# Human Abuse Potential of Intranasal Serdexmethylphenidate (SDX), a Novel Prodrug of d-Methylphenidate, in Recreational Stimulant Abusers

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## BACKGROUND

- Serdexmethylphenidate (SDX) is a prodrug of d-methylphenidate (d-MPH) currently being developed as the major active pharmaceutical ingredient (API) in KP415, an investigational product for the treatment of ADHD
- SDX as the intact prodrug produces no discernible pharmacodynamic effects and is gradually converted to the active moiety, d-MPH, when administered orally
- Nonmedical use of Schedule II prescription stimulants, including methylphenidate products, has been widely reported in adolescents and adults <sup>1-3</sup>
- Among those reporting past-month nonmedical use of stimulants, approximately 40% reported intranasal (IN) administration, presumably to produce a more rapid and intense "high" 1-3
- Chronic abuse of stimulants, particularly via non-oral routes, can lead to a constellation of health-related problems, including cardiovascular and cerebrovascular toxicity, lowering of seizure thresholds, increased risk of acquiring blood-borne infections, malnutrition, and miscarriage in pregnant women 4,5
- It is therefore important to evaluate novel stimulant-like drugs such as SDX for their abuse potential by all relevant routes of abuse

## OBJECTIVE

 To evaluate the human abuse potential of IN SDX in recreational stimulant abusers

# METHODS

#### Study Design and Subjects

- This was a Phase 1, double-blind, placebo- and active-controlled, single-dose, randomized crossover study of IN administration of SDX compared with d-MPH HCl in recreational stimulant users
- Eligible subjects were recreational stimulant users 18-55 years of age who had >10 lifetime experiences with any stimulant (e.g., cocaine, amphetamines, MPH), had used CNS stimulants by the nasal route more than once within the 12 weeks prior to Screening, and had used any stimulant for non-therapeutic purposes ≥5 times within the last 6 months.
- Subjects who were able to discriminate a dose of 40 mg IN d-MPH API from placebo were randomized to receive the following IN treatments (one per treatment period):
- Treatment A: SDX API 80 mg (equimolar to 40 mg d-MPH HCI)
- Treatment B: d-MPH HCI API 40 mg + 40 mg microcrystalline cellulose (MCC)
- Treatment C: Matching placebo (80 mg MCC)
- The dose of the active comparator was selected on the basis of findings from a prior dose-ranging pharmacodynamic study in recreational stimulant abusers, where 40 mg IN d-MPH HCl engendered robust positive subjective effects with acceptable negative effects<sup>6</sup>
- Written informed consent was obtained and the study protocol was approved by an Institutional Review Board

#### Pharmacokinetic Assessments and Analyses

- Blood samples were collected for the measurement of the plasma concentrations of SDX, d-MPH, I-MPH, and ritalinic acid up to 48 hours post-dose
- Primary PK endpoints were maximum plasma concentration ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), mean systemic exposure (AUC<sub>0-last</sub>), and mean total systemic exposure (AUC<sub>0-inf</sub>) of d-MPH

## Pharmacodynamic Assessments and Statistical Analyses

- Visual analog scale (VAS) assessments recommended for use in human abuse potential studies<sup>7</sup> were conducted at various times post-dose, including:
- Drug Liking (primary endpoint), Feeling High, Good Effects, Bad Effects, and Any Effects, assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose
- Take Drug Again and Overall Drug Liking (both secondary endpoints), assessed at 12 and 24 hours postdose
- Addiction Research Center Inventory-Amphetamine Scale (ARCI-A), which assesses stimulant effects; and ARCI-Benzedrine Group (ARCI-BG) Scale, which assesses energy and intellectual efficiency, both measured at 0.5, 1, 2, 4, and 8 hours post-dose
- Pharmacodynamic analyses were performed using a mixed effects Analysis of Covariance (ANCOVA) model based on the Completers Population, with LS mean differences and associated CIs calculated for each pairwise comparison between treatments
- For endpoints with non-normal distribution of residual errors, treatment differences were evaluated for symmetric distribution. If symmetric, these comparisons were analyzed using a paired t-test, and if non-symmetric, the Sign test was used
- The primary endpoint, Drug Liking VAS  $E_{max}$  was analyzed using one-sided, hypothesis tests at a significance level of  $\alpha$ =0.05 and reported with one-sided 95% confidence intervals (CIs), with margins ( $\delta$ ) defined as shown below:

