

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212994Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABELS
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 2, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 212994
Product Name and Strength:	Azstarys (serdexmethylphenidate and dexamethylphenidate) capsules, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, and 52.3 mg/10.4 mg
Applicant/Sponsor Name:	Commave Therapeutics SA
OSE RCM #:	2020-459-1
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on March 1, 2021 for Azstarys. The Division of Psychiatry (DP) requested that we review the revised container labels for Azstarys (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review and in follow-up email correspondence with the Applicant.^{a,b}

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^a Holmes, L. Labels and Labeling Review for Azstarys (NDA 212994). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 22. RCM No.: 2020-459.

^b Bender, W. FDA Communication: NDA 212994/Azstarys Carton/Container label for Azstarys. Silver Spring (MD): FDA, CDER, OND, DP (US); 2021 FEB 25.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LORETTA HOLMES
03/02/2021 11:52:21 AM

SEVAN H KOLEJIAN
03/02/2021 12:27:34 PM

Memorandum to File: Clinical Inspections

Date	February 18, 2021
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Bender, Regulatory Project Manager Greg Dubitsky, M.D., Medical Officer Jean Kim, M.D., Clinical Team Leader Division of Psychiatry Products (DPP)
Application	NDA 212994
Applicant	Commave Therapeutics, SA
Drug	Dexmethylphenidate (b) (4)
NME / Original NDA	No
Review Timeframe	Standard
Proposed Indication	Attention Deficit Hyperactivity Disorder (patients of age ≥ 6 years)
Consultation Date	June 30, 2020
CIS Goal Date	January 4, 2021
Action Goal Date	March 2, 2021
PDUFA Due Date	March 2, 2021

OSI received a consult from DPP on 6/30/2020 that identified the following two clinical investigator (CI) sites for Good Clinical Practice (GCP) inspections:

1. Dr. Andrew Cutler (Florida); Protocol KP415-E01, Site 04
2. Dr. Ann C. Childress (Nevada); Protocol KP415-E01, Site 03

An inspection assignment for the two CI sites was issued on 07/06/2020, and the Office of Regulatory Affairs (ORA) attempted to schedule these inspections. However, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and

welfare of the FDA employees and the site study staff, the need for the planned inspections in support of NDA 212994 review was reevaluated. Following discussions between OSI and DPP, a decision was made that the assessment of the application could proceed without GCP inspections. Therefore, at this time, OSI is unable to determine if Protocol KP415-E01 was conducted adequately and whether the study data are reliable in support of the proposed indication.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Document Room / NDA 212994
DPP / Clinical Team Leader / Jean Kim
DPP / Medical Officer / Gregory Dubitsky
DPP / Regulatory Project Manager / William Bender
OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JONG HOON LEE
02/18/2021 04:26:17 PM

PHILLIP D KRONSTEIN
02/18/2021 04:38:19 PM

KASSA AYALEW
02/23/2021 07:25:14 AM



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 16, 2021

To: Tiffany Farchione, MD, Director
Division of Psychiatry

Through: Dominic Chiapperino, PhD, Director
Joshua Lloyd, MD, Medical Officer Team Leader
Controlled Substance Staff

From: Shalini Bansil, MD, Medical Officer
Silvia Calderon, PhD, Senior Pharmacologist
Controlled Substance Staff

Subject: **Product:** Serdexmethylphenidate and Dexmethylphenidate Capsules (also known as “KP415”); Tradename Azstarys
Dosages: 28/6 mg, 42/9 mg or 56/12 mg of serdexmethylphenidate chloride/ dexmethylphenidate once daily
NDA Number: 212994, product developed under IND 130463
Indication(s): treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older
Applicant: KemPharm, Inc.; Commave Therapeutics SA
PDUFA Goal Date: March 2, 2021

Materials Reviewed:

- Abuse-related data in Original NDA submission dated March 2, 2020, and subsequent amendments
- Statistical review of human abuse potential studies; Division of Biometrics VI; Ling Chen, PhD: DARRTS February 1, 2021.

Table of Contents

I. SUMMARY	2
1. Background.....	2

2. Conclusions.....	3
3. Recommendations.....	5
II. DISCUSSION.....	6
1. Chemistry.....	6
1.1 Substance Information.....	6
1.2 Drug Product	7
1.3 In vitro Stability Studies.....	9
2. Nonclinical Pharmacology.....	16
3. Clinical Pharmacology.....	18
4. Clinical Studies	23
4.1 Human Abuse Potential Studies	23
4.2 Adverse Event Profile Through all Phases of Development.....	59
4.3 Safety Profile	64
4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials.	64
4.5 Tolerance and Physical Dependence Studies in Humans.....	64
5. Regulatory Issues and Assessment	65
III. References.....	65

I. SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Psychiatry (DP), dated March 16, 2020, to the Controlled Substance Staff (CSS) to evaluate the abuse-related nonclinical and clinical data submitted for serdexmethylphenidate and dexmethylphenidate capsules (SDX/d-MPH; also known by the codename “KP415”); tradename Azstarys, by KemPharm, Inc. (referred to as “the Applicant”) under NDA 212994. SDX/d-MPH capsules were developed under IND 130463 and are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

SDX/d-MPH capsules contain immediate-release SDX, a prodrug of d-MPH, co-formulated with immediate-release d-MPH. The drug product is formulated in a fixed molar dose ratio of 70% SDX Cl:30% d-MPH HCl. According to the Applicant, this ratio provides both a rapid onset and extended-duration of d-MPH exposure. After oral administration, early exposure to d-MPH is governed primarily by the d-MPH HCl component and mid- to late-day exposure is governed by the gradual conversion of the SDX prodrug component to d-MPH. The Applicant states that SDX is a prodrug of d-MPH and is devoid of pharmacologic activity on its own. Its only role is to provide delayed delivery of d-MPH to the patient by converting to active d-MPH in the lower gastrointestinal tract.

The final to-be-marketed formulation has been developed in three dosage strengths: 28 mg/ 6 mg, 42 mg/ 9 mg, and 56 mg/12 mg SDX Cl/d-MPH Cl, corresponding to total d-MPH HCl-equivalent doses of 20, 30, and 40 mg, respectively.

The Applicant submitted this 505(b)(2) NDA, relying on the Agency's prior findings of safety and efficacy for Focalin XR (dexmethylphenidate hydrochloride) extended-release capsules, a once daily d-MPH drug product. The d-MPH component is listed as a schedule II controlled substance under the Controlled Substances Act (CSA); however, SDX is not currently scheduled under the CSA. Therefore, a full abuse potential assessment was required for SDX. Based on this assessment, the Applicant recommends that SDX be listed as a schedule IV controlled substance under the CSA (C-IV).

Regardless of findings related to the abuse potential of SDX, because the product contains d-MPH, the to-be-marketed drug product formulation, if approved, will be controlled as schedule II.

2. Conclusions

1. Chemically, SDX consists of a single d-MPH molecule covalently attached via a carbamate bond to a methylene linker, which in turn is connected to the nitrogen of the pyridine ring of a nicotinoyl-serine moiety. The carbamate linkage between d-MPH and methylene-nicotinoyl-serine makes SDX a new molecular entity (NME).
2. SDX has chemical characteristics that impart to the molecule low lipophilicity, low blood barrier penetration, low gastrointestinal absorption and chemical stability in acidic and basic media.
 - a. The chemical bond between the methylene oxide linker and the pyridine nitrogen is a covalent bond that forms a pyridinium (ammonium) quaternary salt. As a quaternary ammonium structure, it may be expected to result in compounds with low lipophilicity that have low blood brain barrier penetration and low gastrointestinal absorption (Holzer 2009).
 - b. The carbamate bond confers chemical stability to the molecule in acidic and basic media limiting the rate of release of d-MPH from SDX (Ghosh and Brindisi 2015).
3. SDX has three chiral centers but as a drug substance in this formulation it is an enantiomerically pure compound with defined configuration at these centers (see the section II's Chemistry Section)
4. SDX is synthesized from d-MPH (schedule II).
5. In vitro stability studies demonstrated that SDX was stable at pH 1-8 for 24 hours with no d-MPH, ritalinic acid, or SDX-acid detected at any time. At pH 9, SDX was stable for at least 1 hour, with minimal conversion to d-MPH at a minimum of 6 hours. At pH 11, SDX at a concentration of 5 mg/ mL aqueous solution, was rapidly converted to ritalinic acid with no d-MPH detected.
6. Upon oral administration of the product (SDX/d-MPH), early exposure to d-MPH is dependent on the immediate release of the d-MPH component of the product, whereas the delayed exposure to d-MPH is dependent on the intestinal conversion of SDX to d-MPH in the lower intestines. The absolute oral bioavailability of SDX was calculated to be lower than 3%.

19. Physical dependence may develop, and withdrawal symptoms may occur after abrupt cessation following prolonged high dosage administration of CNS stimulants; however, these AEs were not observed after abrupt cessation of SDX/d-MPH treatment in clinical studies.
20. Considering the conclusion that SDX warrants control in schedule IV, should NDA 212994 be approved, the approval of NDA 212994 would be pursuant to section 505(x) of the Food, Drug & Cosmetic Act, such that the approval would only be effective following the publication in the Federal Register by DEA of its Interim Final Rule (IFR) to place SDX in schedule IV. We expect this scheduling action would occur within 90 days of FDA approval of NDA.¹

3. Recommendations

The Applicant recommends the SDX component be listed as schedule IV under the CSA and that the overall SDX/d-MPH drug product be controlled as a C-II because the product contains the schedule II substance d-MPH. We agree with the Applicant's recommendations and have the following recommendations for DP:

- Based on the oral human abuse potential (HAP) study, which showed that serdexmethylphenidate (SDX) has lower abuse potential than Focalin XR (schedule II), similar abuse potential to phentermine (schedule IV), and greater abuse potential than placebo, we recommend that SDX be placed in schedule IV of the Controlled Substances Act (CSA). A scheduling recommendation for SDX has been prepared for DEA, which we expect will transmit from the Office of the Assistant Secretary for Health to the DEA prior to DP's action on NDA 212994.
- Since the drug product SDX/d-MPH contains d-MPH, a schedule II substance, we recommend that the overall SDX/d-MPH product be controlled as schedule II.
- Labeling negotiations are ongoing with the Applicant at the time of this writing, however, we do not recommend including human abuse potential data for SDX alone in Section 9 of the labeling. Although these data are relevant to the scheduling decision for the SDX substance, they are not relevant to inform prescribers on the abuse potential and risks of the overall product since it contains d-MPH.

¹ This 90-day period is required by the provisions of the 2015 legislation, the Improving Regulatory Transparency for New Medical Therapies Act [21 U.S.C 355(x) and 811(j)].

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Drug Substance. Serdexmethylphenidate chloride (SDX Cl) **Note:** This review will be referring to SDX CL when describing specific properties of the drug substance.

This section only discusses the chemical properties of SDX Cl as they relate to its abuse potential.

SDX Cl is one of the active pharmaceutical ingredients in AZSTARYS, and it is a prodrug of d-MPH.

SDX chemically consists of a single molecule of d-MPH, which is covalently attached via a carbamate bond to a methylene oxide linker, which is connected to the nitrogen of a pyridine ring of a nicotinoyl-L-serine group. The chemical bond between the methylene oxide linker and the pyridine nitrogen is also a covalent bond and, in this way, forms a pyridinium quaternary salt. As a quaternary salt, it can exist as an ion pair where the pyridinium portion carries the positive charge that requires a counter ion (e.g., chloride). SDX's quaternary ammonium structure may be expected to result in compounds with low lipophilicity, low blood brain barrier penetration and low gastrointestinal absorption (Holzer 2009).

