S8

Human Abuse Potential of Oral Serdexmethylphenidate (SDX), a Novel Prodrug of d-Methylphenidate, Compared to Focalin® XR and Phentermine in Recreational Stimulant Abusers

Rene Braeckman[1], Sven Guenther[1], Travis C. Mickle[1], Andrew C. Barrett[1], Lynn Webster[2]

[1] KemPharm, Inc., Celebration, FL; [2] PRA Health Sciences, Salt Lake City, UT

BACKGROUND

- Serdexmethylphenidate (SDX) is a novel prodrug of d-methylphenidate (d-MPH) that is currently under development as the major active pharmaceutical ingredient (API) in KP415, an investigational product for the treatment of ADHD
- SDX has negligible binding (K_i >10 μM) at monoamine transporters and a host of other CNS targets associated with "off-site" pharmacology.
- SDX does not produce any discernable pharmacodynamic effects until it is converted to d-MPH, a process which occurs efficiently after oral but not intranasal or intravenous administration[1,2] (see also Poster S7)
- As SDX is a new chemical entity that is currently unscheduled under the Controlled Substances Act, it is important to evaluate its abuse potential relative to other known stimulants

OBJECTIVE

- To examine the human abuse potential of supratherapeutic oral doses of SDX compared to Focalin XR (Schedule II stimulant) and phentermine (Schedule IV stimulant) in recreational stimulant users

METHODS

Study Design and Subjects

- This was a Phase 1, randomized, double-blind, single-dose, active- and placebo-controlled crossover study of oral SDX compared with Focalin XR and phentermine in recreational stimulant users
- Eligible subjects were recreational stimulant users between 18 and 50 years of age who had >10 lifetime experiences with any stimulant (e.g., cocaine, amphetamines, MPH), had used any stimulant for non-therapeutic purposes ≥5 times within the last 6 months, and had used cocaine within 6 months prior to Screening
- Subjects who were able to discriminate a dose of 80 mg Focalin XR from placebo were randomized to receive the following treatments (one per treatment period) separated by a minimum 96-hour washout period:
  - ***Treatment A:*** 120 mg SDX (equimolar to 60 mg d-MPH HCl)
  - ***Treatment B:*** 240 mg SDX (equimolar to 120 mg d-MPH HCl)
  - ***Treatment C:*** 80 mg Focalin XR (primary positive control)
  - ***Treatment D:*** 60 mg phentermine (secondary positive control)
  - ***Treatment E:*** Placebo
- Written informed consent was obtained and the study protocol was approved by an Institutional Review Board

Pharmacodynamic Assessments and Statistical Analyses

- Visual analog scale (VAS) assessments recommended for use in human abuse potential studies[3] were conducted at various times post-dose, including:
  - "At-the-moment" effects: Drug Liking (primary endpoint), Feeling High, Good Effects, and Bad Effects, assessed at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 24 hours post-dose
  - Balance of effects: Take Drug Again and Overall Drug Liking (secondary endpoints), assessed retrospectively at 12 and 24 hours postdose
- For the primary endpoint and other endpoints, an appropriate statistical model was selected (using the Completers Population) based on testing each endpoint for first-order carryover effects, normality, and symmetry
- The ANCOVA model included terms for treatment, period, sequence and first-order carryover effect as fixed effects, with subject nested within sequence as a random effect.
- For endpoints that were not normally distributed, treatment differences were evaluated for symmetric distribution. If symmetric, these were analyzed using a paired t-test, and if non-symmetric, the Sign test was used
- The primary endpoint, the maximal (E_{max}) score for Drug Liking VAS, was analyzed using one-sided hypothesis tests at a significance level of α=0.05 and reported with one-sided 95% confidence intervals (CIs), with margins (δ) defined as shown in **Table 1** below:

Table 1. Statistical analysis of primary endpoint, Drug Liking VAS E_{max}

Hypotheses	Comparison	Null hypothesis (H_0)	Alternative hypothesis (H_A)
1: primary positive control validity	• Focalin XR (C) to Placebo (E)	$\mu_C - \mu_E \leq 15$ (δ1)	$\mu_C - \mu_E > 15$ (δ1)
2: relative abuse potential	• Focalin XR (C) to SDX 120 mg (A)	$\mu_C - \mu_A \leq 10$ (δ2)	$\mu_C - \mu_A > 10$ (δ2)
3: relative abuse potential	• Focalin XR (C) to SDX 240 mg (B)	$\mu_C - \mu_B \leq 10$ (δ2)	$\mu_C - \mu_B > 10$ (δ2)
4: absolute abuse potential	• SDX 120 mg (A) to Placebo (E)	$\mu_A - \mu_E \geq 11$ (δ3)	$\mu_A - \mu_E < 11$ (δ3)
	• SDX 240 mg (B) to Placebo (E)	$\mu_B - \mu_E \geq 11$ (δ3)	$\mu_B - \mu_E < 11$ (δ3)
5: secondary positive control validity	• Phentermine (D) to placebo (E)	$\mu_D - \mu_E \leq 10$ (δ4)	$\mu_D - \mu_E > 10$ (δ4)
6: exploratory relative abuse potential	• Phentermine (D) to SDX 120 mg (A)	$\mu_D - \mu_A \leq 10$ (δ2)	$\mu_D - \mu_A > 10$ (δ2)
	• Phentermine (D) to SDX 240 mg (B)	$\mu_D - \mu_B \leq 10$ (δ2)	$\mu_D - \mu_B > 10$ (δ2)