Comparison	Null hypothesis (H <sub>0</sub> )	Alternative hypothesis (H <sub>a</sub> )
d-MPH HCI (B) to Placebo (C)	$\mu_{\rm B} - \mu_{\rm C} \le 15 \ (\delta 1)$	$\mu_{\rm B} - \mu_{\rm C} > 15 \ (\delta 1)$
d-MPH HCI (B) to SDX (A)	$\mu_B - \mu_A \le 10 \ (\delta 2)$	$\mu_{\rm B} - \mu_{\rm A} > 10 \ (\delta 2)$
SDX (A) to Placebo (C)	$\mu_A - \mu_C \ge 11 (\delta 3)$	$\mu_{A} - \mu_{C} < 11 (\delta 3)$

• Secondary and exploratory endpoints were analyzed using two-sided, confirmatory hypothesis tests (e.g.,  $H_0$ :  $\mu_B - \mu_C = 0$ ;  $H_A$ :  $\mu_B - \mu_C \neq 0$ ) at a significance level of  $\alpha$ =0.05 and reported with two-sided 95% CIs, with the exception of the SDX vs. placebo comparison, which was performed using a two-sided hypothesis test at a significance level of  $\alpha$ =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, clinical laboratory tests Columbia Suicide Severity Rating Scale (C-SSRS) assessments, and nasal cavity assessments

## RESULTS

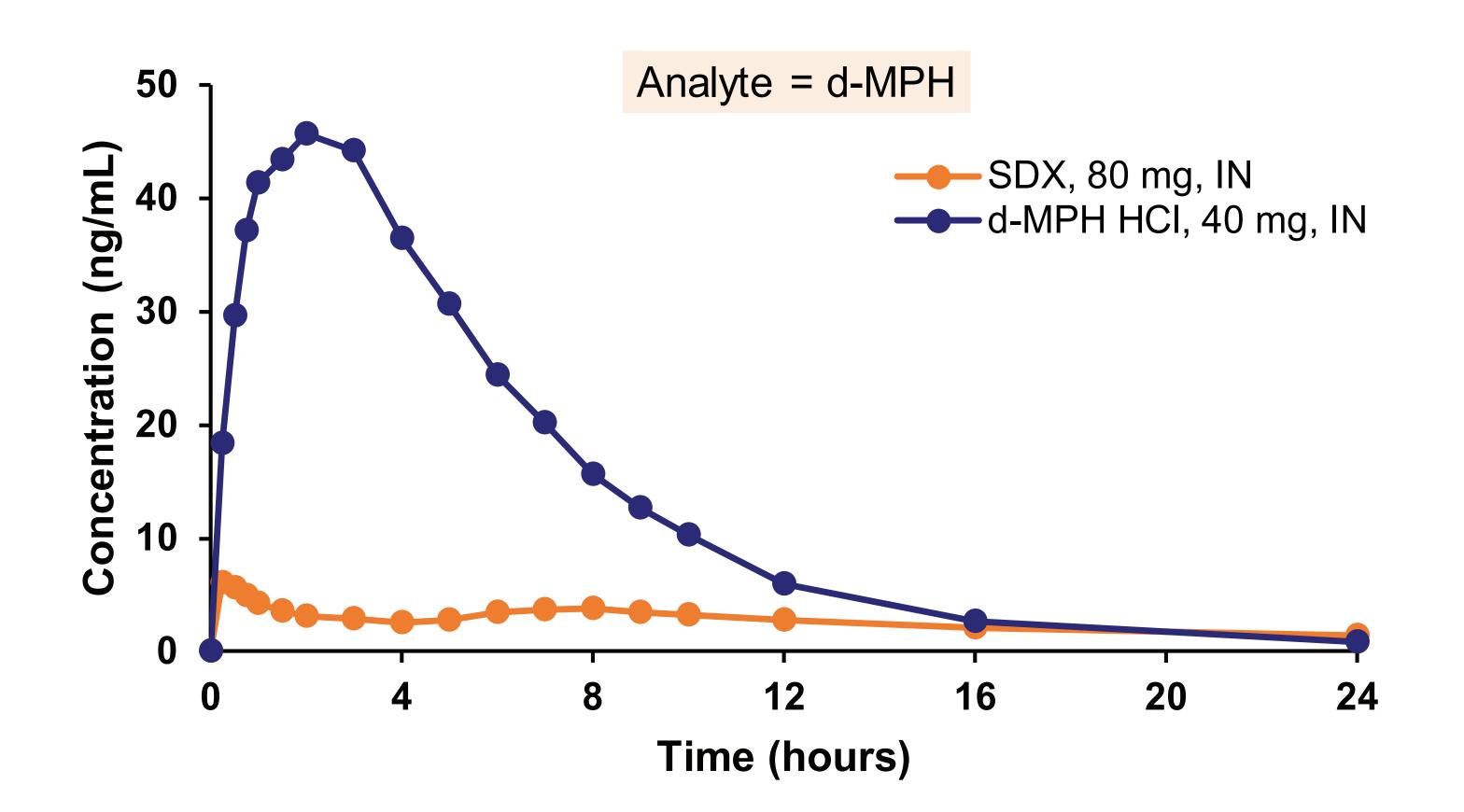
#### Subject Disposition and Demographics