The carbamate bond confers chemical stability to the molecule in acidic and basic media, and this is one of the reasons that the carbamate function is present in many prodrugs (e.g., gabapentin enacarbil), as the rate of hydrolysis determines their pharmacological activity (Ghosh and Brindisi 2015).

SDX has three chiral centers, and as such eight optical isomers of the molecule can exist. However, SDX is an enantiopure compound of chemical structure and conformation as shown in **Figure 1**.

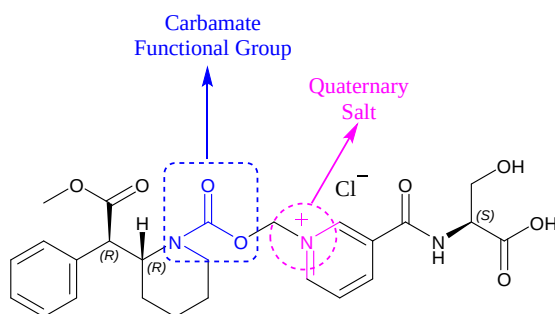


Figure 1- Chemical structure of SDX Cl. Relevant chemical functionality (e.g., carbamate and quaternary salt) highlighted in blue and pink.

SDX Cl is chemically known as the 3-[[[(1S)-1-carboxy-2-hydroxyethyl]amino]carbonyl]-1-[[[(2R)-2-[(1 R)-2-methoxy-2-oxo-1-phenylethyl]-1-piperidinyl]carbonyl]oxy]methyl]-pyridinium, chloride, and identified by CAS Register Number: 1996626-30-2. It has a molecular formula of $C_{25}H_{30}N_3O_8.Cl$ and a molecular weight of 537.97 g/mol. The inner salt has a molecular formula of $C_{25}H_{29}N_3O_8$ and a molecular weight of 500.5 g/mol. Considering that each mol of d-MPH HCl weighs 269.77 grams, 28 mg of SDX Cl are equivalent to 14 mg of d-MPH HCl, 42 mg of SDX Cl are equivalent to 21 mg of d-MPH HCl and 56 mg of SDX Cl are equivalent to 28 d-MPH HCl.

As described by the Applicant in Module 3.2.S.1.3, General Properties, SDX Cl is a white to off-white (b) (4). SDX Cl was found to be freely soluble in water (b) (4)

SDX Cl Drug substance manufacturing process

1.2 Drug Product

The drug product consists of serdexmethylphenidate chloride (SDX Cl) and dexmethylphenidate hydrochloride (d-MPH HCl) formulated as immediate-release capsules that contain fixed molar dose ratios of 70% SDX Cl to 30 % d-MPH HCl. The drug product, referred to in this review as SDX/d-MPH, will be available in three strengths containing 28 mg SDX Cl/6 mg d-MPH HCl, 42 mg SDX Cl/ (b) (4) mg d-MPH HCl, and 56 mg SDX Cl/12 mg d-MPH HCl. The equivalent dose of d-MPH HCl per the amount of SDX Cl present in the product is (b) (4). As shown in **Table 1**, the total dose of d-MPH HCl expressed in molar equivalents is 20 mg (for the 28 mg/ 6 mg SDX/d-MPH strength), 30 mg (for the 42 mg/9 mg SDX/d-MPH strength), and 40 mg (for the 56 mg/ 12 mg SDX/d-MPH strength). See NDA 212994, Module 3.2.P, Drug Product Description and Composition.

Table 1. SDX/MPH Capsules dosage strengths and amount of d-MPH and SDX in each strength (Adapted from NDA 212994, Module 3.2.P, Drug Product Description and Composition).

SDX Cl/d-MPH HCl Dosage strengths (mg)	Molar equivalents of d-MPH HCl (mg)	Total molar equivalents d-MPH HCl (mg)	Molar dose ratio SDX Cl: d-MPH HCl
28/6	(b) (4)	20	70:30
42/9		30	70:30
56/12		40	70:30

The d-MPH immediate-release component in the drug product provides a fast onset of exposure to d-MPH, while the SDX component provides a delayed release of d-MPH, based on its delayed metabolism and absorption (See the Pharmacokinetic section for further information).

SDX is a new molecular entity and there are no approved products containing this active pharmaceutical ingredient. If approved, SDX/d-MPH, will be the first product on the market containing SDX.

d-MPH HCl is available as immediate-release tablets (Focalin and generics) in strengths ranging from 2.5 mg to 10 mg, and as extended-release tablets (Focalin XR and generics) in strengths ranging from 5 mg to 40 mg. Focalin XR capsules contain half the dose as immediate-release beads and half as delayed-release beads.

Product composition and manufacturing



Table 2 describes the product composition and the function of each of the excipients. As seen by the composition of the product, the proposed formulation does not include any excipients that will impart abuse-deterrent properties.

Table 2. Composition of SDX/d-MPH Capsules (Adapted from NDA 212994, Module 3.2.P, Drug Product Description and Composition) **Note:** The term SDX/d-MPH is used in this review as an abbreviation of SDX Cl/d-MPH Cl.

Component	Function	w/w%	Strength (SDX/d-MPH)		
			28 mg/6 mg	42 mg/9 mg	56 mg/12 mg
			Quantity (mg/capsule)		
(b) (4)					
Serdexmethylphenidate Chloride	API	(b) (4)	28.00	42.00	56.00
Dexmethylphenidate Hydrochloride	API		6.00	9.00	12.00
Microcrystalline cellulose, USP/NF	(b) (4)				
Crospovidone, USP/NF					
Magnesium stearate, USP/NF					
(b) (4)					
Talc, USP/NF					
Colloidal silicon dioxide, USP/NF					
Magnesium stearate, USP/NF					
Total (b) (4) per Capsule					

1.3 In vitro Stability Studies

SDX serves as a prodrug of dexmethylphenidate. This section describes the studies conducted by the Applicant to assess the amounts of d-MPH that could be obtained upon manipulation of SDX/d-MPH capsules and upon chemical manipulation of SDX drug substance under various experimental conditions. The Applicant described these studies and included corresponding study reports under NDA 212994, Module 3.2.P.2, Drug Product, Pharmaceutical Development.

The in vitro studies were conducted with SDX Cl drug substance and with the highest dosage strength (56/12 mg) of the product (SDX/d-MPH). The Applicant reports that the main objectives of these studies were to assess:

- 1) The potential to hydrolyze SDX to d-MPH to generate d-MPH in a higher amount than the amount present in the product capsule. For example, to obtain more than the 12 mg of d-MPH HCl from a 56 mg /12 mg SDX Cl -d-MPH Cl capsule.
- 2) The stability of SDX and d-MPH under various experimental conditions
- 3) The amount of d-MPH released from SDX Cl (single entity) or from SDX/d-MPH product relative to the amount of d-MPH released from the commercial Focalin XR (d-MPH HCl extended-release capsules)

In all studies, the Applicant measured SDX, d-MPH and pharmacologically inactive degradation products that could be formed under the experimental conditions. These degradation products are

Table 3 Summary of tampering studies. This table is a copy of Table 16 included by the Applicant in Module 3.2.P.2, Drug Product, Pharmaceutical Development.

Study	Test Article	Description	Objective
	Reference		
Solubility Profiles	SDX Cl	Determination of drug substance solubilities at pH 1-13 and salinity 0-1.2%	- To assess the solubility of SDX Cl and d-MPH HCl - To inform the design of the Small Volume Extraction study of SDX/d-MPH
	d-MPH HCl		
Large Volume Extractions	SDX/d-MPH	Large Volume Extraction of drug product with commonly available solvents	- To assess recovery of SDX and d-MPH from SDX/d-MPH in various solvents for oral consumption or further manipulation - To compare d-MPH yield between SDX/d-MPH and Focalin XR
	Focalin XR (crushed)		
Small Volume Extractions	SDX/d-MPH	Small Volume Extraction of drug product with tap water and water adjusted to pH 4, 6, and 8	- To assess the recovery of d-MPH in aqueous solution suitable for IV injection - To compare d-MPH yield between SDX/d-MPH and Focalin XR
	Focalin XR (crushed)		
Hydrolysis of drug substances	SDX Cl	Drug substances subjected directly to hydrolytic conditions (acids and bases)	- To assess the potential of in vitro SDX conversion to d-MPH - To assess the stability of d-MPH under hydrolytic conditions
	d-MPH HCl		
Hydrolysis of drug product	SDX/d-MPH	Drug product subjected to hydrolytic conditions (acids and bases) directly and following large volume extractions	- To assess the potential of in vitro SDX conversion to d-MPH in drug product - To assess the stability of d-MPH under hydrolytic conditions in drug product - To compare d-MPH recoveries between direct hydrolysis and hydrolysis after extraction
Melting point determination of drug substances	SDX Cl	Melting point determination of drug substances by DSC followed by analysis of melted residues by HPLC	- To determine the appropriate temperature range for heating studies with SDX/d-MPH - To assess potential conversion of SDX to d-MPH when heated
	d-MPH HCl		
Volatility determination of drug substances	SDX Cl	Volatility and decomposition point determination of drug substances and d-MPH freebase by TGA and HS-GC-MS including analysis of evaporated volatiles	- To determine the appropriate temperature range for heating studies with SDX/d-MPH - To determine the presence of d-MPH in gases evaporated from SDX Cl upon heating - To assess the necessity to perform "smokeability" experiments
	d-MPH freebase		
Heating and microwaving of drug product	SDX/d-MPH	Heating of SDX/d-MPH in an oven up to 200°C and in a microwave at 750 Watt	- To assess the stability of SDX Cl and d-MPH HCl in drug product when heated - To assess the potential of in vitro SDX conversion to d-MPH by heating of drug product

- *Summary of in vitro findings (Note:* All the chemistry information related to the way currently marketed extended-release products containing d-MPH (e.g., Focalin XR) can be easily manipulated for purposes of abuse should be redacted for public release).

The following subsections summarize the Applicant findings, as reported in NDA 212994 Module 3.2.P.2, Drug Product, Pharmaceutical Development.

(b) (4)

2. Nonclinical Pharmacology

Receptor binding studies

The Applicant conducted in vitro binding studies to determine the binding profile of SDX Cl to the dopamine (DAT), norepinephrine (NET), and serotonin (SERT) transporters (Study AB54825) and to identify any other potential binding to other receptors with which known drugs of abuse interact (Study AB54826).

Study AB54825 was conducted to determine the SDX Cl IC_{50} values for the DAT, NET and SERT transporters. Six concentrations of SDX Cl, ranging from 0.03 to 10 μ M, and selective reference controls were included in the study. These controls were GBR-12909 for the DAT transporter with a K_i : 1.30 nM; Desipramine for the NET transporter with a K_i : 0.92 nM; and Fluoxetine for the SERT transporter with a K_i : 1.40 nM. A significant response in the study was defined as ≥ 50 % inhibition.

Binding to the DAT human transporter was determined in CHO-S cell expressing human DAT transporters, using [^{125} I]-RTI-55 as the radioligand and in the presence of 10 μ M nomifensine to estimate non-specific binding. In this assay GBR-12909 served as the reference control with a calculated IC_{50} of 1.36 nM, which was within the historical IC_{50} range (Full experimental conditions are described in NDA 212994, Module 4.2.1.1. Primary Pharmacodynamics, Study AB54825 Study Report).

