Poster S38

# Dose Proportionality and Effects of Food on the Pharmacokinetics of Single-Entity Serdexmethylphenidate

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## INTRODUCTION

- Serdexmethylphenidate (SDX) 70%/d-methylphenidate (d-MPH) 30% (AZSTARYS™) is available as a once-daily, orally administered capsule for the treatment of attention-deficit hyperactivity disorder (ADHD).
- Early exposure to the medication is governed by d-MPH, and mid- to late-day exposure is governed primarily by its prodrug, SDX, which is gradually converted to d-MPH throughout the day.
- The onset and duration of d-MPH action is a critical determinant of ADHD symptom control over the course of the day; thus, it is important to understand the pharmacokinetics (PK) of the prodrug SDX alone, which is converted to d-MPH.

## OBJECTIVES

- Study 1, to evaluate the dose proportionality of single-entity SDX-derived d-MPH after single doses of 20, 40, or 60 mg of SDX chloride.
- Study 2, to assess the effects of food on the PK of SDX-derived d-MPH after administration of 60-mg SDX chloride capsules.

## METHODS

### Subjects and Study Design

- For both studies, eligible subjects were healthy men and nonpregnant women 18-55 years of age.
- Study 1 was a phase 1, open-label, single-dose, randomized, parallel-group, PK and dose-proportionality study.
  - 24 subjects (8 per dose) received single doses of 20, 40, or 60 mg SDX chloride gelatin capsules at a prespecified time following an overnight fast of at least 10 hours. The subjects fasted for 4 hours thereafter.
  - Blood samples were obtained predose (0 hour; within 1 hour prior to dosing) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4.5, 6, 8, 10, 12, 13, 16, 24, 36, 48, and 60 hours (±5 minutes) postdose to assess the PK profiles of SDX and d-MPH.
- Study 2 was a phase 1, open-label, single-dose, randomized, parallel-group study of the effect of food on the PK of 60-mg SDX chloride gelatin capsules.
  - 14 subjects received single doses of 60 mg SDX chloride under fasted and fed conditions.
    - Under fasted conditions, all subjects were required to fast for at least 10 hours prior to dosing with study drug until approximately 4 hours after dosing with SDX chloride.
    - Under fed conditions, subjects were required to fast for at least 10 hours prior to receiving the standard breakfast (500 kilocalories, with 57% of the calories as carbohydrates, 14% as protein, and 29% as fat) served 20 minutes prior to SDX chloride administration.
  - Blood samples were collected predose (0 hour; within 1 hour prior to dosing) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4.5, 6, 8, 10, 12, 16, 24, and 36 hours (±5 minutes) postdose for PK analysis.
- For both studies, adverse events were continuously monitored, assessed, and recorded from predose until end of the treatment period.

### Assessments

- For studies 1 and 2, the PK parameters area under the curve (AUC), maximum concentration in plasma ($C_{max}$), time to reach maximum concentration ($T_{max}$) were calculated from plasma concentrations of d-MPH using standard, noncompartmental methods.

### Statistical Analysis

- For Study 1, dose proportionality was assessed by comparing $AUC_{0\text{-}inf}$ across each SDX dose level and dose linearity was assessed using power analysis.
- For Study 2, the values of $T_{max}$ and apparent terminal half-life ($T_{1/2}$) for d-MPH were compared between fed and fasted conditions using the Wilcoxon signed rank test.

## RESULTS

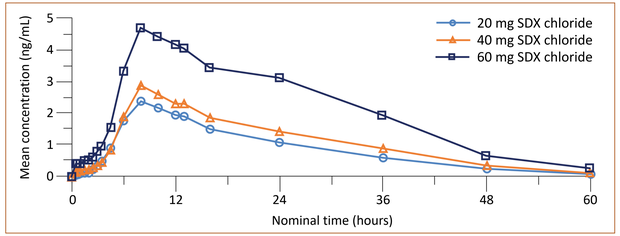
### Subject Demographics

- For Study 1, 24 subjects were enrolled—7 women and 17 men. All 24 subjects enrolled were administered 1 of the 3 doses of SDX chloride capsule (8 subjects received a 20-mg dose, 8 subjects received a 40-mg dose, and 8 subjects received a 60-mg dose).
- For Study 2, 14 subjects were enrolled—6 women and 8 men. All 14 enrolled subjects completed the study.
- Body mass index of subjects in both studies ranged from 19.6 to 31.5 kg/m$^2$.

### Pharmacokinetic Data

- Study 1
  - The plasma concentrations of d-MPH increased with increasing dosages of SDX chloride (**Figure 1**).
    - d-MPH peaked between 8.6-9.5 hours and was eliminated by 60 hours, but the prodrug SDX peaked much earlier, between 1.4-2.6 hours, and was largely eliminated by 24 hours (data not shown).

**Figure 1. Mean plasma d-MPH concentration-time data after single oral dose administrations of 20 mg, 40 mg, and 60 mg SDX chloride (linear scale).**




  - d-MPH AUC and $C_{max}$ values increased in plasma with increasing dosages of SDX chloride (**Table 1**).