- A total of 45 subjects (mean age = 36.0 years, 73.3% male) completed all 3 treatment periods and thus comprised the Completer Population
- Subjects had used stimulants (by any route) a median (range) of 30 (6-100) times in the past 6 months and reported IN use of stimulants a median (range) of 10 (2-50) times in the 12 weeks prior to Screening

#### **Pharmacokinetics**

- Figure 1 shows plasma d-MPH concentrations derived from IN SDX and d-MPH HCI
- Peak (C<sub>max</sub>) and overall (AUC<sub>inf</sub>) d-MPH exposure following SDX administration were approximately 13.2% and 24.3% of the respective exposure parameters observed following d-MPH HCl administration

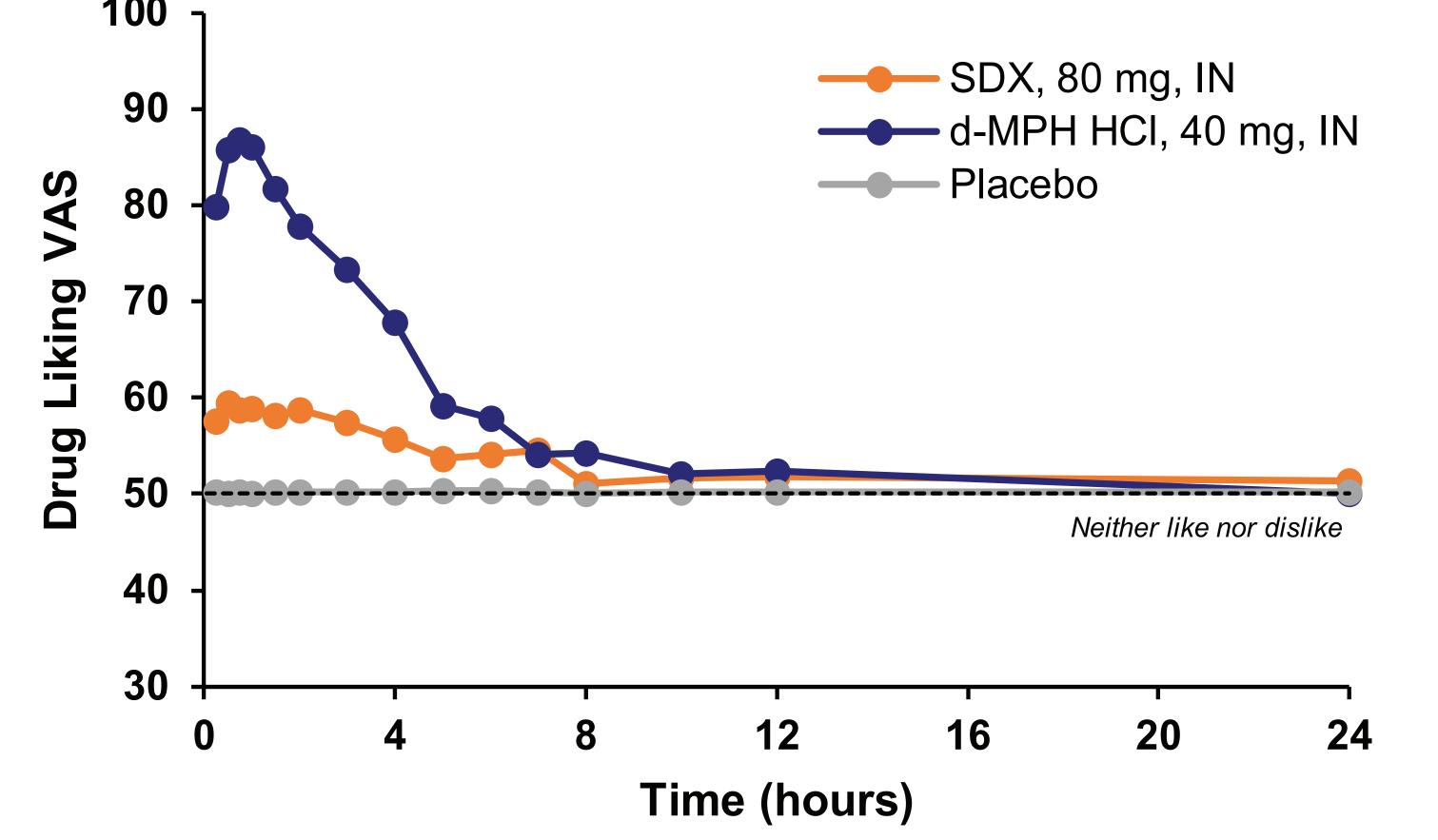
Figure 1. d-MPH concentrations following IN administration of SDX and d-MPH HCI