Binding to the NET human transporter was measured in dog kidney MDCK cell expressing human NET transporters, using [^{125} I]-RTI-55 as the radioligand and in the presence of 10 μ M desipramine to estimate non-specific binding. In this assay, desipramine served as reference control, with a calculated IC_{50} of 0.38 nM, which was within the historical IC_{50} range (Full experimental conditions are described in NDA 212994, Module 4.2.1.1. Primary Pharmacodynamics, Study AB54825 Study Report).

Binding to the SERT human transporter was measured in HEK-293 cell expressing the human SERT transporter, using [^{3} H]-Paroxetine as the radioligand and 10 μ M imipramine to estimate non-specific binding. Fluoxetine served as reference control, with a calculated IC_{50} of 25.0 nM, which was within the historical IC_{50} range (Full experimental conditions are described in NDA 212994, Module 4.2.1.1. Primary Pharmacodynamics, Study AB54825 Study Report).

Study AB54825 showed that no significant binding of SDX Cl to any of the monoaminergic transporters was noted, and consequently IC_{50} values were found to be >10 μ M. This binding study indicates that, unlike d-MPH, SDX Cl does not interact with monoamine transporters (DAT and NET).

The Applicant conducted additional binding studies (Study AB54826) to determine the affinity of SDX Cl for other receptor systems, ion gated channels and transporters included in a 68 molecular target screening panel. Also, in this case, the potential binding of SDX Cl, to the various targets was assessed at 10 μ M concentration, and a significant response was defined as ≥ 50 % binding inhibition. Study findings showed that SDX Cl did not bind to any of the pharmacological targets tested.

In conclusion, 1) SDX Cl, does not interact with the DAT and NET transporters, which are the primary site of action of methylphenidate. 2) SDX Cl does not have affinity for receptors systems associated with the site of action of known drugs of abuse. 3) Based on binding studies, it is expected that SDX Cl will be active only upon metabolism to d-MPH.

- *Behavioral studies*

CNS safety Pharmacology (Study 0200RK19.001)

A general behavior study was conducted by Calvert Labs, PA and in compliance with GLP regulations. The study was conducted in male and female Sprague Dawley rats (three groups of ten rats, five/sex), and SDX Cl was administered orally at 12.5, 25, and 50 mg/kg. d-MPH was used as the positive control at 25 mg/kg dose (10 rats, 5/sex). An additional group of ten rats (5/sex) received placebo. The animals were observed for apparent pharmacological or toxicological signs at 15, 30, and 45 minutes, 1, 2, 3,4, and 24 hours following oral administration.

The animals were observed for the occurrence of various signs of CNS effects (seizures/convulsions, body tremors, ataxia, abnormal posture, excretion, awareness reaction, motor activity, piloerection, stereotypy, decreased respiration, vocalization, irritability), startle responses (response to clapping), increased salivation and /or tearing, abdominal tone, and loss of righting reflex. Body temperature (rectal temperature at 60 minutes post dose) and pupil size were also recorded.

The Applicant reports that the oral administration of d-MPH (25 mg/kg) produced increased activity in all female rats and increased pupil size in male and female rats that were observed 45 minutes after dosing and lasted for 3 hours in males and up to 4 hours in females.

No signs of CNS activity were observed in any of the animals receiving vehicle or any of the lower SDX Cl doses (12.5 and 25 mg/kg), up the 24 hours post dose observational period. At the highest SDX Cl dose tested (50 mg/kg), increased activity was observed in all female rats starting at 45 minutes post dose and lasting up to 3 hours and dilated pupils were observed in all female rats from 45 minutes up to 4 hours. Dilated pupils were observed in some male rats but not in all at the high doses tested. (*Note: it is unknown if Sprague Dawley female rats are more sensitive than male rats to the effects of d-MPH, but the data presented by the Applicant seem to suggest this notion*).

Body temperatures were not affected in any of the animals by SDX Cl at 50 mg/kg or d-MPH HCl at 25 mg/kg dose.

The study results demonstrate that the highest dose tested of SDX Cl (50 mg/kg) displays some signs of stimulant activity in rats.

Drug Discrimination and Self-administration

No drug discrimination or self-administration studies were conducted with either SDX Cl or with the product (SDX/d-MPH).

3. Clinical Pharmacology

- Absorption, Distribution, Metabolism and Excretion of SDX Cl

This section summarizes some of the Applicant's key clinical pharmacology findings, as described in Module 2.5 Clinical Overview, NDA 212994.

Absorption

Considering that the activity of SDX Cl resides in its conversion to d-MPH, the Applicant conducted several studies to evaluate the sites of absorption and metabolism of SDX Cl. Upon oral administration of the product (SDX/d-MPH), early exposure to d-MPH is dependent on the immediate release of the d-MPH component of the product, whereas the delayed exposure to d-MPH is dependent on the conversion of SDX Cl to d-MPH in the lower intestines.

The Applicant states that, upon oral administration, a very small fraction of the drug is absorbed in the intestinal tract, where it remains intact until its metabolized to d-MPH in the lower intestine. The Applicant states that, based on PK findings from a clinical study of IV administration of SDX Cl (KP415.A03) and several oral studies, the absolute oral bioavailability of the drug is lower than 3 % (range: 1 % to 4 %) and that the small fraction of SDX that is absorbed remains largely intact in blood until excreted unchanged in the urine.

For purposes of the CSS analysis and as discussed in the chemistry section, due to the charged nature of the molecule (quaternary salt), SDX Cl has poor permeability across cellular membranes resulting in poor systemic absorption and poor tissue penetration. In CSS's experience, SDX distinguishes itself from other prodrugs that CSS has reviewed in that SDX is metabolized and absorbed in the lower intestines. This is unlike other prodrugs that are absorbed in the small intestine and are metabolized in the liver or hydrolyzed in blood. Tramadol is an example of the former because it is primarily converted to its active M1 metabolite in the liver, and lisdexamphetamine is an example of the latter because is hydrolyzed to dexamphetamine in the red blood cells but not in the intestine or liver (Pennick 2010, Janssen 2019).

Distribution

The Applicant states that, based on data from Study CYP1555-R2, SDX Cl and d-MPH exhibited minimal binding to human plasma proteins in vitro (56 % for SDX Cl vs 47.3 % for d-MPH). In addition, the Applicant states that the SDX CL has a low mean body weight-normalized volume of distribution (Study415.A03) of 0.353 L/kg, in contrast to that of d-MPH (4.75 L/kg). From the point of view of the assessment of the abuse potential of SDX, the low volume of distribution indicates that when compared to d-MPH, SDX Cl may have a lower abuse potential because SDX Cl is not distributed to the

tissues (e.g., brain) and remains in the blood compartment, in which its conversion to d-MPH is considered minimal.

Metabolism

As stated above, SDX Cl is likely mainly converted to d-MPH in the lower gastrointestinal tract. However, the enzymes involved in the conversion process have not been identified.

The Applicant states that ritalinic acid was the most abundant metabolite identified in urine, feces and plasma upon oral administration of [¹⁴C]-SDX Cl (Study KP415.111). One unique metabolite of SDX Cl was identified in feces, and thus not absorbed, at very low levels. No unique SDX Cl metabolite were detected in plasma.

Based on data from a different study, Study KP415-VSTA-013, the Applicant concluded that SDX Cl is stable in human whole blood, plasma, simulated intestinal fluid, simulated gastric fluid, human liver, human kidney, human intestinal and human lung S9 fractions. It was also noted that, in whole blood, a slow low disappearance of SDX was observed at 90 minutes (73.8% remained), with minimal formation of d-MPH and no formation of ritalinic acid.

Excretion

The extent of excretion of SDX Cl in humans was determined by single administration of a single oral [¹⁴C]-SDX Cl dose to human volunteers, under fasted conditions (Study KP415.111). At 168 hours after oral administration, 62.1 % and 36.8% of radioactivity was recovered in urine and feces, respectively (98.9 % total recovery). The mean cumulative percentages of radioactive dose recovered at 72 hours post dose in urine corresponded to SDX Cl (0.43%), SDX Cl-derived d-MPH (2.74%) and ritalinic acid (45.2%), and other minor metabolites. Ritalinic acid was the most abundant metabolite in plasma, urine and feces following oral dosing with SDX Cl. The Applicant states that 18 % of the SDX Cl dose is excreted as ritalinic acid in feces and postulates that this percentage may represent the amount of SDX-derived ritalinic acid formed in the lower intestine, which may be less permeable to ritalinic acid than to the SDX Cl-derived d-MPH or that maybe excretion takes place faster than absorption.

- Human Pharmacokinetic data

The Sponsor conducted 10 studies to address the pharmacokinetic profile of SDX Cl when administered alone or in combination with d-MPH under several conditions (fed and fasted) and in different populations (healthy volunteers, adult and young patients) and after single- and multiple-dose administration. Within these studies and as part of the human abuse potential assessment, the Applicant determined the pharmacokinetic parameters of single doses of SDX Cl and of d-MPH administered by the oral, intranasal (IN) and intravenous (IV) routes to healthy volunteers with a prior history of recreational use of stimulants. These studies are: Study KP 415.A01 (Oral HAP study), KP415.A02 (IN HAP study and KP415.A03 (IV HAP Study).

This section will summarize the Applicant's findings from the pharmacokinetic component of the three HAP studies mentioned above, as described by the Applicant (NDA 212994, Module 5, Clinical Study Reports, 5.3.5.4, Other Study Reports). See Section 4.1 Clinical Studies Section, Human Abuse Potential Studies for detailed analysis of the pharmacokinetic and pharmacodynamic findings.

PK parameters for SDX Cl and for d-MPH after oral single dose administration of 120 mg and 240 mg SDX Cl in comparison to the Pharmacokinetic profile of d-MPH after single oral administration of 80 mg of Focalin XR (Study KP415.A01)

Table 4 shows the Applicant's calculated pharmacokinetic parameters for SDX Cl (analyte), for d-MPH (analyte) originated from SDX Cl (prodrug), and for d-MPH upon oral administration of single doses of 120 mg and 240 mg of SDX Cl and of 80 mg Focalin XR.

Table 4: Selected PK Parameters for SDX Cl prodrug and d-MPH (Data extracted from Table S3 and Table S4 as presented in the Clinical Study Report, KP415.A01)

Parameter	Statistic	SDX Cl 120 mg (N=45)		SDX Cl 240 mg (N=45)		Focalin 80 mg (N=45)	
		SDX analyte	d-MPH analyte	SDX analyte	d-MPH analyte	d- MPH IR beads (40 mg)	d-MPH ER beads (40 mg)
C _{max} (ng/mL)	N	45	45	45	45	45	44
	Mean	53.2	7.2	122.5	13.6	38.7	42.7
	SD	32.48	2.35	65.19	6.14	10.51	12.13
	%CV	61.0	32.7	53.2	45.1	27.2	28.4
	Geometric Mean	46.9	6.8	108.4	12.5	37.2	41
T _{max} (h)	N	45	45	45	45	45	44
	Median	2.0	9.0	3.0	11.0	1.5	6.0
	Min, Max	0.5, 8.1	6, 36	0.5, 8.2	7, 36	1, 7	2, 14
AUC _{inf} (h*ng/mL)	N	45	30	45	28	45	
	Mean	375	183	837	368	390	
	SD	161.7	67.3	315.8	138.9	130.0	
	%CV	43.1	36.8	37.7	37.7	33.3	
	Geometric Mean	347	172	784	347	371	
T _{1/2} (h)	N	45	30	45	28	45	
	Median	6.42	10.0	6.27	10.8	3.7	
	Min, Max	3.33,9 .62	5.04,18.93	3.30-9.27	3.94, 18.29	2.87, 6.64	

As seen in **Table 4**, there is some absorption of SDX Cl upon oral administration, with median maximum plasma levels reached at 2 and 3 hours (T_{max}), depending on the dose taken. The SDX Cl prodrug geometric peak exposure (C_{max}) was 2.3-fold higher for the 240 mg dose than for 120 mg dose. The median T_{1/2} for SDX Cl was similar at both doses and around 6 hours. The geometric mean C_{max} exposure for the d-MPH-derived SDX CL for the 120 mg and 240 mg dose was lower than the geometric mean C_{max} exposure of the comparator.