- Secondary and exploratory endpoints were analyzed using two-sided, confirmatory hypothesis tests (e.g., H_0: $\mu_C - \mu_A = 0$; H_A: $\mu_C - \mu_A \neq 0$) at a significance level of α=0.05 and reported with two-sided 95% CIs, with the exception of the SDX vs. placebo comparisons, which were performed using a two-sided hypothesis test at a significance level of α=0.10 and reported with two-sided 90% CI

Safety

- Assessment included incidence of adverse events (AEs), physical examination findings, vital signs, electrocardiogram (ECG) parameters, and clinical laboratory tests

RESULTS

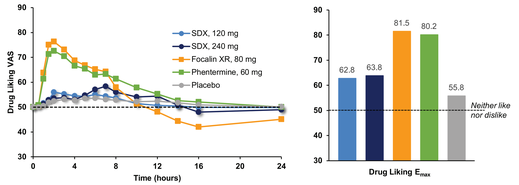
Subject Disposition and Demographics

- A total of 45 subjects (mean age = 30.2, 73% male) completed all 5 treatment periods and thus comprise the Completer Population

Pharmacodynamics

- **Figure 1** (left panel) shows that Focalin XR and phentermine produced robust increases in mean Drug Liking VAS scores that peaked at approximately 2 hours postdose and returned to neutral scores at 10-12 hours postdose
- In contrast, both doses of SDX produced only modest increases in mean Drug Liking VAS scores that did not exceed 60 at any individual time point assessed
- **Figure 1** (right panel) demonstrates that both doses of SDX produced Drug Liking E_{max} VAS scores that were more similar to placebo than to either active comparator

Figure 1. Drug Liking VAS[a] values over time (left panel) and Drug Liking VAS E_{max} scores (right panel)



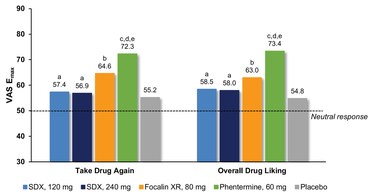
- **Table 2** shows that Focalin XR produced a mean E_{max} score on the primary endpoint that showed greater Drug Liking compared to 120 mg SDX and 240 mg SDX by at least 10 points
- For the absolute abuse potential comparisons, although the difference in mean E_{max} scores between both doses of SDX and placebo was <11 points, the differences were not statistically significantly less than 11
- For the exploratory comparisons, 60 mg phentermine produced a mean E_{max} score on the primary endpoint that showed greater Drug Liking by more than 10 points compared to 120 mg SDX but not compared to 240 mg SDX

Table 2. Inferential analysis results for Drug Liking VAS E_{max}

Pairwise Comparisons	Margin (δ)	Drug Liking E_{max}		
		LS Mean Difference (SE)	95% CI, one-sided	P-value
Focalin XR - Placebo	15	25.01 (2.61)	20.69, ∞	**<0.0001**
Focalin XR – SDX 120 mg	10	18.22 (2.63)	13.87, ∞	**0.0011**
Focalin XR – SDX 240 mg	10	16.74 (2.64)	12.37, ∞	**0.0058**
SDX 120 mg - Placebo	11	6.69 (2.65)	-∞, 11.17	0.0567
SDX 240 mg - Placebo	11	8.27 (2.63)	-∞, 12.62	0.1502
Phentermine - Placebo	10	22.27 (2.63)	17.91, ∞	**<0.0001**
Phentermine - SDX 120 mg	10	15.48 (2.63)	11.12, ∞	**0.0195**
Phentermine - SDX 240 mg	10	14.00 (2.65)	9.62, ∞	0.0664