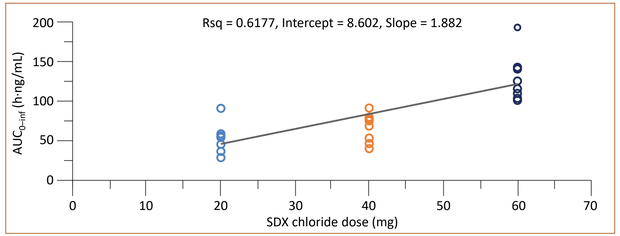
**Table 1. Plasma PK parameters of d-MPH after single oral dose administration of 20 mg, 40 mg, or 60 mg SDX chloride.**

| | | 20 mg SDX chloride | | 40 mg SDX chloride | | 60 mg SDX chloride | |
|---|---|---|---|---|---|---|---|
| **PK parameter** | n | Mean | CV% | Mean | CV% | Mean | CV% |
| **$AUC_{0\text{-}last}$ (h·ng/mL)** | 8 | **50.13** | 31.30 | **63.84** | 26.43 | **125.9** | 20.98 |
| **$AUC_{0\text{-}inf}$ (h·ng/mL)** | 8 | **54.39** | 33.91 | **67.58** | 26.41 | **129.7** | 23.01 |
| **$C_{max}$ (ng/mL)** | 8 | **2.47** | 32.91 | **2.97** | 40.83 | **4.85** | 20.62 |
| **$T_{max}$ (h)** | 8 | 8.63 | 23.95 | 9.50 | 29.23 | 9.38 | 22.04 |

*AUC, area under the plasma vs time curve; $AUC_{0\text{-}inf}$, AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$, AUC from time 0 to the time of the last quantifiable concentration; $C_{max}$, maximum concentration in plasma; CV, coefficient of variance; d-MPH, d-methylphenidate; PK, pharmacokinetics; SDX, serdexmethylphenidate; $T_{max}$, time to reach maximum concentration.*

  - Total d-MPH exposure as assessed by $AUC_{inf}$ increased in a dose-proportional manner with a fairly good correlation overall and a linear regression line that goes through zero or close to zero (**Figure 2**)

**Figure 2. Assessment of plasma d-MPH $AUC_{0\text{-}inf}$ vs SDX chloride dose.**




*$AUC_{0\text{-}inf}$, area under the plasma vs time curve from time 0 extrapolated to infinity.*

- Study 2
  - The effect of food was assessed on d-MPH exposure following a single dose of 60 mg SDX chloride.
  - Food increased d-MPH exposure ($AUC_{0\text{-}last}$) by approximately 20% (**Table 2**).

**Table 2. Plasma PK of d-MPH after single oral dose administration of 60 mg SDX chloride under fasted and fed conditions.**

| | 60 mg SDX chloride fasted | | | 60 mg SDX chloride fed | | |
|---|---|---|---|---|---|---|
| **PK parameter** | n | Mean | CV% | n | Mean | CV% |
| **$AUC_{0\text{-}last}$ (h·ng/mL)** | 14 | **107.0** | 18.88 | 14 | **132.8** | 24.89 |
| **$AUC_{0\text{-}inf}$ (h·ng/mL)** | 12 | 167.5 | 28.54 | 13 | 170.1 | 29.95 |
| **$C_{max}$ (ng/mL)** | 14 | 5.97 | 34.16 | 14 | 7.09 | 29.89 |
| **$T_{max}$ (h)** | 14 | 10.29 | 72.29 | 14 | 8.89 | 51.54 |

*AUC, area under the plasma vs time curve; $AUC_{0\text{-}inf}$, AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$, AUC from time 0 to the time of the last quantifiable concentration; $C_{max}$, maximum concentration in plasma; CV, coefficient of variance; d-MPH, d-methylphenidate; PK, pharmacokinetics; SDX, serdexmethylphenidate; $T_{max}$, time to reach maximum concentration.*

  - Statistical comparison indicated that mean peak d-MPH exposure ($C_{max}$) and total d-MPH exposure from predose to the last quantifiable concentration ($AUC_{0\text{-}last}$), were higher after 60 mg SDX chloride administration under fed conditions vs fasted conditions.
    - Geometric mean ratios (fed vs fasted) for $C_{max}$ and $AUC_{0\text{-}last}$ were 120.97% (90% CI 102.15-143.25) and 122.74% (90% CI 112.3-134.15), respectively.
  - Median d-MPH $T_{max}$ occurred 8 hours after dosing under both conditions (**Table 3**).

**Table 3. Wilcoxon signed rank test comparing d-MPH $T_{max}$ and $T_{1/2}$ values of fed vs fasted after single oral dose administration of 60 mg SDX chloride.**

| Dependent variable | Test fed, h, median (range) | Reference fasted, h, median (range) | Wilcoxon test statistic | *P* value | Median difference, h | 90% CI lower, h | 90% CI upper, h |
|---|---|---|---|---|---|---|---|
| **$T_{max}$** | **8.00** (4.50-24.00) | **8.00** (8.00-36.00) | −8.5 | 0.3398 | −1.00 | −2.01 | 1.00 |
| **$T_{1/2}$** | 14.47 (9.45-23.18) | 16.72 (9.44-38.51) | −26 | 0.0186 | −8.54 | −18.58 | −2.45 |

*CI, confidence interval; d-MPH, d-methylphenidate; SDX, serdexmethylphenidate; $T_{1/2}$, apparent terminal half-life; $T_{max}$, time to reach maximum concentration.*

### Adverse Events

- No notable safety signals were identified in either study.

## CONCLUSIONS

- In Study 1, based on graphical evaluation of the PK parameters vs dose, d-MPH exposure appeared to increase proportionally with SDX dose.
- In Study 2, food had no clinically meaningful impact on the production and absorption of SDX-derived d-MPH.

**DISCLOSURES: RB**, **ACB**, **SG**, and **TCM** are employees and shareholders of KemPharm, Inc. **CO** is an employee and shareholder of Corium, Inc.
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