As shown in **Table 4**, upon oral administration of 120 mg and 240 mg of SDX Cl, the concentration of d-MPH originated from SDX Cl increases slowly, with a T_{max} of 9 and 11 hours, respectively. Following single-dose administration of Focalin XR 80 mg, the concentration of d-MPH increases rapidly with two observed T_{max} values that correspond to the immediate release of d-MPH from the IR component of the formulation (1.5 hours) and a second T_{max} of 6.0 hours post dose that corresponds with the release of d-MPH from the delayed-release component of the formulation. The corresponding C_{max} values (C_{max} IR component: 38.7 ng/mL and C_{max} delayed-release component: 42.7 ng/mL) were higher than the C_{max} observed for d-MPH generated from both doses of SDX Cl (7.2 and 13.6 ng/mL for the 120 and 240 mg SDX Cl doses).

Median half-life values for d-MPH after oral 120 mg and 240 mg SDX Cl doses were much longer than the mean half-life for d-MPH after oral administration of 80 mg Focalin XR (10.0 hours for 120 mg SDX, 10.8 hours for 240 mg SDX, and 3.7 hours for 80 mg Focalin XR).

PK parameters for SDX Cl and d-MPH after IN single-dose administration of 80 mg SDX Cl (API) and of 40 mg d-MPH API (Study KP415.02)

The Applicant calculated pharmacokinetic parameters for SDX Cl, d-MPH of SDX Cl origin, and d-MPH after single IN administration of 80 mg SDX Cl API and 40 mg d-MPH API.

As seen in **Table 5**, C_{max}, AUC 0-3 hours and AUC 0-4 hours² for d-MPH was higher following insufflation of d-MPH API compared to insufflation of SDX Cl. Mean C_{max} for d-MPH was approximately 7-fold higher than for SDX Cl (50.9±14.4 ng/mL vs 7.26±3.61 ng/mL). These data suggest that there may be very limited conversion of SDX Cl to d-MPH in the intranasal mucosa.

Although median T_{max} values were shorter for SDX Cl-derived d-MPH (median T_{max} 0.55 h) relative to the T_{max} of d-MPH after IN administration of d-MPH API (median T_{max} 2.03 h), the concentrations of SDX Cl-derived d-MPH were much lower than that of the d-MPH for d-MPH API. Half-life values were shorter for d-MPH than for SDX Cl- derived d-MPH (T_{1/2} 4.32 h vs 9.39 h).

For SDX Cl, there was a rapid increase in mean SDX Cl plasma concentration following IN administration of the API, reaching mean C_{max} values of 3005 ng/mL at a median T_{max} of 0.292 hours.

² In the evaluation of generic opioid abuse-deterrent formulations, the clinical pharmacology team in the Office of Generic Drugs concluded that partial area under the curve analyses at 3 hours and 4 hours were the pharmacokinetic parameters that best correlated with the Drug Liking pharmacodynamic effects observed in intranasal human abuse potential studies conducted with an innovator opioid product [Zhao, L. (2019). "Quantitative Analysis of Opioid ADF PK/PD- Presentation at the 2019 American Society for Clinical Pharmacology and Therapeutics." Access at <https://www.ascpt.org/Meetings/Past-Future-Annual-Meetings/ASCPT-2019/Friday-March-15-Presentations>.] Based on these findings, the Office of Generic Drugs issued several product-specific guidances that recommended the calculation of early partial areas under the curves as supportive data in the comparative pharmacokinetic studies for abuse-deterrent formulations (e.g., Oxycodone HCl ER tablet (Oxycontin; NDA 022272)), Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Oxycodone%20hydrochloride%20oral%20ER%20tablet%20NDA%20022272RV07-18.pdf)

Table 5: Descriptive statistics of pharmacokinetic parameters for SDX Cl, SDX Cl-derived d-MPH and d-MPH after single IV administration of 80 mg SDX Cl API and of 40 mg d-MPH API (Values extrapolated from the Applicant's Table 31 and Table 34 in Study Report KP415.A02)

Parameter	Statistic	SDX Cl API 80 mg (N=46)		d-MPH API 40 mg (N=46)
		SDX analyte	d-MPH analyte	d-MPH analyte
C _{max} (ng/mL)	Mean (SD)	3005 (1281)	7.26 (3.61)	50.9 (14.4)
	Median	2820	6.50	47.1
	Range	746-6670	1.52-16.6	25.1-87.3
	Geometric Mean	2739	6.43	49
T _{max} (h)	Median	0.292	0.550	2.03
	Min, Max	0.267-0.800	0.267-24	0.550-3.03
AUC _{0-0.5h} (h*ng/mL)	Mean (SD)	NR	2.15 (1.27)	7.733 (4.21)
	Median	NR	1.67	7.18
	Range	NR	0.461-5.56	1.64-20.4
	Geometric Mean	NR	1.82	6.71
AUC _{0-3h} (h*ng/mL)	Mean (SD)	NR	11.6 (5.81)	116 (36.5)
	Median	NR	10.3	105
	Range	NR	2.63-26.5	56.0-210
	Geometric Mean	NR	10.1	110
AUC _{0-inf} (h*ng/mL)	Mean (SD)	7125 (2740)	84.5 (37.2)	339 (96.0)
	Median	7103	78.5	313
	Range	220-12900	38.6-2.64	166-565
	Geometric Mean	6548	79.0	327
T _{1/2} (h)	Mean (SD)	3.70 (1.39)	9.39 (2.98)	4.32 (1.88)
	Median	3.30	8.79	3.68
	Min, Max	2.19-8.44	4.13-16.7	2.62-14.1

PK parameters for SDX Cl and for d-MPH after IV single-dose administration of 30 mg SDX Cl (API) and 15 mg d-MPH API in 1 minute. (Study KP415.03)

Study KP415.A03 evaluated the abuse potential of intravenous SDX Cl 30 mg relative to that of intravenous d-MPH 15 mg administered in 1-minute.

The Applicant calculated pharmacokinetic parameters for SDX Cl, SDX Cl-derived d-MPH and d-MPH upon IV administration of the APIs. As expected, plasma concentrations of both drugs rose rapidly upon injection. Upon IV administration (1 minute) of SDX Cl 30 mg, mean peak SDX concentrations

reached 3,550 ng/mL at 5 minutes post dose, with minimal conversion to d-MPH. Upon IV administration of d-MPH, mean peak plasma concentrations reached 60.1 ng/mL (SD 15.2, N=30) at 15 minutes post dose. Plasma concentrations for both drugs declined in a monophasic manner after reaching C_{max}.

The Applicant reports that after an investigation of the bioanalytical data, the Applicant identified that a small fraction of SDX Cl was converted into d-MPH during the handling of the plasma samples. The Applicant did not state if the ex-vivo conversion took place either prior to the analytical analysis, during the analysis or at the same time prior and during the analysis. Although these findings will indicate that the reported SDX Cl-derived d-MPH plasma concentration may have been overestimated, the overall study findings confirm that there was a very limited conversion of SDX Cl to d-MPH when administered intravenously, as evidenced by calculated exposure. The AUC to infinity (AUC_{0-inf}) for SDX Cl-derived d-MPH was 12.7 % of the exposure observed upon IV administration of d-MPH.

4. Clinical Studies

4.1 Human Abuse Potential Studies

A Phase 1, randomized, double-blind, placebo-controlled, single-dose, 5-way crossover study to determine the abuse potential and pharmacokinetics of 120 and 240 mg SDX in capsules compared with 80 mg of Focalin XR and 60 mg Phentermine after oral administration in healthy, nondependent, recreational stimulant users. KP415.A01.

SDX is a prodrug of d-methylphenidate (d-MPH). The Applicant is developing an oral capsule product containing SDX alone under the codename of KP484.

The main purpose of this study was to assess the human abuse potential (HAP) and PK of SDX after oral administration of capsules at therapeutic and supratherapeutic doses relative to Focalin XR (dexmethylphenidate HCl) extended-release, phentermine, and placebo when administered orally in healthy, nondependent, individuals who recreationally use stimulants.

Objectives

Primary

- To assess the abuse potential of SDX in capsules at maximum therapeutic and supratherapeutic doses relative to Focalin XR and phentermine and placebo.
- To assess the PK of intact SDX and SDX-derived d-methylphenidate (d-MPH), after maximum therapeutic and supratherapeutic single oral doses of SDX in capsules

Secondary

- To assess the safety and tolerability of maximum therapeutic and supratherapeutic single oral doses of SDX in capsules in healthy, nondependent, individuals who recreationally use stimulants

The study was a Phase 1, randomized, double-blind, single-dose, active-and placebo-controlled, 5-treatment, 5-period, 10-sequence, crossover study evaluating the abuse potential and PK of 120 mg and

240 mg SDX in capsules, extended-release d-MPH (Focalin XR 80 mg), 60 mg phentermine, and placebo, after oral administration in healthy, nondependent, individuals who recreationally use stimulants.

The study consisted of a Screening Period, an in-clinic Drug Discrimination Phase, an in-clinic Treatment Phase, and a Follow-up Visit:

Inclusion Criteria

A subject was eligible for inclusion in the study if all the following criteria were met:

- Subjects must have been individuals who recreationally use stimulants, who were not currently physically dependent on CNS stimulants (in the opinion of the Investigator) but had ≥ 10 lifetime experiences with any stimulant (e.g., amphetamines, cocaine, and/or MPH)
- Subjects must have used any stimulant for non-therapeutic purposes at least 5 times within the last 6 months prior to the Screening Visit
- Subjects were healthy male or female subjects 18 to 50 years of age (inclusive)

Exclusion Criteria

A subject who met any of the following exclusion criteria was not enrolled into the study:

- Subject was currently seeking treatment for substance-related disorders (excluding nicotine and caffeine)
- Subject had a history or presence of drug or alcohol dependence

Drug Discrimination (Qualification) Phase

Subjects who successfully completed the Screening Period returned to the clinic to complete the Drug Discrimination Phase. The Drug Discrimination Test was performed to ensure that subjects could differentiate between the effects of a single dose of Focalin XR and placebo administered orally. Subjects who successfully completed the Drug Discrimination Phase and who qualified for the Treatment Phase returned to the research clinic as inpatients to enter the Treatment Phase.

