**Assessment of the Intravenous Abuse Potential Of Serdexamifenphendate (SDX), a Novel, Investigational Prodrug Of D-Methylphenidate (DMPH), from Nonclinical and Clinical Studies**

**Methodology**

**Primary and Secondary Pharmacology**

The primary pharmacology of SDX (0.03 to 10 μM) was evaluated in binding competition assays using human recombinant dopamine (DAT), norepinephrine (NE), and serotonin (5HT) receptors. For experiments with human recombinant DAT and NET, aliquots were incubated with [3H]RTI-55, respectively, for experiments with human recombinant SERT, aliquots were incubated with [3H]paroxetine.

**Safety**

In vitro Metabolic Stability

The metabolic stability of SDX (10 μM) was evaluated in human whole blood, plasma, and human liver S9 fractions. Triptacol samples were collected at select time points after 5 to 90 minutes of incubation.

**RESULTS**

**Primary and Secondary Pharmacology**

- No significant binding was noted for SDX at DAT, NET, or SERT. All IC50 values were higher than 100 μM.
- In the second screen of "off-target" pharmacology, SDX (10 μM) produced no significant binding at any of the 88 molecular targets assayed.

**In vivo Metabolic Stability**

- Low levels of d-MPH were formed in all 3 matrices, human whole blood (5.4% ± 1.0%, plasma 1.8% ± 0.5%, and liver 9.5% ± 1.16) at 90 minutes (data not shown).
- Reasons for no d-MPH at Time 0: its quantitative increase relative to concentration is difficult to estimate using the PAR method.
- Plasma-d-MPH concentration was maximal early exposure (Cmax), overall d-MPH exposure through 2 hours (AUC0-2), and time to peak (Tmax).

**Intravenous Pharmacokinetics in Rats**

- In male Sprague-Dawley rats, SDX (4.75 mg/kg) and d-MPH HCl (2.39 mg/kg) were administered via the femoral vein at equimolar doses corresponding to 2.06 mg/kg d-MPH.
- SDX (4.75 mg/kg) concentrations were assessed via serial PK sampling up to 2 hours postdose.
- Parameters included: maximal d-MPH exposure (Cmax), overall d-MPH exposure through 2 hours (AUC0-2), and time to peak (Tmax).

**Intravenous Pharmacokinetics in Humans**

- This was a Phase 1, double-blind, placebo- and active-controlled, single-dose, randomized crossover study of IV administration of SDX API compared with d-MPH API in recreational stimulant users experienced with non-clinical administration of stimulants, including cocaine.
- Subjects who were able to discriminate a dose of IV d-MPH API from placebo were randomized to receive the following 4 IV treatments (one per treatment period).
- Treatment A: SDX API 30 mg equivalent to 5 mg d-MPH HCl (15 mg).
- Treatment B: SDX API 15 mg equivalent to 2.5 mg d-MPH HCl (15 mg).
- Treatment C: Placebo.

**Pharmacodynamic Assessments and Analyses**

- Blood samples were collected for the measurement of plasma concentrations of SDX, D-MPH, methylphenidate (MPH), and d-MPH acid up to 36 hours postdose.
- Primary PK endpoints were Cmax, Tmax, AUC0-24, and AUC24 (DMPH only).

**Pharmacodynamics and Statistical Analyses**

- Visual analog scale (VAS) assessments were conducted at various times postdose, including:
  - Drug Again: Liking, Feeling High, Good Effects, and Bad Effects, assessed at 2, 5, 15, 30, 45, and 60 minutes postdose.
  - Take Drug Again and Overall Drug Liking, assessed at 12 and 24 hours posttreatment.
- Pharmacodynamic analyses were performed using a mixed effects Analysis of Covariance (ANCOVA) model based on the Completers Population, with LS means differences and associated confidence intervals calculated for each pair of comparisons between treatments.
- 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 and key secondary endpoints, Drug Again, Take Drug Again, and Overall Drug Liking, were assessed using unpaired t-tests, symmetricly normalized. Median (IQR) values at level of 0.05 and reported with 95% confidence intervals (CIs), with margins (Δ) defined as shown below.

**Objective**

- To evaluate the performance of SDX in a series of in vivo and in vitro studies that are relevant for understanding its IV abuse potential.

**Conclusion**

- SDX had no appreciable pharmacological activity at monoaminergic transporters or other molecular targets when tested up to a concentration of 10 μM.
- SDX remained largely intact, with little conversion to d-MPH, in KemPharm, Inc. Celciation, FL, USA. Design support was provided by Research Triangle Institute.
- IV administration of SDX to rats and humans yielded very low concentrations of d-MPH.
- IV administration of SDX to recreational stimulant abusers produced pharmacodynamic effects that are comparable to placebo and significantly less than d-MPH HCl administered at an equimolar dose.
- The performance of SDX in these studies provides converging evidence that the drug is unlikely to be addictive for IV Abuse Potential.

**Assumptions**

- Note: Assessed on a 0-100 point bipolar scale.

**Figure 1.** In human metabolic stability of SDX

**Figure 2.** Plasma d-MPH concentrations following IV SDX and d-MPH HCI in rats

**Figure 3.** Effect of SDX on IV Abuse Potential

**Figure 4.** SDX, 30 mg, IV

**Figure 5.** "At the moment" Drug Liking and Overall Drug Liking VAS scores for IV SDX, d-MPH HCI, and placebo

**Figure 6.** Emax scores for Take Drug Again, Feeling High, Good Effects, and Bad Effects VAS

**Note:** Assessed on a 0-100 point bipolar scale.