#### Pharmacodynamics

- **Figure 2** shows that mean Drug Liking VAS scores for d-MPH HCl increased rapidly, with a score of 79.8 at 0.25 hr post-dose and peak scores of >85 occurring 0.5-1 hr post-dose.
- In contrast, mean Drug Liking VAS scores for SDX remained below 60 for the entire assessment interval

Figure 2. Drug Liking VAS<sup>a</sup> values over time for IN administration of SDX, d-MPH HCI, and placebo



- <sup>a</sup> Subjects responded to the question: "At this moment, my liking for the drug is?", with 0=strong disliking, 50=neither like nor dislike, and 100=strong liking
- Mean Drug Liking VAS E<sub>max</sub> values were 93.2, 71.0, and 51.1 after IN administration of d-MPH HCI, SDX, and placebo, respectively
- As shown in Table 2, d-MPH HCl produced significantly greater Drug Liking VAS scores than placebo, thus confirming study validity
- Drug Liking VAS E<sub>max</sub> scores for SDX were significantly lower than d-MPH yet not equivalent to placebo
- Figure 3 shows VAS E<sub>max</sub> values for the secondary endpoints Take Drug Again and Overall Drug Liking
  For both endpoints, VAS E<sub>max</sub> scores for SDX were significantly lower

compared to d-MPH HCI and significantly higher compared to placebo

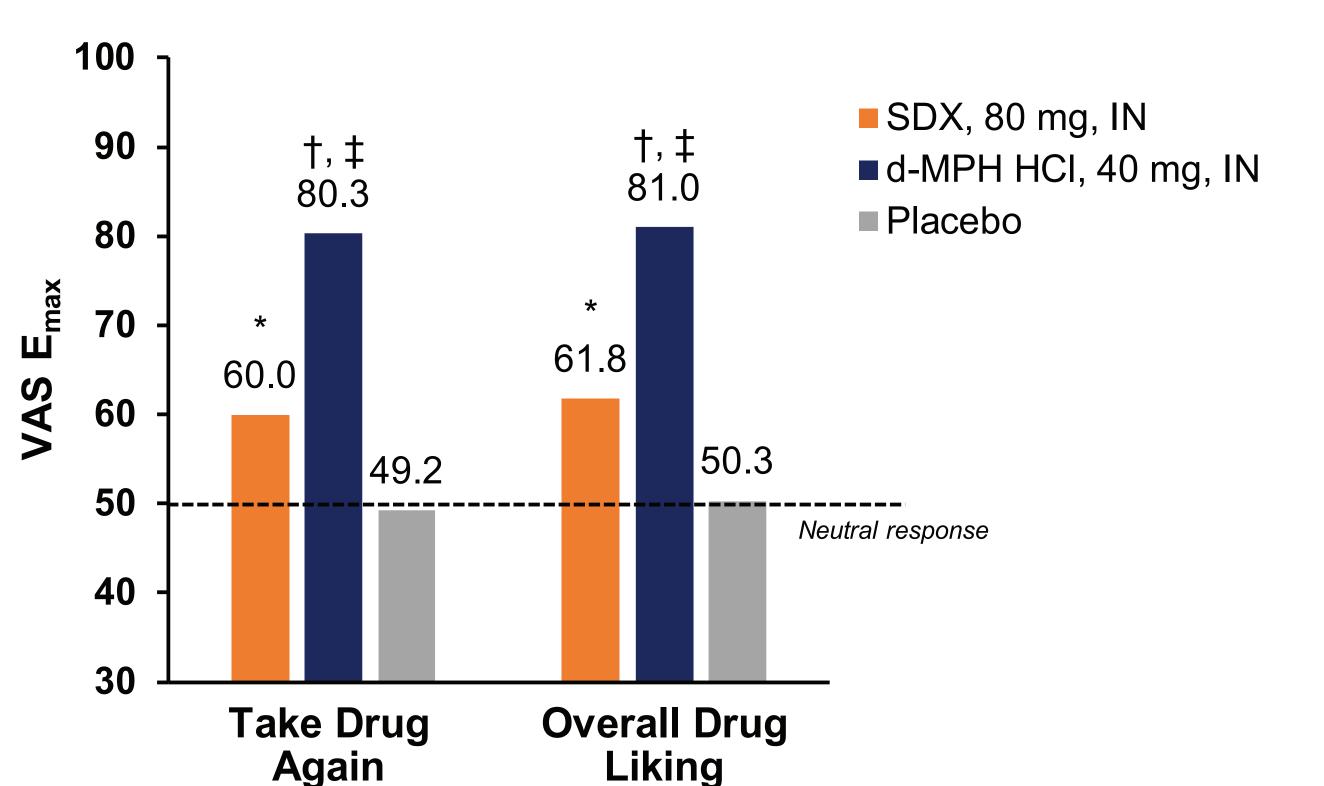
 Figure 4 demonstrates similar trends in treatment effects for other secondary endpoints (High, Good Effects, Any Effects), whereby SDX produced positive effects significantly lower than d-MPH HCl yet significantly higher than placebo