The Drug Discrimination Phase was a double-blind, oral, single-dose, 2-treatment, 2-period, 2-sequence, randomized, crossover design. Subjects received single oral doses of the following treatments separated by a 48-hour washout period:

- Treatment X: 80 mg Focalin XR (2 x 40 mg capsules, over-encapsulated)
- Treatment Y: Placebo (2 matching placebo capsules)

Drug Liking scores in the Drug Discrimination Phase were used to determine whether subjects could discriminate between Focalin XR and placebo and, in combination with safety and tolerability data, whether subjects would be eligible for the Treatment Phase according to the following criteria:

- Peak score (Emax) of at least 65 points for Focalin XR on the Drug Liking Visual Analog Scale (VAS) and at least 15 points higher in response to Focalin XR versus placebo response
- Placebo response is in the range of 40 to 60 points (inclusive) on the Drug Liking VAS (so that subjects neither endorsed liking nor disliking of placebo)

The washout period between the last dose of study drug in the Drug Discrimination Phase and the first dose of study drug in the Treatment Phase, was at least 72 hours and no more than 35 days.

Treatment Phase

After subjects completed and passed the Drug Discrimination Phase, they were eligible to enter into the Treatment Phase. The Treatment Phase was a double-blind, oral, single-dose, 5-treatment, 5-period, 10-sequence, randomized, crossover design separated by a minimum 96-hour washout period, with the following treatments:

- Treatment A: 120 mg SDX (test product)
- Treatment B: 240 mg SDX (test product)
- Treatment C: 80 mg Focalin XR (primary positive control)
- Treatment D: 60 mg phentermine (secondary positive control)
- Treatment E: Placebo (matching capsules)

This study included administration of 120 and 240 mg of SDX representing 1- and 2-times the highest estimated therapeutic dose of KP484, an SDX-alone prodrug product (capsule) currently being developed for the treatment of ADHD in adults. The maximum single dose of SDX in SDX/d-MPH capsules is 56 mg. Similarly, the active control ER d-MPH (Focalin XR, primary positive control, schedule II in the CSA) was administered at twice the maximum daily oral dose of 80 mg. The second active control, phentermine (secondary positive control), a CNS stimulant (schedule IV in the CSA), was also administered at twice the maximum daily oral dose of 60 mg.

Plasma samples for PK from all subjects were planned to be analyzed after Treatments A, B, and C to assess PK of intact SDX, SDX-derived d-MPH, l-MPH (if applicable) and ritalinic acid (a known metabolite of MPH).

Study drugs were administered in the morning after a minimum 8-hour fast. In both the Drug Discrimination and Treatment Phases, all subjects were required to fast for at least 8 hours prior to dosing with study drug until approximately 4 hours after dosing with study drug. Subjects were not allowed to smoke or use tobacco products from 1 hour prior to dosing to 4 hours post-dosing with the study drug.

Visual Analog Scales: Pharmacodynamic assessments were made using unipolar or bipolar visual analog scales (VAS). Each VAS was scored from 0 to 100. Unipolar VAS were presented with anchors such as “Not at all” (score=0) to “Extremely” (score=100), where the neutral point equals 0 (High VAS). Bipolar VAS were administered, in which 50 mm represents the neutral point (for Drug Liking, Overall Drug Liking, and Take Drug Again). The neutral point was labeled with an anchor, such as “neither like nor dislike.”

The Addiction Research Center Inventory (ARCI) was also administered. The ARCI assessments consist of a true-false questionnaire with empirically-derived scales sensitive to certain drugs or groups of drugs. Two ARCI scales were used in the current study: ARCI-Amphetamine (ARCI-A) and ARCI-Benzedrine Group (ARCI-BG). The ARCI-A questionnaire assesses stimulant effects; the ARCI-BG questionnaire assesses energy and intellectual efficiency (11 questions for ARCI-A; 13 questions for

ARCI-BG). The maximum score is 11 for ARCI-A and 13 for ARCI-BG. A higher score indicates higher subjective effects.

Pharmacodynamic endpoints

Primary endpoint:

- The maximum (peak) effect (Emax) for Drug Liking (“at this moment”), assessed on a bipolar (0–100 point) VAS

Secondary Endpoints:

- Emax Overall Drug Liking (ODL) VAS (“Overall, my liking for this drug is”)
- Emax Take Drug Again (TDA) VAS (“I would take this drug again”)
- Take Drug Again and Overall Drug Liking VAS assessments were performed at 12 and 24 hours post-dose

Exploratory endpoints:

- Emax for Feeling High (“At this moment, I feel high”), Good Effects, Bad Effects, Any Effects, and Drowsiness/Alertness VAS scores and for ARCI-A and ARCI-BG, and TEmax and AUEs for Drug Liking

The comparisons between Focalin XR 80 mg and each dose of SDX were the primary and secondary analyses. The comparisons between 60 mg phentermine and each dose of SDX were prespecified as exploratory comparisons. Validation of the study required that the positive control (Focalin XR) be significantly higher on the Drug Liking Emax compared to placebo by a margin of 15 points. The Applicant prespecified margins to evaluate the differences between treatment arms.

Results: A total of 230 subjects were screened, of whom 112 passed screening and were enrolled in the Qualification Phase of the study. Sixty-two of the subjects in the Qualification Phase were discontinued prior to the Treatment Phase; 34 of these subjects were discontinued due to qualification failure (i.e., they did not pass the Drug Discrimination Test). Of the 50 subjects who entered the Treatment Phase, 45 subjects completed the study, and 5 subjects (10%) discontinued. Reasons for discontinuation included withdrawal by subject (2 subjects), AE (1 subject), and non-compliance (2 subjects). The Safety Set, which includes all subjects who received at least 1 study drug in the Treatment Phase, comprised 50 subjects. The Completers Set, which includes subjects who received all study treatments and completed all treatment periods of the Treatment Phase comprised 45 subjects. The Safety Set included 37 male and 13 female subjects between 20 and 49 years of age.

Pharmacodynamic Results:

Results presented in **Table 6** (derived from Applicant Table 11) below are the Qualification Phase data for subjects who were randomized to the Treatment Phase and received all study treatments (i.e., Treatment Phase Completer Population).

Table 6 (derived from Applicant Table 11) Descriptive Statistics for Drug Liking VAS Assessment Parameters – Qualification Phase

Statistic	80 mg Focalin XR	Placebo
Mean (SD)	90.1 (10.19)	50.4 (1.66)

SD = standard deviation; VAS = visual analog scale; XR = extended-release

The following, unless otherwise noted, represents the figures, tables, and analysis of the Division of Biometrics VI (Ling Chen, PhD: DARRTS February 1, 2021). In this report, the Biometrics reviewer used the following notations for treatments in Study KP415.A01:

FOC80: 80 mg Focalin XR

KP120: 120 mg SDX

KP240: 240 mg SDX

P: Placebo

PHE60: 60 mg phentermine

Table 7 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 5 treatments in the study for the primary endpoint Drug Liking Emax.

Table 7: Summary statistics for Drug Liking Emax and TE Max (n=45)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Drug Liking Emax	FOC80	81.5	12.5	50	74	82	90	100
	KP120	62.8	16.4	50	50.5	53	77.5	100
	KP240	63.8	15.7	50	50	59	75.5	100
	P	55.8	11.8	50	50	51	52.5	100
	PHE60	80.2	14.3	50	68.5	84	90.5	100
Drug Liking TEmax (hr)	FOC80	2.6	2.4	0.5	1.5	2	2	14
	KP120	4.3	4.5	0.5	0.5	3	6	24
	KP240	4.2	4.1	0.5	0.5	3	7	16
	P	2.6	4.2	0.5	0.5	1	3	24
	PHE60	2.6	1.7	0.5	1.5	2	3	8

Figure 3 shows the mean time course profiles by treatment for Drug Liking VAS. As shown in the figure, both Focalin XR and phentermine had higher mean drug liking scores and earlier TEmax than either dose of KP415 prodrug (SDX). The profile of 80 mg Focalin XR was below 50 after hour 10, which indicates some subjects might experience bad effects at those time points and this might affect their overall assessment of 80 mg Focalin XR.

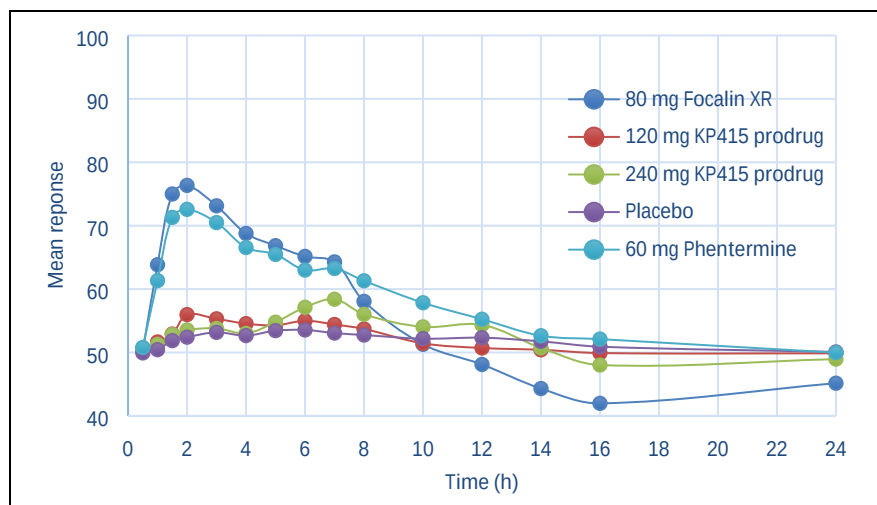


Figure 3: Mean time course profiles by treatment for Drug Liking VAS (n=45) – oral administration

For examining the abuse potential of KP415 prodrug, the Biometrics reviewer studied the following comparisons:

80 mg Focalin XR versus Placebo
 120 mg KP415 prodrug (SDX) versus 80 mg Focalin XR
 240 mg KP415 prodrug (SDX) versus 80 mg Focalin XR
 120 mg KP415 prodrug (SDX) versus P
 240 mg KP415 prodrug (SDX) versus P

In addition, for exploration, the following comparisons are also considered:

60 mg Phentermine versus Placebo
 120 mg KP415 prodrug (SDX) versus 60 mg Phentermine
 240 mg KP415 prodrug (SDX) versus 60 mg Phentermine

Table 8 shows the results from the primary analysis and exploratory analysis on Drug Liking Emax.

Table 8: Results from the primary analysis and exploratory analysis on Drug Liking Emax (n=45)

# of Completers	TRT	FOC80	KP120	KP240	P	PHE60	Comments
45	LSmean (StdErr)	80.4 (2.2)	62.2 (2.2)	63.7 (2.2)	55.4 (2.2)	77.7 (2.2)	
Comparisons	LSmean Diff	StdErr	Test Value	p-value	95% CI		
					LCL	UCL	
FOC80 vs P	25.0	2.6	15	<.0001	20.7	Infty	Primary Analysis
FOC80 vs KP120	18.2	2.6	10	0.0011	13.9	Infty	
KP120 vs P	6.8	2.6	11	0.0567	-Infty	11.2	
FOC80 vs KP240	16.7	2.6	10	0.0058	12.4	Infty	
KP240 vs P	8.3	2.6	11	0.1502	-Infty	12.6	
PHE60 vs P	22.3	2.6	15	0.0032	17.9	Infty	Exploratory Analysis
PHE60 vs KP120	15.5	2.6	10	0.0195	11.1	Infty	
PHE60 vs KP240	14.0	2.6	10	0.0664	9.6	Infty	

Note: The p-value in red indicates the test was not significant.

