Steady-State Pharmacokinetics and Relative Bioavailability of Serdexmethylphenidate/d-Methylphenidate, a Treatment for Attention Deficit Hyperactivity Disorder Containing a Novel Prodrug of d-Methylphenidate

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BACKGROUND

- Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood and adolescence, with an estimated 6.1 million US children aged 2 to 17 years ever having received a diagnosis as of 2016[1]
- 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 comprise 70% SDX, a novel prodrug of d-MPH, and 30% d-MPH[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 objectives of these studies were to:
  - **Study 1:** assess the relative bioavailability of d-MPH after a single oral dose of SDX/d-MPH compared with extended-release (ER) d-MPH hydrochloride (HCl)
  - **Study 2:** assess the steady-state pharmacokinetics (PK) of SDX/d-MPH (equimolar to 40 mg d-MPH HCl)

METHODS

Subjects and Study Design

Study 1:

- The study was a phase 1, open-label, 2-treatment, 2-period, 2-sequence, randomized, crossover relative bioavailability study comparing a single oral dose of SDX/d-MPH with ER d-MPH HCl under fasted conditions
- Eligible subjects were healthy males and nonpregnant, nonbreastfeeding females aged 18 to 55 years
- The study included a screening period of up to 28 days, a treatment phase with 2 treatment periods, and a follow-up visit that occurred within 1 week of administration of the last dose of the study drug
- 30 subjects received single, molar-equivalent doses of 52.3/10.4 mg SDX/d-MPH (40 mg total d-MPH HCl) and 40 mg ER d-MPH HCl
- All subjects were to receive each treatment at each of the 2 treatment periods, respectively, in a crossover fashion. Treatments were separated by a minimum 96-hour washout period
- Treatment was administered after an overnight fast of 10 hours, which continued until at least 4 hours post dose
- PK sampling was conducted pre dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 6.5, 7, 8, 10, 12, 13, 16, 24, 36, 48, 60, and 72 hours post dose during both treatment phases
- Safety assessments were performed throughout the study

Study 2:

- This study was a phase 1, open-label, randomized, multiple dose treatment study evaluating the steady state PK of 52.3/10.4 mg SDX/d-MPH capsules after oral administration under fasted conditions
- Eligible subjects were healthy males and nonpregnant, nonbreastfeeding females 18 to 55 years of age
- Following a 96-hour washout period, 23 subjects received 4 doses of 52.3/10.4 mg SDX/d-MPH once daily for 4 days to evaluate the steady-state PK
- On the first day of the study, PK sampling was conducted pre dose and at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, and 24 hours post dose. The 24-hour postdose PK sample was taken before administration of the second dose of study drug
- During days 2 to 3, PK sampling was conducted at 2, 8, and 24 hours post dose. The 24-hour postdose PK samples were taken before administration of the third and fourth doses of study drug
- On day 4, PK sampling was conducted at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, 24, 36, 48, 60, and 72 hours
- Safety assessments were performed throughout the study

Pharmacokinetic and Statistical Analyses

Study 1:

- The following were among the PK parameters derived for d-MPH from the plasma concentration-time data: C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$
- Statistical comparison of the PK parameters of exposure for d-MPH between the 2 treatments was performed using an analysis of variance (ANOVA) model for a 2-way crossover design on the ln-transformed data with sequence, period, and treatment as the fixed effects and subject within sequence as a random effect
  - Since the d-MPH plasma concentration-time profile after oral administration of ER d-MPH HCl shows 2 peaks **(Table 1),** the first peak concentration ($C_{max}1$) was used in the statistical comparison between treatments (as the first peak of d-MPH is related to onset of action)

Study 2:

- The following were among the PK parameters derived for d-MPH from the plasma concentration-time data: C_{max}, C_{min} (at 24 hours post dose), T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24h}$, and $T_{1/2}$

RESULTS

Subject Disposition and Demographics

Study 1:

- 29 subjects completed both treatment periods of the study; 1 subject discontinued due to personal reasons
- The mean age was 35.1 years, and the majority of subjects were white (53.3%) and male (66.7%)

Study 2:

- 23 subjects completed the multiple-dose treatment phase of the study
- The mean age was 37.2 years, and the majority of subjects were black (50%) and male (75%)

Pharmacokinetic Assessments

Study 1:

- 40 mg ER d-MPH HCl displayed a PK profile with 2 peaks separated by approximately 4 hours **(Figure 1)**
- The d-MPH PK profile of SDX/d-MPH showed a single peak at approximately 1.5 to 2 hours post dose, followed by a slow decline in d-MPH plasma concentrations ($T_{1/2}$ = 10.1 hours)
- Statistical comparison of C_{max} and $AUC_{0\text{-}inf}$ indicated these values were 39% and 25% lower, respectively, for single doses of 52.3/10.4 mg SDX/d-MPH capsules relative to single doses of 40 mg ER d-MPH capsules