able 2. Inferential analysis results for Drug Liking VAS E

			max	
Drug Liking E <sub>max</sub>				
Pairwise Comparisons	Margin (δ)	Mean (SE) / Median of Intra-subject Difference	One-sided 95% CI	P-value
d-MPH HCI - Placebo*	15	45.0	41.0, ∞	<0.0001
d-MPH HCI - SDX**	10	22.27 (2.96)	17.3, ∞	<0.0001
SDX - Placebo**	11	19.87 (2.79)	-∞, 24.6	0.9986

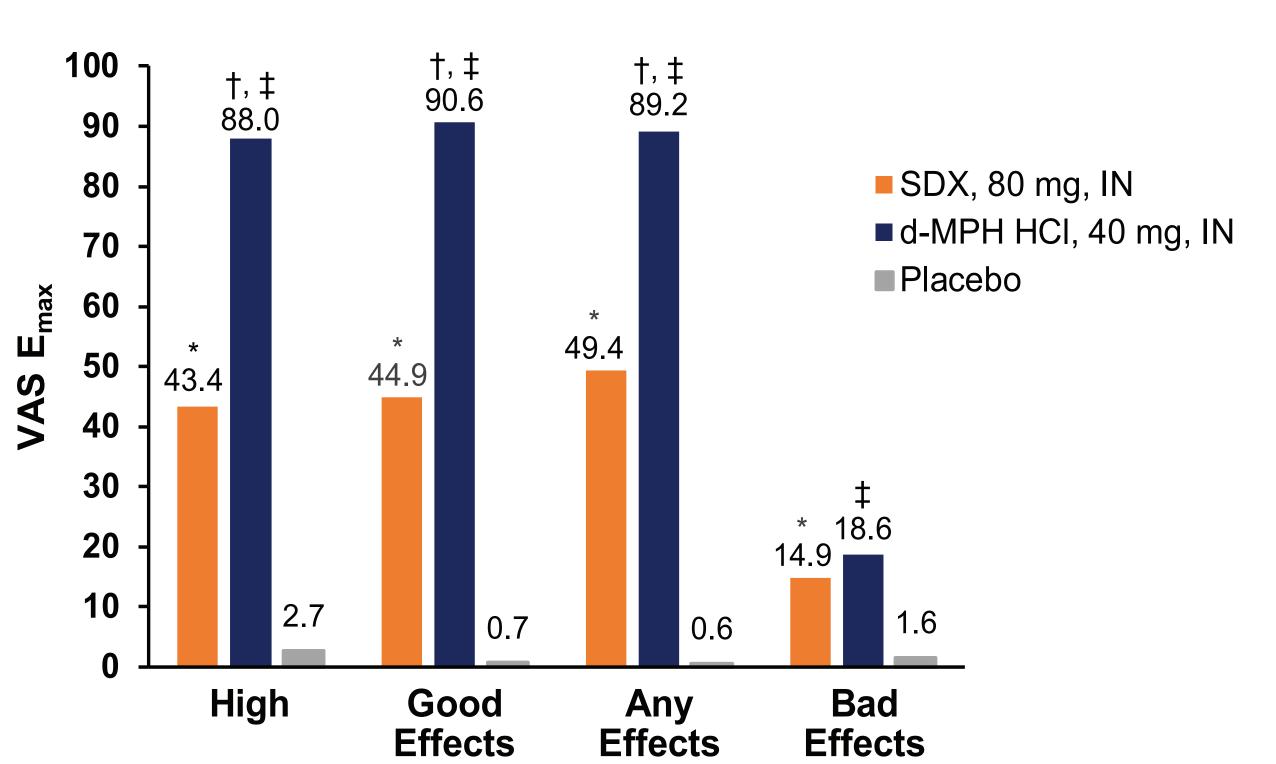
\*The sign test was used to assess the median difference between the two treatments; median is presented \*\*A paired t test was used to assess the mean difference between the two treatments; mean (SE) is presented

