

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

Charles Oh¹, Meg Corliss¹, Andrew C. Barrett², Andrea Marraffino³, Andrew J. Cutler⁴, Scott H. Kollins⁵, Matthew N. Brams⁶

¹Corium, Inc., Grand Rapids, MI, USA; ²KemPharm, Inc., Celebration, FL, USA; ³Meridian Research, Maitland, FL, USA; ⁴SUNY Upstate Medical University and Neuroscience Education Institute, Lakewood Ranch, FL, USA; ⁵Duke University School of Medicine, Durham, NC, USA; ⁶Bayou City Research, Houston, TX, USA

BACKGROUND

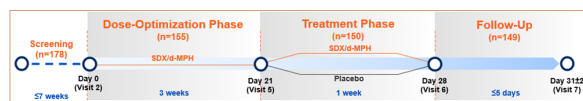
- Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood and adolescence with approximately 10% of US children aged 4 to 17 years ever having received an ADHD diagnosis as of 2016¹
- A need remains for methylphenidate products with earlier onset, longer duration of efficacy, and consistent therapeutic effect throughout the day
- Serdexmethylphenidate (SDX)/dexamethylphenidate (d-MPH) is a central nervous system (CNS) stimulant indicated for the treatment of ADHD in patients 6 years of age and older²
- SDX/d-MPH capsules contain a fixed molar ratio of 70% SDX, a novel prodrug of d-MPH, and 30% d-MPH HCl²
- 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 ADHD³ 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
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- 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 scale⁵
- 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)

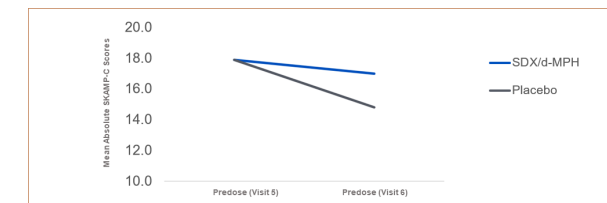
Treatment Group	N	Mean Baseline Score [†] (SD)	LS Mean Change From Baseline [‡] (SE)	Placebo-Subtracted Difference [§] (95% CI)
SDX/d-MPH (26.1/5.2, 39.2/7.8, 52.3/10.4 mg/day)	74	17.9 (9.2)	-4.87 (0.62)	-5.4 (-7.1, -3.7)
Placebo	76	17.9 (10.4)	0.54 (0.70)	

[†] 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.

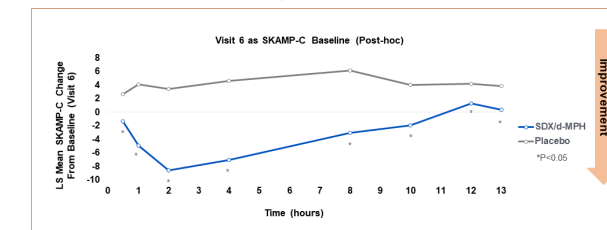
[§] Difference (active drug minus placebo) in least-squares mean change from baseline.

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 of 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
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Table 3. TEAEs Reported in >2% of Subjects During the Treatment Phase

TEAE, n (%)	SDX/d-MPH (n=74)	Placebo (n=76)
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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

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REFERENCES: 1. Danielson ML, et al. *J Clin Child Adolesc Psychol*. 2018;47(2):199-212. doi:10.1080/15374416.2017.1417860. 2. AZSTARYS [package insert]. Corium Inc; 2021. 3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. American Psychiatric Association; 2013. 4. DuPaul GJ, et al. *ADHD Rating Scale-5 for Children and Adolescents: Checklists, Norms, and Clinical Interpretation*. Guilford Press; 2016. 5. Swanson JM, et al. The University of California, Irvine, Laboratory School Protocol for Pharmacokinetic and Pharmacodynamic Studies. In: Greenhill L, Osman B, eds. *Ritalin*. 2nd ed. Mary Ann Liebert; 1999:405-430.

