Serdexmethylphenidate/d-Methylphenidate Capsules for Children With ADHD: Effects on SKAMP-C Evaluated Over 13 Hours in a Randomized, Double-blind, Placebo-controlled Laboratory Classroom Study

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BACKGROUND

- Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood and adolescence with approximately 10% of US children aged 4 to 17 years ever having received an ADHD diagnosis as of 2016[1]
- A need remains for methylphenidate products with earlier onset, longer duration of efficacy, and consistent therapeutic effect throughout the day
- 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[2]
- SDX/d-MPH capsules contain a fixed molar ratio of 70% SDX, a novel prodrug of d-MPH, and 30% d-MPH HCl[2]
- Early-day d-MPH exposure is governed by the 30% molar load of d-MPH HCl and mid- to late-day exposure is governed primarily by the 70% molar load of SDX, which is gradually converted to d-MPH throughout the day
- The objective of this study was to evaluate the efficacy, safety, and tolerability of once-daily SDX/d-MPH capsules versus placebo in children 6 to 12 years of age with ADHD

METHODS

Study Design and Subjects

- This was a multicenter, randomized, parallel, double-blind, placebo-controlled analog laboratory classroom clinical study
- The study included 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[3] per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
- For inclusion, subjects required 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)[4]
- All subjects on current ADHD medications discontinued their therapy 5 days prior to Visit 2, as this was the start of the Dose Optimization Phase (Day 0)

Figure 1. Study Design

- During the 21-day, open-label Dose Optimization Phase, subjects received a starting dose of 39.2/7.8 mg SDX/d-MPH
- Dose adjustments, if needed, were performed at approximately weekly intervals based on Clinical Global Impressions–Improvement (CGI-I) scores, safety, and interviews with parents, guardians, or caretakers
- Upon completing the 21-day, open-label Dose Optimization Phase, eligible 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 during the 7-day treatment period

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

- At the end of the 1-week treatment period, raters evaluated attention and behavior, using the SKAMP scale, of the patients in the laboratory classroom setting over the 13-hour period (Visit 6; day 28)
- Safety assessments were conducted at each visit, which included monitoring of treatment-emergent adverse events (TEAEs), vital signs, ECG parameters, physical exams, clinical laboratory tests, and suicide risk

Statistical Analyses

- The primary efficacy assessment was mean change from baseline (predose) in Swanson, Kotkin, Agler, M-Flynn and Pelham-Combined (SKAMP-C) to scores collected postdose across the laboratory classroom day from 0.5 to 13 hours
  - The SKAMP scale is a validated rating of subjective impairment of classroom behaviors comprised of 13 items, while the SKAMP-C score is obtained by summing the rating values for the 13 items of the SKAMP scale[5]
- 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
- To evaluate the onset and duration of efficacy, a post hoc analysis was conducted to assess the change in postdose SKAMP-C scores throughout the day relative to SKAMP-C scores at baseline prior to dosing
  - Other studies of MPH products have used the morning of the laboratory classroom day (Visit 6), or analogous study visit, as the baseline for SKAMP-C scores

RESULTS

Subject Disposition and Demographics

- 155 subjects were enrolled in the Dose Optimization Phase, and 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 a single subject in the placebo group who was lost to follow-up
- The mean age was 9.6 years, and a majority of subjects were white (50.7%) and male (61.3%) in the intention-to-treat (ITT) population (N=150)

Efficacy Assessments

- When assessments were averaged across all time points (the primary endpoint), SKAMP-C scores were significantly improved for children treated with SDX/d-MPH compared with placebo (LS means treatment difference [95% CI] -5.41 [-7.10, -3.71]; P<0.001; **Table 2**)
- The SKAMP-C score change from baseline at Visit 6 predose score for the SDX/d-MPH group was significantly higher compared with the placebo group (LS means difference [95% CI] 2.37 [0.07, 4.68]; P=0.044)
- Similar to other analog classroom studies of MPH products, SDX/d-MPH predose SKAMP-C scores compared to those treated with placebo were higher at Visit 6 (day 28; **Figure 2**)
- To provide results that align with other MPH clinical trial designs, a post hoc analysis was performed using predose measurements taken on Visit 6 (day 28) as baseline measurements