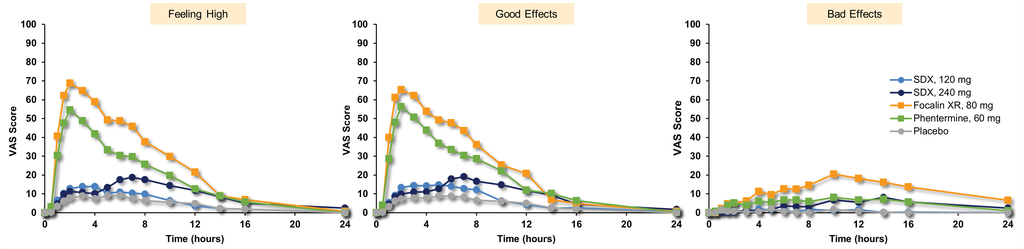
- **Figure 2** shows that for the secondary endpoints, E_{max} scores for both doses of SDX were significantly lower than phentermine and statistically similar to placebo
- No significant differences were observed between Focalin XR and either dose of SDX, possibly due to Bad Effects observed for Focalin XR that impacted the overall balance of effects

Figure 2. VAS E_{max} values for Take Drug Again and Overall Drug Liking



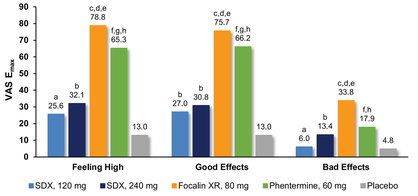
[a] statistically similar to placebo (p>0.05), [b] significantly higher vs placebo (p<0.05), [c] significantly higher vs SDX, 120 mg (p<0.001), [d] significantly higher vs SDX, 240 mg (p<0.001), [e] significantly higher vs placebo (p<0.0001).

Figure 3. VAS scores over time for Feeling High, Good Effects, and Bad Effects



- As shown in **Figure 3**, time-dependent effects for Feeling High and Good Effects resembled that for Drug Liking, whereby Focalin XR and phentermine produced robust increases in positive effects and SDX produced only modest increases in positive effects
- Bad Effects increased gradually up to 10 hours postdose following Focalin XR, but were less pronounced following SDX and phentermine
- **Figure 4** provides E_{max} scores and inferential statistical comparisons for Feeling High, Good Effects, and Bad Effects

Figure 4. VAS E_{max} values for Feeling High, Good Effects, and Bad Effects



[a] statistically similar to placebo (p>0.05), [b] significantly higher vs placebo (p<0.05), [c] significantly higher vs SDX, 120 mg (p<0.0001), [d] significantly higher vs SDX, 240 mg (p<0.001), [e] significantly higher vs placebo (p<0.0001), [f] significantly higher vs SDX, 120 mg (p<0.01), [g] significantly higher vs SDX, 240 mg (p<0.0001), [h] significantly higher vs placebo (p<0.01).

Tolerability and Safety

- **Table 3** indicates that AEs typical of stimulants (e.g., euphoric mood, hypervigilance, palpitations) were more common for Focalin XR than SDX
- There were no clinically significant clinical laboratory values, ECG results, or out-of-range vital signs following SDX

Table 3. Treatment-emergent adverse events occurring in ≥20% of subjects in the Safety Population overall

Adverse Event	120 mg SDX (N=47) n (%)	240 mg SDX (N=48) n (%)	80 mg Focalin XR (N=45) n (%)	60 mg Phentermine (N=47) n (%)	Placebo (N=46) n (%)
Euphoric mood	3 (6.4)	4 (8.3)	12 (26.7)	14 (29.8)	2 (4.3)
Palpitations	2 (4.3)	6 (12.5)	14 (31.1)	7 (14.9)	0 (0)
Hypervigilance	3 (6.4)	7 (14.6)	10 (22.2)	8 (17.0)	1 (2.2)
Headache	3 (6.4)	5 (10.4)	10 (22.2)	3 (6.4)	2 (4.3)
Dry mouth	0 (0)	2 (4.2)	11 (24.4)	3 (6.4)	0 (0)
Hyperhidrosis	1 (2.1)	2 (4.2)	9 (20.0)	5 (10.6)	0 (0)

CONCLUSIONS

- **Oral SDX produced a gradual onset of abuse-related effects and maximal effects for the primary endpoint and other endpoints were generally significantly lower than a Schedule II and a Schedule IV stimulant**
- **These data suggest that SDX may have lower oral abuse potential than currently available stimulant products**
- **Oral SDX produced fewer stimulant-like AEs compared to Focalin XR and no new AEs were identified with supratherapeutic doses**

Disclosures

RB, SG, TCM, and ACB are employees and shareholders of KemPharm, Inc. BS is an employee of Syneos Health. This study was funded by KemPharm, Inc., Celebration, FL. Design support was provided by Research Triangle Graphics, LLC.

References

1. Braeckman et al. Poster presentation at AACAP, October 23-28, 2018; Seattle, WA. **2.** Shram et al. Poster presentation at ACNP, December 9-13, 2018; Hollywood, FL.
3. Food and Drug Administration (2017). Assessment of abuse potential of drugs. Guidance for Industry.