Single-dose Pharmacokinetics of Serdexmethylphenidate/d-Methylphenidate Capsules in Children and Adolescents With ADHD and Healthy Adults: An Evaluation of Age and Body Weight

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BACKGROUND

- Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood and adolescence[1]
- Serdexmethylphenidate (SDX)/d-methylphenidate (d-MPH) capsules are an approved ADHD product designed to provide rapid onset and extended duration of symptom improvement[2]
- SDX/d-MPH capsules on a molar basis contain 70% SDX, a prodrug of d-MPH that is gradually converted to d-MPH, and 30% d-MPH, which provides rapid exposure to d-MPH after administration[2]
- The objectives of these studies were to:
  - **Study 1:** Examine the single-dose pharmacokinetics (PK) of SDX/d-MPH and determine the effect of body weight (BW) on the PK properties in children and adolescents with ADHD
  - **Study 2:** Examine single-dose PK of SDX/d-MPH in healthy adults under fed conditions

METHODS

Study Design and Subjects

- Both studies were phase 1, open-label, single-dose oral administration of SDX/d-MPH capsules
- In study 1, after a standardized meal, subjects (aged 6–17 years, N=30) received treatments stratified into 3 age and 2 dose groups (**Table 1**)
  - 6- to 8-year-olds (**Cohort 1**, n=10) received 26.1/5.2 mg, 9- to 12-year-olds (**Cohort 2**, n=10) received 52.3/10.4 mg, and 13- to 17-year-olds (**Cohort 3**) received either 26.1/5.2 mg (n=5) or 52.3/10.4 mg (n=5)
  - The majority of subjects were male (66.7%), and all subjects were Black or African American
  - Blood samples for PK were collected pre dose and at multiple time points post dose
- In study 2, adults (n=28) received SDX/d-MPH 52.3/10.4 mg either in a fasting or fed state in a randomized, crossover design; all subjects received treatment after a high-fat meal (fed arm)
  - The PK of the fed arm of this study was used as the reference in adults
  - The mean age of subjects was 34 years, and a majority of subjects were white (62.5%) and female (62.5%)

Statistical Analyses

- In both studies, the following plasma pharmacokinetic parameters for d-MPH were calculated: C_{max}, T_{max}, $T_{½}$, CL/F, Vz/F, AUC_{last}, and AUC_{inf} for d-MPH and SDX

RESULTS

Pharmacokinetic Assessments

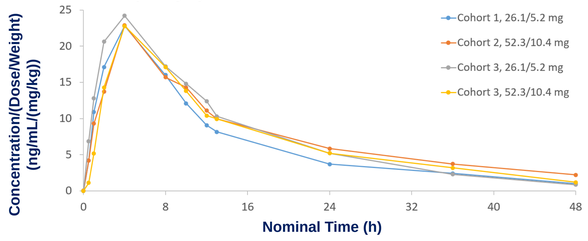
Study 1:

- Dose-normalized (to the 52.3/10.4 mg dose) peak and overall exposure to d-MPH was highest in Cohort 1 (C_{max}=34.4 ng/mL, AUC_{0-24}=362.0 h*ng/mL), followed by Cohort 2 (C_{max}=25.9 ng/mL, AUC_{0-24}=294.1 h*ng/mL), and lowest in Cohort 3 (C_{max}=17.8 ng/mL and 14.0 ng/mL; AUC_{0-24}=195.0 ng/mL and 171.1 h*ng/mL, for the low and high doses, respectively)
- When normalized for both dose and BW, mean C_{max} and AUC_{0-24} values were similar across cohorts
- Clearance (CL/F) values were lower in Cohorts 1 and 2 (96.85 and 97.44 L/h, respectively) than Cohort 3 (170.3 L/h for low dose and 172.3 L/h for high dose)
- When adjusted for BW differences, CL/F values were similar
- A nonlinear regression model indicated a moderate correlation (R^2=0.628) between d-MPH CL/F and BW

Study 2:

- The shape of the PK curve in adults (**Figure 2**) was similar to those obtained in children and adolescents during Study 1 (**Figure 1**) when administered under fed conditions (standardized meal for children and adolescents; high-fat meal for adults)
  - No appreciable difference in maximum and total d-MPH exposure was observed for males and females

Figure 1. Mean Dose/Weight-Normalized Plasma Concentration-Time Profiles of d-MPH in Children and Adolescents (Study 1)



Safety and Tolerability

- No serious AEs or deaths were reported
- During the first study, 5 subjects reported 6 TEAEs, including upper abdominal pain, pyrexia, pharyngitis, upper respiratory tract infection, headache, and pruritis; 2 were considered related to the study drug
- In the second study, 6 subjects reported 10 TEAEs, including increased energy, dry mouth, and palpitations; these were graded as mild and were assessed as probably or possibly related to the treatment

Body weight is an **appropriate scaling factor** for d-MPH **exposure** after **oral SDX/d-MPH** dosing in children and adolescents.