The results from the Biometrics reviewer's primary analysis on Drug Liking Emax showed that:

80 mg Focalin XR produced a mean response that was significantly larger than placebo with a test margin of 15 points ($p < 0.0001$), which was the basis for validating the analyses on the Completers Set. Both the 120 and 240 mg doses of KP415 prodrug (SDX) produced mean responses that were significantly smaller than 80 mg Focalin XR with a test margin of 10 points ($p \leq 0.0058$) indicating that KP415 prodrug (SDX) has lower abuse potential than Focalin XR. Both 120 and 240 mg doses of KP415 prodrug (SDX) failed to demonstrate no significant difference in mean compared to placebo with a test margin of 11 points ($p \geq 0.0567$).

The results from the Biometrics reviewer's exploratory comparisons on Drug Liking Emax showed that:

60 mg Phentermine produced a mean response significantly larger than placebo with a test margin of 15 points ($p = 0.0032$) indicating that the subjects were able to distinguish 60 mg Phentermine from placebo though Phentermine was not tested during the Qualification Phase. 120 mg KP415 prodrug (SDX) produced a mean response significantly smaller than 60 mg phentermine with a test margin of 10 points ($p = 0.0195$) indicating that the lower dose of KP415 prodrug has less abuse potential than Phentermine 60 mg. 240 mg KP415 prodrug (SDX) did not produce a mean response significantly smaller than 60 mg dose of phentermine with a test margin of 10 points ($p = 0.0664$).

Table 9 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the five treatments in the study for the two secondary endpoints.

Table 9: Summary statistics for Take Drug Again and Overall Drug Liking Emax (n=45)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Take Drug Liking Emax	FOC80	64.6	27.9	0	50	69	87.5	100
	KP120	57.4	18.3	0	50	50	64.5	100
	KP240	56.9	21.9	0	50	50	68	100
	P	55.2	13.3	46	50	50	51	100
	PHE60	72.3	22.3	0	58	75	89.5	100
Overall Drug Liking Emax	FOC80	63.0	26.6	0	46	71	82.5	100
	KP120	58.5	15.4	34	50	50	68.5	100
	KP240	58.0	20.0	11	50	51	68	100
	P	54.8	12.2	45	50	50	51	100
	PHE60	73.4	22.1	0	61.5	77	90	100

Table 10 shows the results from the Secondary analysis and Exploratory Analysis on Overall Drug Liking Emax and Take Drug Again Emax (n=45).

Table 10: Results from the secondary analysis and exploratory analysis on Overall Drug Liking Emax and Take Drug Again Emax (n=45)

Endpoint	# of Completers	TRT	FOC80	KP120	KP240	P	PHE60
	45	Mean (StdErr)	63.0 (4.0)	58.5 (2.3)	58.0 (3.0)	54.8 (1.8)	73.4 (3.3)
	Comparisons	Mean / Med Diff	StdErr/ (Q1, Q3)	Test Value	p-value	95% CI	
Overall Drug Liking Emax						LCL	UCL
						0.2	16.3
						1.0	20.0
						4.0	22.0
						11.5	25.7
						7.0	22.7
Take Drug Again Emax						7.1	23.6
						1.1	17.6
						-2.7	17.1
						-3.8	19.1
						9.9	24.3
						7.5	22.3
Overall Drug Liking Emax						8.3	22.4
						0.0266	17.6
						0.1496	17.1
						0.1846	19.1
						<.0001	24.3
						0.0002	22.3
Take Drug Again Emax						<.0001	22.4
						0.0266	17.6
						0.1496	17.1
						0.1846	19.1
						<.0001	24.3
						0.0002	22.3

Note: The p-value of a failed test is in red

The results from the secondary analysis showed that, for both Overall Drug Liking Emax and Take Drug Again Emax:

80 mg Focalin XR and 60 mg Phentermine produced significantly larger mean responses than placebo. The mean or median difference between 80 mg Focalin XR and each dose of KP415 prodrug (SDX) was not significantly different from zero. The mean difference between 60 mg phentermine and each dose of KP415 prodrug (SDX) was significantly greater than zero, indicating that, for these endpoints, KP415 prodrug (SDX) had similar abuse potential to Focalin XR 80 mg but less abuse potential compared to Phentermine 60 mg.

Tables 11 and 12 summarize the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the five treatments in the study for the exploratory endpoints, Good Effects Emax, Bad Effects Emax, change from pre-dose response of High Emax, and ARCI A and ARCI BG Emax

Table 11: Summary Statistics of selected exploratory endpoints (n=45)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Good Effects Emax	FOC80	75.7	26.3	0	58	85	99	100
	KP120	27.0	32.8	0	0	10	54	100
	KP240	30.8	37.0	0	0	15	64	100
	P	13.0	26.8	0	0	0	7.5	100
	PHE60	66.2	32.5	0	38	75	95.5	100
Bad Effects Emax	FOC80	33.8	34.9	0	0	21	67	100
	KP120	6.0	14.2	0	0	0	1.5	64
	KP240	13.4	25.0	0	0	0	12	89
	P	4.8	15.1	0	0	0	1.5	72
	PHE60	17.9	26.2	0	0	7	25	100
High Emax	FOC80	78.8	25.6	0	62	83	100	100
	KP120	25.6	32.8	0	0	7	53.5	100
	KP240	32.1	37.7	0	0	19	62	100
	P	13.0	28.2	0	0	0	7	100
	PHE60	65.3	33.5	0	38	76	97.5	100

Emax of High VAS was calculated based on change from predose response.

Table 12: Summary statistics for Emax scores for ARCI A and BG groups

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
ARCI Amphetamine Group Emax	FOC80	5.1	3.2	-1	3	4	7.5	11
	KP120	2.6	3.0	-1	0	2	4.5	11
	KP240	2.1	2.7	-1	0	1	4	9
	P	0.8	2.0	-1	0	0	1	11
	PHE60	4.8	3.2	-1	2	4	8	11
ARCI Benzedrine Group Emax	FOC80	4.3	3.7	-1	1	4	8	12
	KP120	2.0	2.8	-1	0	1	3	10
	KP240	2.0	2.9	-3	0.5	1	2.5	11
	P	0.6	1.1	-1	0	0	1	6
	PHE60	4.1	3.5	-1	1	4	7	10

The descriptive statistics on the exploratory measures (Good Effects VAS, ARCI A, and ARCI BG) and their Emax scores supported the findings from the primary analysis for these comparisons indicating greater abuse potential of Focalin versus KP 415 prodrug (SDX). The descriptive statistics of these exploratory endpoints supported that both doses of KP 415 prodrug (SDX) had less abuse potential compared to 60 mg phentermine.

Table 13 lists the results from the analysis on High Emax.

Table 13: Results from the analysis on High Emax (n=45)- oral administration

# of Completers	TRT	FOC80	KP120	KP240	P	PHE60	Comments
45	LSmean (StdErr)	75.5 (4.8)	23.1 (4.8)	31.5 (4.8)	12.7 (4.6)	59.1 (4.8)	
Comparisons	LSmean Diff	StdErr	Test Value	p-value	95% / 90% CI		
					LCL	UCL	
FOC80 vs P	62.8	5.9	0	<.0001	51.2	74.4	Primary Analysis
FOC80 vs KP120	52.4	5.9	0	<.0001	40.7	64.1	
KP120 vs P	10.4	6.0	0	0.0827	0.5	20.3	
FOC80 vs KP240	44.0	6.0	0	<.0001	32.3	55.8	
KP240 vs P	18.8	5.9	0	0.0018	9.0	28.5	
PHE60 vs P	46.4	5.9	0	<.0001	34.7	58.1	Exploratory Analysis
PHE60 vs KP120	36.0	5.9	0	<.0001	24.3	47.7	
PHE60 vs KP240	27.7	6.0	0	<.0001	15.9	39.4	

The results from the analysis on High Emax show that:

1. 80 mg Focalin XR and 60 mg Phentermine produced significantly larger mean responses than those by placebo and each dose of KP415 prodrug (SDX).
2. The means produced by both doses of KP415 prodrug (SDX) were significantly larger than that by placebo.

The mean time profiles for bad effects are shown in **Figure 4** and were below 10 for all treatments except 80 mg Focalin XR. The peak mean response for Bad Effects VAS produced by 80 mg Focalin XR was 20.5 and was reached at hour 10. This indicates that Focalin XR produces 'bad' effects 10 hours post administration and is consistent with the findings of Drug Liking scores below 50 (drug disliking) after 10 hours of dosing (see Figure 1). The negative effects produced by Focalin XR after 10 hours of dosing may explain the lack of difference between KP415 prodrug (SDX) and Focalin XR for endpoints collected at 12 and 24 hours post dose (Take Drug Again and Overall Drug Liking).

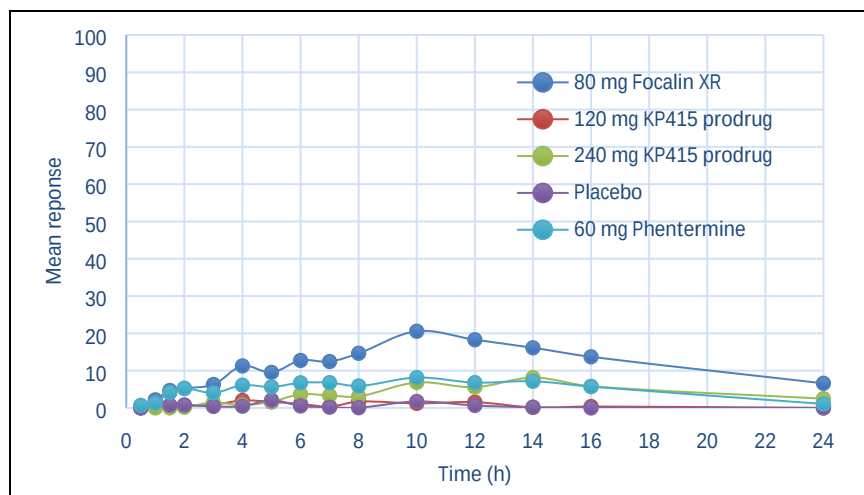


Figure 4: The mean time course profiles by treatment for Bad Effects VAS (n=45) – oral administration

Pharmacokinetic Results: Mean (SD) plasma concentration of d-MPH over time is displayed on a linear scale in **Figure 5** (Applicant Figure 13). Following single-dose oral administration of 120 mg and 240 mg KP415 prodrug (SDX), d-MPH concentration versus time profiles were similar in shape and increased with increasing dose. At both the 120 mg and 240 mg dose levels of KP415 prodrug (SDX), d-MPH concentrations increased slowly over the first 4 hours. From 4 to 8 hours post dose, plasma concentrations increased more rapidly until reaching peak values at approximately 9 and 11 hours post dose for the KP415 prodrug (SDX). Following single-dose oral administration of 80 mg Focalin XR, concentrations of d-MPH increased rapidly, reaching an initial peak value at 1.5 hours followed by a decline until 4 hours post dose, at which point concentrations increased again, reaching a second peak value comparable to the initial one at approximately 6 hours post dose.