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

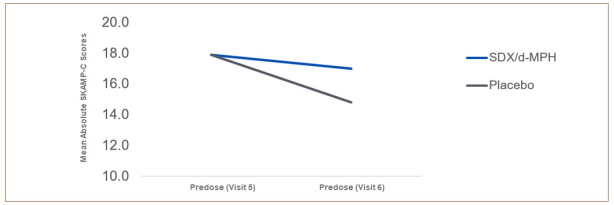
Treatment Group	N	Mean Baseline Score† (SD)	LS Mean Change From Baseline‡ (SE)	Placebo-Subtracted Difference§ (95% CI)
SDX/d-MPH (26.1/5.2, 39.2/7.8, 52.3/10.4 mg/day)	74	17.9 (9.2)	-4.87 (0.62)	-5.4 (-7.1, -3.7)
Placebo	76	17.9 (10.4)	0.54 (0.70)	

† 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.

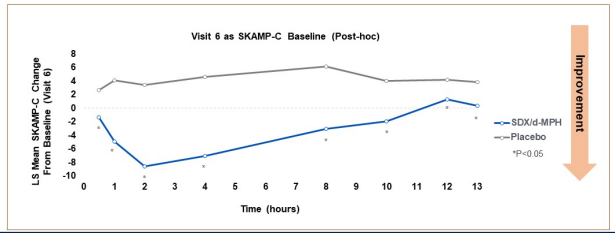
§ Difference (active drug minus placebo) in least-squares mean change from baseline.

Figure 2. Mean Absolute SKAMP-C Scores



- **Figure 3** illustrates onset and duration of efficacy with SDX/d-MPH over a 13-hour classroom day using Visit 6 as the baseline
- Similar to the prespecified analysis, SKAMP-C scores in the post hoc analysis were significantly improved for children treated with SDX/d-MPH compared with placebo
- The onset of treatment effect (improvement in SKAMP-C scores from predose Visit 6) began at 0.5 hours postdose (LS means difference [95% CI] -3.97 [-6.37, -1.57]; P<0.001) and continued for 13 hours postdose (LS means difference [95% CI] -3.49 [-5.89, -1.09]; P=0.004)

Figure 3. Mean SKAMP-C Score Changes in Subjects Treated With SDX/d-MPH or Placebo Using Visit 6 as the Baseline



Safety and Tolerability

- No serious AEs, deaths, or overdoses were reported
- During the Dose Optimization Phase, 2 subjects experienced an AE of severe insomnia, which led to discontinuation from the study
- **Table 3** illustrates the most common TEAEs reported during the double-blind Treatment Phase
- The majority of TEAEs were graded as mild or moderate in severity
- The TEAEs in the study were similar to those reported for approved MPH products

Table 3. 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 from baseline to early termination or end-of-study were minimal and comparable between the SDX/d-MPH and placebo groups

CONCLUSIONS

- SDX/d-MPH showed efficacy compared with placebo for treating ADHD in children 6–12 years of age
- In a post hoc analysis, SDX/d-MPH showed both early onset (30 minutes) and extended duration (13 hours postdose) of efficacy as measured by SKAMP-C
- SDX/d-MPH was generally well-tolerated, no notable safety signals were identified, and adverse events were typical of stimulant treatment
- By combining SDX, a novel prodrug of d-MPH, with d-MPH HCl, SDX/d-MPH can potentially address certain unmet needs with currently approved stimulant products

DISCLOSURES: CO and MC are employees and shareholders of Corium, Inc. ACB is an employee and shareholder of KemPharm, Inc. This study was funded by KemPharm, Inc., Celebration, FL. Poster design support was provided by Simpson Healthcare.

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