/day)	74	17.9 (9.2)	-4.87 (0.62)	-5.4 (-7.1, -3.7)
Placebo	76	17.9 (10.4)	0.54 (0.70)	

† *Baseline score assessed predose on the practice classroom day/randomization visit after 2 days of active drug washout (Visit 5).*

‡ *Classroom day least-squares mean change from baseline over hours 0.5, 1, 2, 4, 8, 10, 12, and 13.*

§ *Difference (active drug minus placebo) in least-squares mean change from baseline.*

- During the Treatment Phase, the mean evening score at Visit 6 significantly improved in the SDX/d-MPH group from Baseline (Visit 2) compared with the placebo group (**Table 3**)
- No treatment-related improvement was observed in the morning score

Table 3. Mean WREMB-R Scores in Subjects Treated With SDX/d-MPH or Placebo During the Treatment Phase

	SDX/d-MPH			Placebo			
WREMB-R Scores	N	Mean (SD)	Mean Difference From Baseline (SD)	N	Mean (SD)	Mean Difference From Baseline (SD)	Treatment Difference *P*-value
Overall							
Baseline (visit 2; day 0)	74	22.6 (5.3)	-11.7 (9.2)	75	23.6 (6.5)	-7.2 (9.1)	0.003
Visit 6 (day 28)	74	10.9 (8.2)		76	16.4 (7.9)		
Morning							
Baseline (visit 2; day 0)	74	5.2 (3.0)	-2.5 (3.4)	75	5.9 (2.7)	-2.2 (3.2)	0.595
Visit 6 (day 28)	74	2.7 (2.9)		76	3.7 (2.8)		
Evening							
Baseline (visit 2; day 0)	74	17.4 (3.9)	-9.2 (6.7)	75	17.7 (4.9)	-5.0 (6.6)	<0.001
Visit 6 (day 28)	74	8.2 (6.1)		76	12.7 (5.8)		

Safety and Tolerability

- No serious AEs, deaths, or overdoses were reported
- During the Dose-Optimization Phase, 2 subjects experienced an AE of severe insomnia leading to discontinuation
- The most common TEAEs reported during the double-blind Treatment Phase are shown in **Table 4**
- The majority of TEAEs were graded as mild or moderate in severity
- The TEAEs were similar to those reported for approved MPH products

Table 4. TEAEs Reported in >2% of Subjects During the Treatment Phase

TEAE, n (%)	SDX/d-MPH (n=74)	Placebo (n=76)
Any TEAE	**23 (31.1%)**	**11 (14.5%)**
Upper respiratory tract infection	2 (2.7%)	4 (5.3%)
Headache	4 (5.4%)	1 (1.3%)
Abdominal pain upper	3 (4.1%)	1 (1.3%)
Insomnia	2 (2.7%)	1 (1.3%)
Pharyngitis	2 (2.7%)	0 (0%)

- Changes in vital signs, ECGs, laboratory measurements, and physical examinations were minimal and comparable between the SDX/d-MPH and Placebo groups

CONCLUSIONS

- SDX/d-MPH showed efficacy relative to placebo for treating ADHD in children 6–12 years of age
- SDX/d-MPH showed improvement in ADHD symptoms overall and in the evening hours as assessed by WREMB-R
- SDX/d-MPH was generally well-tolerated, no notable safety signals were identified, and adverse events were similar to those reported for approved MPH products

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