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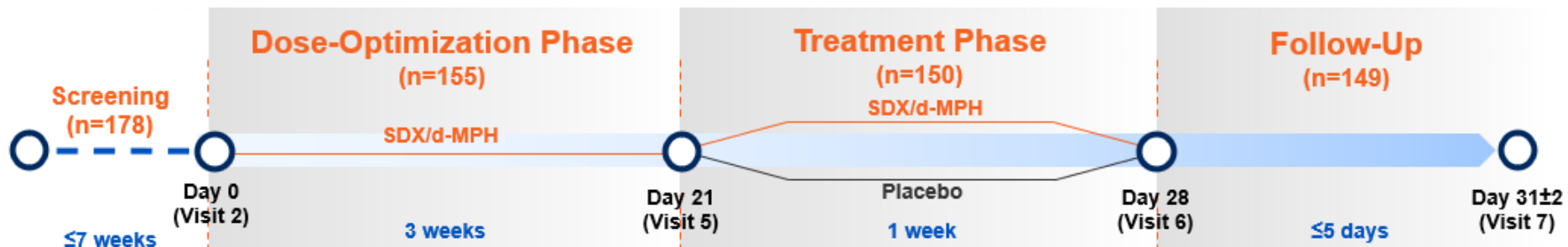
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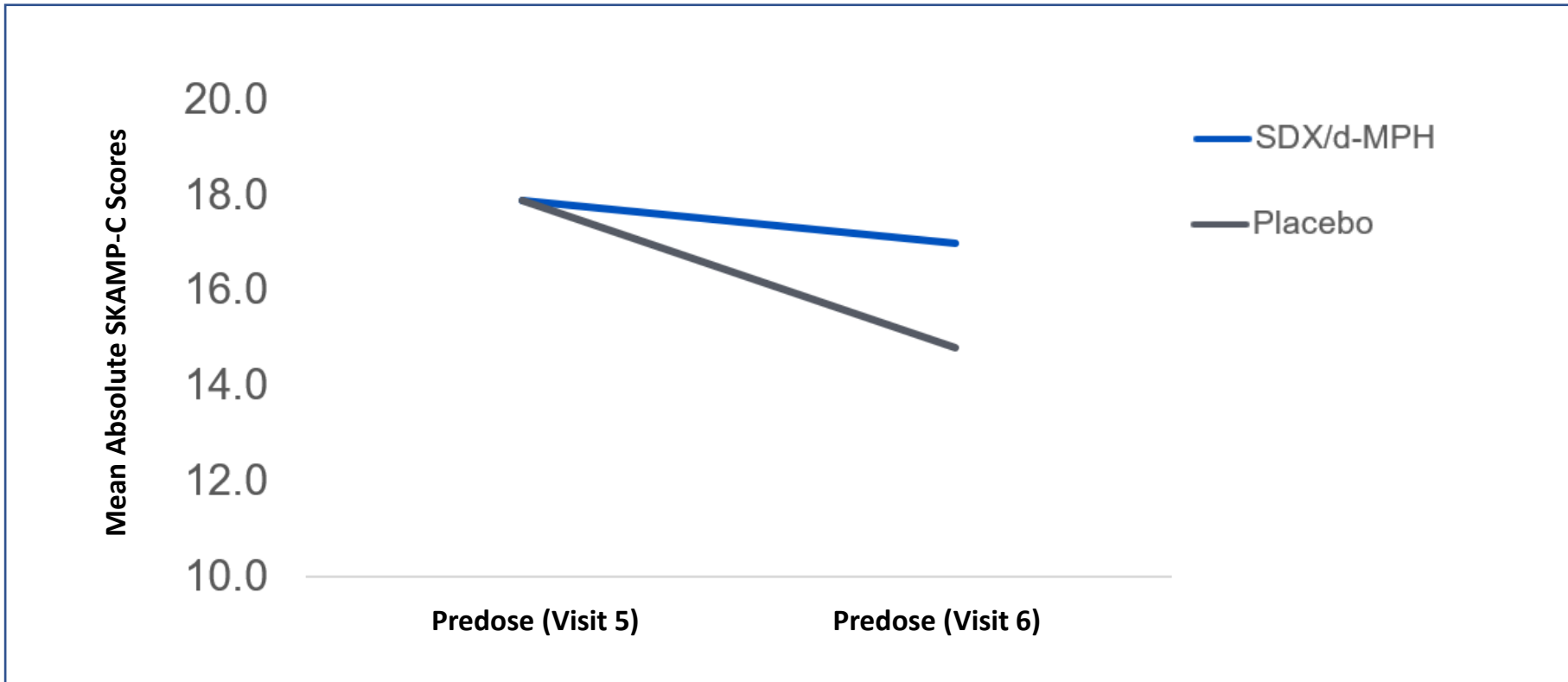