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ADDITIONAL TABLES & FIGURES

Figure 2. Mean Plasma Concentration-Time Profile of d-MPH in Adults after a Single Oral dose of SDX/d-MPH Capsules, 52.3/10.4 mg (Study 2)

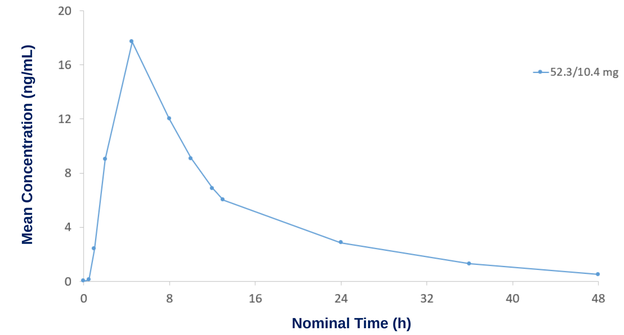

Table 1. Weight and Mean PK Parameters (SD) of d-MPH after Single Oral Dose of SDX/d-MPH Capsules in Children 6 to 17 Years of Age (Study 1) and Adults (Study 2)

	Study 1: Cohort 1 6-8 Years*	*Study 1*: Cohort 2 9-12 Years*	*Study 1*: Cohort 3 13-17 Years*	*Study 1*: Cohort 3 13-17 Years*	*Study 2*: Adults†
	26.1/5.2 mg (N=10)	52.3/10.4 mg (N=10)	26.1/5.2 mg (N=5)	52.3/10.4 mg (N=5)	52.3/10.4 mg (N=28)
Weight (kg)					
Mean (SEM)	29.33 (1.511)	39.75 (2.549)	65.68 (5.106)	65.02 (2.916)	74.33 (3.711)
Pharmacokinetic Parameters					
C_{max} (ng/mL)	17.2 (5.02)	25.9 (9.69)	8.88 (3.18)	14.0 (1.72)	18.5 (4.91)
AUC_{last} (hr*ng/mL)	219.8 (72.33)	391.6 (129.9)	116.5 (39.17)	217.0 (24.43)	225.1 (83.97)
AUC_{inf} (hr*ng/mL)	228.2 (79.35)	459.7 (145.4)	125.3 (40.97)	234.6 (25.64)	229.8 (84.34)
T_{max}‡ (hr)	4.0 (1.0-4.0)	4.0 (1.0-10.0)	4.0 (2.0-4.0)	4.0 (4.0-4.0)	4.50 (3.0-7.0)
$T_{1/2}$ (hr)	12.57 (2.79)	19.36 (8.98)	10.28 (2.75)	11.08 (4.01)	8.20 (1.27)
CL/F/W (L/hr/kg)	3.36 (1.36)	2.45 (0.74)	2.56 (0.25)	2.66 (0.27)	2.53 (0.82)
Vz/F/W (L/kg)	57.48 (14.54)	66.02 (31.96)	37.60 (8.36)	41.84 (13.58)	29.4 (9.65)

**Breakfast was given 20 minutes prior to drug administration.*
†A high-fat breakfast was given 30 minutes prior to drug administration.
‡Data presented as median (range).

CONCLUSIONS

- **Body weight is an appropriate scaling factor for d-MPH exposure after oral SDX/d-MPH dosing in children and adolescents**
- **d-MPH exposure was comparable between children, adolescents, and adults after oral SDX/d-MPH dosing**
- **SDX/d-MPH was generally well-tolerated, no notable safety signals were identified, and adverse events were typical of stimulant treatment**

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

REFERENCES: 1. Danielson ML, et al. *J Clin Child Adolesc Psychol.* 2018;47(2):199-212. doi:10.1080/15374416.2017.1417860 **2.** AZSTARYS [prescribing information]. Corium Inc; 2021