Figure 3. VAS E<sub>max</sub> values for Take Drug Again and Overall Drug Liking



\*significantly higher vs. placebo (p<0.01), †significantly higher vs. SDX (p<0.01), ‡significantly higher vs. placebo (p<0.001)

Figure 4. VAS E<sub>max</sub> values for High, Good Effects, Any Effects, and Bad Effects



\*significantly higher vs. placebo (p<0.01), †significantly higher vs. SDX (p<0.01), ‡significantly higher vs. placebo (p<0.0001)

• SDX produced significantly lower scores on the ARCI-A and ARCI-BG scales compared to d-MPH HCl (p<0.001 for both comparisons), and significantly higher scores compared to placebo (p<0.0001 for both comparisons, data not shown)

### Ease of Insufflation

Assessed on a 0-100 point unipolar scale

 SDX (mean = 65.8) was rated by subjects as significantly more difficult to insufflate compared to d-MPH HCI (18.1, p<0.0001) and placebo (6.9, p<0.0001)</li>

## **Tolerability and Safety**

• **Table 3** indicates that AEs typical of stimulants (euphoric mood, hypervigilance, palpitations, tachycardia) were more common during d-MPH HCl vs. SDX treatment, whereas AEs associated with insufflation (nasal discomfort/congestion, lacrimation increased) were more common during SDX treatment

• There were no clinically significant clinical laboratory values, ECG results, or out-of-range vital signs following IN SDX

Table 3. Treatment-emergent adverse events occurring in ≥10% of subjects following any treatment (Safety Population)

MedDRA System Organ Class Preferred Term	SDX (N=46) n (%)	d-MPH HCI (N=46) n (%)	Placebo (N=48) n (%)
Psychiatric disorders	13 (28.3)	41 (89.1)	0 (0.0)
Euphoric mood	9 (19.6)	29 (63.0)	0 (0.0)
Hypervigilance	6 (10.0)	16 (34.8)	1 (2.1)
Respiratory, thoracic, and mediastinal disorders	25 (54.3)	10 (21.7)	1 (2.1)
Nasal discomfort	13 (28.3)	3 (6.5)	0 (0.0)
Nasal congestion	10 (21.7)	1 (2.2)	0 (0.0)
Cardiac disorders	2 (4.3)	19 (41.3)	1 (2.1)
Palpitations	2 (4.3)	11 (23.9)	0 (0.0)
Sinus tachycardia	0 (0.0)	7 (15.2)	1 (2.1)
Tachycardia	0 (0.0)	8 (17.4)	0 (0.0)
Nervous system disorders	11 (23.9)	9 (19.6)	2 (4.2)
Headache	5 (10.9)	7 (15.2)	2 (4.2)
Eye disorders	8 (17.4)	3 (6.5)	0 (0.0)
Lacrimation increased	8 (17.4)	0 (0.0)	0 (0.0)

# CONCLUSIONS

- IN administration of SDX resulted in markedly lower peak and overall exposure to d-MPH compared to IN administration of d-MPH HCI
- IN SDX produced abuse-related effects that were significantly lower than IN d-MPH HCI yet significantly higher than placebo
- IN SDX was significantly more difficult to insufflate than d-MPH HCI and produced fewer prototypical stimulant-like AEs
- Collectively, IN SDX produced pharmacodynmic effects consistent with lower abuse potential than IN d-MPH HCI

## 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.

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