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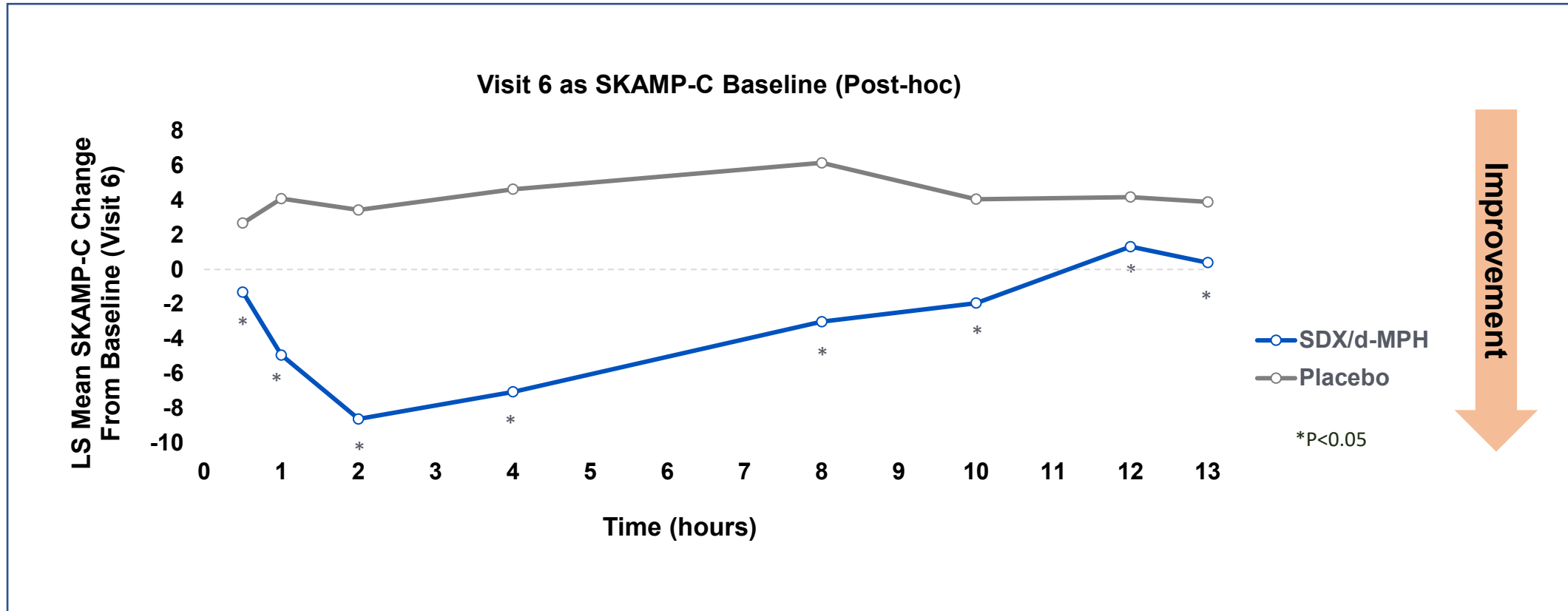


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