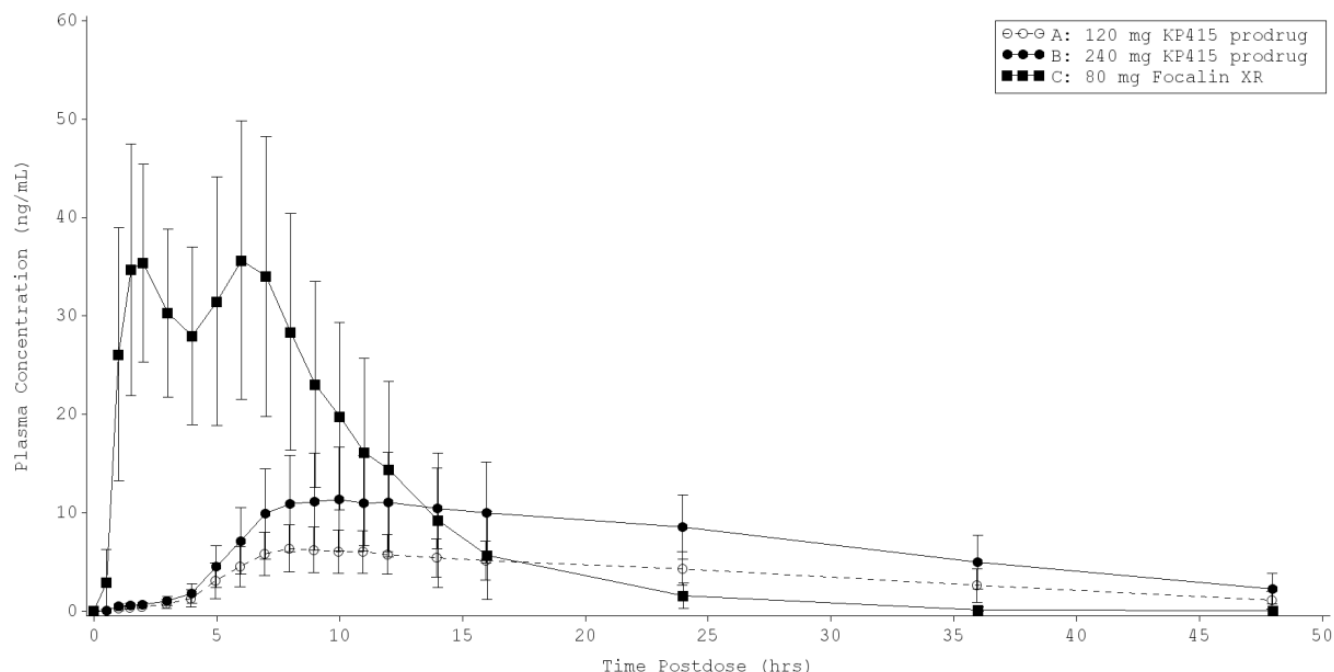


Figure 5 (Applicant Figure 13): Plot of Mean ($\pm$ SD) Plasma Concentrations of D-methylphenidate versus Time on a Linear Scale, Completers Set (n=45)

Abuse-related adverse events: **Table 14** displays the abuse-related adverse events in Study KP 415.A01. This table was compiled from the AE tables submitted by the Applicant. Increased energy was reported to a greater extent with Phentermine and Focalin XR than SDX. Subjects in the SDX treatment arms reported rates of energy increased similar to placebo. Euphoric mood was reported to a greater extent in Focalin XR- and Phentermine-treated subjects than those administered either dose of SDX. However, subjects treated with either dose of SDX had a higher rate of euphoric mood than placebo.

Table 14: Abuse related adverse events KP 415.A01

	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 (%)
Energy increased	0	1 (2.1)	3 (6.7)	4 (8.5)	1 (2.2)
Feeling jittery	0	0	3 (6.7)	1 (2.1)	0
Feeling of relaxation	0	0	1 (2.2)	1 (2.1)	0
Feeling abnormal	0	1 (2.1)	0	1 (2.1)	0
Somnolence	0	1 (2.1)	1 (2.2)	0	0
Psychomotor hyperactivity	0	0	1 (2.2)	0	0

Euphoric mood	3 (6.4)	4 (8.3)	12 (26.6)	14 (29.8)	2 (4.3)
Hypervigilance	3 (6.4)	7 (14.5)	10 (22.2)	8 (17.0)	1 (2.2)
Anxiety	0	2 (4.2)	5 (11.1)	3 (6.4)	0
Restlessness	0	0	5 (11.1)	0	1 (2.2)
Agitation	0	0	0	4 (8.5)	0
Irritability	1 (2.1)	1 (2.1)	1 (2.2)	0	0
Change in sustained attention	0	1 (2.1)	2 (4.4)	0	0
Hypnagogic hallucination	0	0	0	1 (2.1)	0
Mood swings	0	0	1 (2.2)	0	0

Comments on study design: This was a randomized, double-blind, placebo-controlled, crossover study, which is an appropriate design for a HAP study so that each subject may act as their control. The positive controls in this study were appropriate as they belonged to the same class (stimulants) as the test drug. Dosages of the test drug and controls were suprathreshold as recommended for HAP studies and wash out times were appropriate representing approximately five times or more the half-lives of the tested drugs (half-life Focalin 3 hours, KP415 prodrug (SDX) 5 hours, and Phentermine 20 hours).

Summary and Conclusions:

- At both the 120 mg and 240 mg dose levels of SDX, d-MPH concentrations increased slowly over the first 4 hours. From 4 to 8 hours post-dose, plasma concentrations increased more rapidly until reaching peak values at approximately 9 and 11 hours post-dose for the SDX. Following single-dose oral administration of 80 mg Focalin XR, concentrations of d-MPH increased rapidly, reaching an initial peak value at 1.5 hours followed by a decline until 4 hours post-dose, at which point concentrations increased again, reaching a second peak value comparable to the initial one at approximately 6 hours post-dose.
- The primary analysis passed the validation test using the Completers Set, as demonstrated by the significantly larger mean produced by 80 mg Focalin XR compared to placebo with a test margin of 15.
- The primary analysis demonstrated significantly lower mean Drug Liking Emax scores for both doses of SDX compared to 80 mg Focalin XR with a test margin of 10 points.
- However, the study demonstrated that there was a significant difference in maximum liking between each dose of SDX and placebo.
- The results from the analysis on the secondary endpoints, Overall Drug Liking Emax and Take Drug Again Emax, demonstrated significant difference in means between 80 mg Focalin XR and placebo.
- However, the results for Overall Drug Liking and Take Drug Again, which are measured at 12 and 24 hours post dosing, was not consistent with the findings on the primary analysis for the comparisons between each dose of SDX and 80 mg Focalin XR. This was probably related to

the levels of Drug Disliking and Bad effects that were observed for Focalin XR after 10 hours of dosing.

- The results for High VAS supported the findings on the primary analysis.
- The descriptive statistics on the exploratory measures (Good Effects VAS, ARCI A, and ARCI BG) and their Emax scores supported the findings from the primary analysis for these comparisons.
- The comparisons between 60 mg phentermine and each dose of SDX were prespecified as exploratory comparisons. The significantly larger mean produced by 60 mg phentermine than that by placebo with a test margin of 15 points validated the exploratory comparisons. These comparisons showed that both doses of SDX produced means significantly smaller than 60 mg phentermine for the primary and secondary endpoints except the comparison between 60 mg phentermine and 240 mg SDX for Drug Liking Emax. Since higher doses are likely to be used by individuals who recreationally use drugs, the comparison between the highest studied dose of SDX (240 mg) and phentermine should be taken into consideration when assessing abuse potential. Based on this, we conclude that SDX has similar abuse potential as phentermine.
- The comparisons for High VAS showed that both doses of SDX had less abuse potential compared to 60 mg phentermine.
- The descriptive statistics of exploratory endpoints supported that both doses of SDX had less abuse potential compared to 60 mg phentermine.
- The adverse event profile is consistent with SDX having lower abuse potential than phentermine and Focalin.
- Although the key secondary endpoints of Overall Drug Liking and Take Drug Again showed no difference between SDX and Focalin XR (for the possible reasons stated above), the primary endpoint and exploratory endpoints are consistent with SDX having a lower abuse potential than Focalin XR, which is a schedule II drug. The finding of SDX having lower abuse potential than phentermine, a schedule IV drug, on all endpoints further indicates that SDX has lower abuse potential than Focalin.
- In conclusion, Study KP415-A01 demonstrated that with oral administration 120 and 240 mg doses of SDX had less abuse potential compared to 80 mg Focalin XR and similar or less abuse potential compared to 60 mg phentermine. However, the study did not demonstrate that both doses of KP415 prodrug had no abuse potential based on the comparison to placebo.

A Phase 1, Double-Blind, Single-Dose, 3-Treatment, 3-Period, 6-Sequence, Randomized Crossover Study to Compare the Abuse Potential and Pharmacokinetics of SDX API with d-Methylphenidate API Administered Intravenously in Healthy, Nondependent, Recreational Stimulant Users KP415.A03

The main purpose of this study was to assess the human abuse potential (HAP) and pharmacokinetics of SDX active pharmaceutical ingredient (API) compared to d-MPH API after IV administration. The API form of SDX and d-MPH were chosen as the drug products because it is unethical to administer the reconstituted contents of solid dosage forms of the drug products in a clinical trial setting due to dangers associated with IV injection of excipients.

While d-MPH is reported to be abused via the IV route, there is limited knowledge regarding the safety and PD effects of d-MPH when administered via this route. Therefore, Part A, a Dose Selection Phase, was implemented to ensure an optimal dose level was selected for the Treatment Phase of Part B, based on tolerability and HAP PD assessments.

Part A of the study was designed as a within-subject single ascending dose study with pre-specified stopping rules.

Part B was a randomized, double-blind, placebo- and active-controlled, crossover study to evaluate the abuse potential of SDX as compared with d-MPH after IV administration.

All administrations of study drug were performed by IV injection of 4 mL in a peripheral vein. The IV injections were done over a 1-minute interval with the subject in the recumbent position.

Primary Objectives

The primary objective for Part A (Cohort 1) was:

To determine the optimal dose of d-MPH API based on tolerability and HAP pharmacodynamic (PD) assessments after a single IV injection in nondependent, individuals who recreationally use stimulants

The primary objectives for Part B (Cohort 2) were:

- To assess the abuse potential of SDX as compared with d-MPH API after a single IV injection in nondependent, individuals who recreationally use stimulants.
- To assess the PK of SDX, SDX-derived d-MPH, l-MPH (if applicable), and ritalinic acid after a single IV injection of SDX API

Secondary Objective

The secondary objective of the study was (Cohort 2):

- To assess the safety of SDX API after a single IV injection

This was a Phase 1 HAP study of SDX API administered IV in healthy, nondependent individuals who recreationally use stimulants. The study consisted of 2 parts:

- Part A (Cohort 1) was the dose escalation part of the study that determined the optimal IV d-MPH API dose to be used in Part B, based on HAP PD and safety assessments
- Part B (Cohort 2) was the main part of the study that evaluated HAP PD and PK after IV SDX doses as compared with d-MPH API.

Inclusion Criteria

Subjects were required to meet each one of the following inclusion criteria at Screening in order to be eligible for participation in the study:

- Subjects were required to be individuals who recreationally use stimulants and who had ≥10 lifetime experiences with any stimulant (e.g., amphetamines, cocaine, and methylphenidate)
- Subjects were required to have used stimulants via a nonoral route of administration
- Subjects were required to have used any stimulant for non-therapeutic purposes at least 5 times within the last 6 months prior to the Screening visit
- Subjects were required to have used cocaine within 6 months prior to the Screening visit

Exclusion Criteria

Subjects were not eligible to participate in this study if any one of the following exclusion criteria were met at Screening:

- Subject was currently seeking treatment for substance-related disorders (excluding nicotine and caffeine)
- Subject had a history or presence of drug or alcohol dependence
- Subject had a positive urine screen for drugs of abuse
- Subject was unable to refrain from smoking or using tobacco products for up to 5 hours: subjects were not allowed to smoke or use tobacco products from 1 hour prior to dosing to 4 hours post-dosing with the study drug.