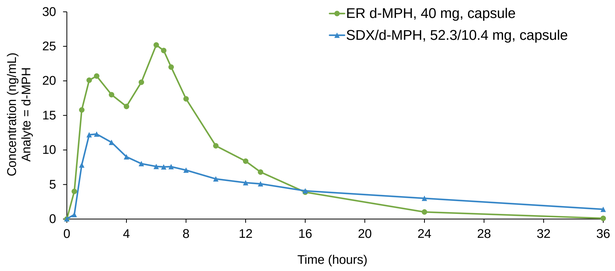
Table 1. Plasma PK Parameters of d-MPH After Single and Multiple Oral-Dose Administrations of 40 mg ER d-MPH HCl and 52.3/10 mg SDX/d-MPH (Study 1* and 2)

Parameters	Study 1		Study 2
	40 mg ER d-MPH (n=29)	52.3/10.4 mg SDX/d-MPH (n=29)	52.3/10.4 mg SDX/d-MPH (n=23)
C_{max}	-	14.0	20.0
C_{max1}	23.0	-	-
C_{max2}	28.2	-	-
AUC_{last}	241.7	178.9	280.52
$AUC_{0\text{-}inf}$	248.2	185.7	291.74

*Because d-MPH plasma concentration-time profile after oral administration of ER d-MPH shows 2 peaks, both observed peak plasma concentrations ($C_{max}1$ and $C_{max}2$) were reported.

d-MPH=dexmethylphenidate; ER=extended release; PK=pharmacokinetic; SDX=serdexmethylphenidate.

Figure 1. Mean Plasma d-MPH Concentration-time Profiles After Single Oral Dose Administrations of ER d-MPH HCl 40 mg and SDX/d-MPH 52.3/10.4 mg (Study 1)

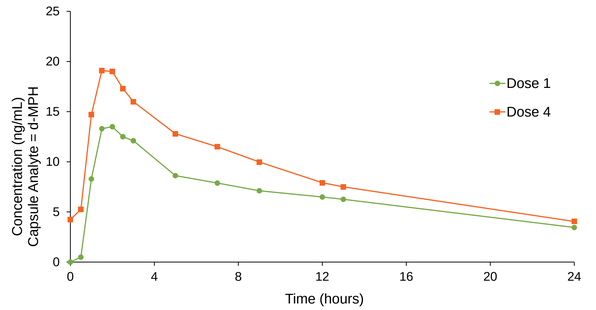


d-MPH=dexmethylphenidate; ER=extended release; PK=pharmacokinetic; SDX=serdexmethylphenidate.

Study 2:

- Plasma d-MPH concentrations following single (dose 1) and multiple-day (dose 4) doses of SDX/d-MPH, 52.3/10.4 mg are shown in **Figure 2**
- Mean maximum (C_{max}), minimum (C_{min}), and overall ($AUC_{0\text{-}24h}$) d-MPH exposures were approximately 35%, 12%, and 36% higher, respectively, after dose 4 of SDX/d-MPH 52.3/10.4 mg, relative to dose 1 (single dose), indicative of some accumulation of d-MPH
- Steady-state plasma concentrations were achieved prior to the third dose (ie, between the second and the third day of multiple dosing)
- No accumulation of the intact prodrug, SDX, was seen during once-daily administration of SDX/d-MPH

Figure 2. Mean Plasma d-MPH Concentration-time Profiles After Dose 1 and Dose 4 Administrations of SDX/d-MPH 52.3/10.4 mg (Study 2)



d-MPH=dexmethylphenidate; SDX=serdexmethylphenidate.

Safety and Tolerability

- No serious adverse events (AEs) or deaths were reported in either study
- Most treatment-emergent AEs (TEAEs) were graded as mild or moderate in severity in both studies

Study 1:

- 28 TEAEs were reported by 12 subjects (40%); the most common AEs were nausea, dizziness, and dyspnoea

Study 2:

- 55 TEAEs were reported by 19 subjects (79.2%); the most common AEs were dry mouth, somnolence, and tachycardia

CONCLUSIONS

- Following single-dose administration, peak and total d-MPH exposures were lower for SDX/d-MPH compared with an equimolar dose of ER d-MPH HCl; efficacy was, however, established with SDX/d-MPH in patients with ADHD 6-12 years of age[2]
- Following repeat-dose administration, modest accumulation of d-MPH was observed and steady-state concentrations of d-MPH were reached prior to administration of the third dose of SDX/d-MPH
- SDX/d-MPH was generally well tolerated, no notable safety signals were identified, and AEs were typical of stimulant treatment
- SDX/d-MPH has the potential to provide a rapid onset and extended duration of action for improving symptoms of ADHD

DISCLOSURES: RB, ACB, SG and TCM 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. Package insert. Corium Inc; 2021.