Part A:

Part A (Cohort 1) consisted of a Screening Period, a Dose Escalation Phase and a Follow-Up Visit.

Dose Escalation Phase: Up to 3 groups of 3 subjects each who successfully completed the Screening Period returned to the clinic to complete the Dose Escalation Phase. The Dose Escalation Phase was an open-label, single-dose, IV, 3-treatment, sequential, within-subject dose escalation design. The stopping rule in the dose escalation sequence was that if dose-limiting adverse events (AEs) were observed in one or more subjects, dose escalation to the higher dose levels was to be stopped. Eligible subjects in Group 1 were to receive single IV doses of 10, 20 and 40 mg of d-MPH API sequentially, with a minimum 48-hour washout between doses. If Group 1 was stopped after the lowest dose (10 mg), a second group may have been enrolled. Eligible subjects in Group 2 were to receive single IV doses of 6, 8 and 10 mg of d-MPH API sequentially, with a minimum 48-hour washout between doses. If Group 2 did not experience dose-limiting AEs at 10 mg d-MPH, a third group was to be enrolled. Eligible subjects in Group 3 were to receive single IV doses of 15 and 20 mg of d-MPH API sequentially, with a minimum 48-hour washout between doses. The study drug was injected over a period of 1 minute with the subject in the recumbent position.

The mean peak Drug Liking score was lowest for d-MPH API 6 mg (68) and highest for d-MPH API 20 mg (80.3); the mean peak score for d-MPH API 15 mg was 69.3. Based on the HAP PD results observed in Group 3 following administration of d-MPH API doses of 15 mg and 20 mg, and elevated blood pressure following administration of d-MPH API 20 mg, the Applicant and Investigator decided that the risks associated with the 20 mg dose did not outweigh the benefits, and a d-MPH API dose of 15 mg was selected for Part B (Cohort 2).

Part B

Part B (Cohort 2) consisted of a Screening Period, a Drug Discrimination Phase (Qualification Phase), a Treatment Phase, and a Follow-Up Visit. All subjects were required to fast for at least 1 hour prior to dosing with study drug until approximately 4 hours after dosing with study drug. The study drug was injected over a period of 1 minute with the subject in the recumbent position. Blood samples for measurement of the plasma concentrations of KP415 prodrug (SDX), d-methylphenidate (d-MPH), l-methylphenidate (l-MPH), and ritalinic acid were collected pre-dose (0 hour; within 1 hour prior to dosing), at 5 minutes post-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 36 hours $\pm$ 5 minutes post-dose.

- Screening Period: Subjects underwent a screening period up to 35 days prior to entering the Drug Discrimination Phase
- Drug Discrimination Phase (Qualification Phase): Subjects who successfully completed the Screening Period returned to the clinic to complete the Drug Discrimination Phase (Qualification Phase). The Drug Discrimination Test was performed to ensure that subjects could differentiate between the effects of a single dose of d-MPH API and placebo administered by IV injection. The Drug Discrimination Phase was a double-blind, single-dose, IV, 2-treatment, 2-period, 2-sequence, randomized crossover design. Subjects received single IV doses of the following treatments separated by a minimum 24-hour washout period:

- Treatment X: d-MPH API 15 mg, IV
- Treatment Y: Matching placebo, IV

HAP PD assessments were performed at different times after the administration of study drug. Safety assessments were performed throughout and at the end of the Drug Discrimination Phase. A subject was eligible for the Treatment Phase only if all of the following eligibility criteria were met in the Drug Discrimination Phase:

- Peak score (Emax) of at least 65 points for d-MPH API on the Drug Liking VAS and at least 15 points higher in response to d-MPH API versus placebo
 - Placebo response was in the range of 40 to 60 points (inclusive) on the Drug Liking VAS
 - Acceptable safety and tolerability after IV administration of the d-MPH API dose
- Treatment Phase: Subjects who successfully completed the Drug Discrimination Test remained as inpatients to enter the Treatment Phase. The washout period between the last dose in the Qualification Phase and first dose in the Treatment Phase was 48 hours. Subjects eligible to continue in the Treatment Phase were randomized into each of the 6 sequences of the Treatment Phase in a 1:1:1:1:1:1 ratio to receive 3 different treatments in a double-blind manner, separated by a minimum 72-hour washout period. The Treatment Phase was a double-blind, single-dose, IV, 3-treatment, 3-period, 6-sequence, randomized crossover design, with the following treatments:

- Treatment A: SDX API 30 mg, IV (molar equivalent for d-MPH to d-MPH API 15 mg dose; SDX API – Test Product)
- Treatment B: d-MPH API 15 mg, IV (Control or Reference Product)
- Treatment C: Matching placebo IV formulation

HAP PD assessments included VAS assessments of Drug Liking, Good Effects, Bad Effects, Any Effects, Feeling High, Alertness/Drowsiness, Take Drug Again, and Overall Drug Liking. All VAS PD assessments except Take Drug Again and Overall Drug Liking were performed at 5 minutes post-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours $\pm$ 5 minutes post-dose. Drug Liking VAS was also determined at 2 minutes post-dose. In addition, pre-dose (0 hour; within 1 hour prior to dosing) HAP PD assessments of Feeling High, Alertness/Drowsiness were collected. The Take Drug Again and Overall Drug Liking VAS assessments were performed at 12 and 24 hours $\pm$ 5 minutes post-dose. ARCI PD assessments were performed pre-dose (0 hour; within 1 hour prior to dosing), and at 0.5, 1, 2, 4, and 8 hours $\pm$ 5 minutes post-dose.

The VASs for Drug Liking (“at this moment”), Overall Drug Liking, and Alertness/Drowsiness (“My mental state is”) used bipolar VAS scoring, with 50 as a neutral score, 0 = Strong Disliking (or Drowsiness), and 100 = Strong Liking (or Alertness).

The VASs for Good Effects (“At this moment, I can feel good drug effects”), Bad Effects (“At this moment, I can feel bad drug effects”), High (“At this moment, I am feeling high”), and Take Drug Again (“I would take this drug again”) used unipolar VAS scoring, with 0 = Definitely Not, and 100 = Definitely Yes.

The ARCI assessments consist of a true–false questionnaire with empirically derived scales sensitive to certain drugs or groups of drugs. Two ARCI subscales were used in the current study: ARCI-A and ARCI-BG. The ARCI-A subscale assesses stimulant effects; the ARCI-BG subscale assesses energy and intellectual efficiency.

Endpoints:

The primary PD endpoint in the Treatment Phase was Drug Liking VAS Emax. The secondary endpoints in the Treatment Phase were as follows:

- Drug Liking VAS (percent reduction in Drug Liking VAS Emax; time of occurrence of Emax [TEmax]; minimum effect [Emin]; time of occurrence of Emin [TEmin]; and area under the effect versus time curve from time 0 to time t [AUE0-t], where t includes all times post-dosing at which effects were measured)
- Global Effects: Take Drug Again VAS (Emax; key secondary endpoint) and Overall Drug Liking VAS (Emax and Emin)
- Positive effects: Feeling High VAS and Good Effects VAS (Emax, TEmax, AUEs)
- Negative effects: Bad Effects VAS (Emax, TEmax, AUEs)
- Other effects: Any Effects VAS (Emax, TEmax, AUEs)
- Stimulant effects: Alertness/Drowsiness VAS, Addiction Research Center Inventory Amphetamine scale (ARCI-A), and ARCI Benzedrine Group scale (ARCI-BG) (Emax, TEmax, Emin, TEmin, AUEs, as applicable)

Pharmacodynamic results

Completers Population: This population included all randomized subjects who completed all treatment periods of the Treatment Phase and had at least one response on the Drug Liking VAS within 2 hours of Tmax for each treatment. This population served as the primary population for

the PK and PD analyses.

A total of 31 subjects were randomized to the Treatment Phase. Thirty subjects completed the study, and 1 subject was discontinued for “other” reasons (family emergency).

Table 15 (Applicant Table 11) displays the Descriptive Statistics of Drug Liking VAS Emax during the Drug Discrimination Phase (Randomized population). As shown in the table, the mean Drug Liking Emax for placebo was 50.2 and for d-MPH API 15 mg was 87.9.

Table 15: (Applicant Table 11) Descriptive Statistics of Drug Liking VAS Emax during the Drug Discrimination Phase (Randomized population)

Statistic	Placebo N=31	d-MPH API 15 mg N=31
Mean (SD)	50.2 (0.63)	87.9 (10.07)

The following notations for the treatments were used in the Biometrics reviewer’s analyses:

- KP415 – 30 mg KP415 prodrug (SDX) API, IV
- d-MPH – 15 mg d-MPH API, IV
- P – Matching placebo IV formulation

The following tables and figures are obtained from the Biometrics review unless otherwise stated.

Table 16 summarizes the mean, standard deviation (SD), minimum, the first quartile (Q1), median (Med), the third quartile (Q3), and maximum of Drug Liking Emax and Drug Liking TEmax for the 3 treatments in the study.

Table 16: Summary statistics for Drug Liking Emax (n=30)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Drug Liking Emax	d-MPH	84.3	13.9	51	76.25	84.5	99.25	100
	KP415	56.6	11.8	50	50	50.5	58.75	100
	P	53.8	8.0	50	50	50	51	78
Drug Liking TEmax (hours)	d-MPH	0.62	0.78	0.03	0.12	0.30	0.79	3.03
	KP415	0.88	1.82	0.03	0.04	0.05	0.79	8.04
	P	1.35	2.86	0.03	0.03	0.04	0.90	12.04

Figure 6 is the mean time course profile by treatment for Drug Liking VAS. **Figure 6** shows that the peak mean response produced by 15 mg d-MPH API was reached at 0.25 hours. The mean time course profile produced by 30 mg KP415 prodrug (SDX) API was almost overlapping with that of placebo.

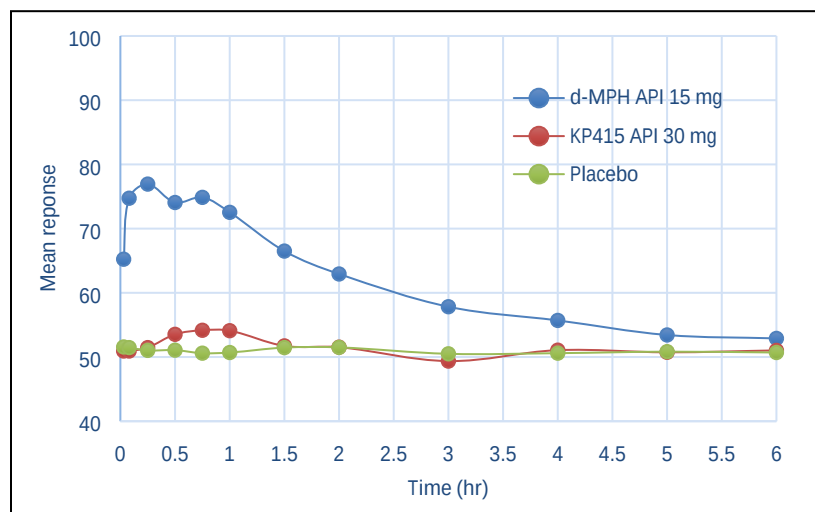


Figure 6: Mean Time Course Profile by Treatment for Drug Liking VAS (n=30) – IV administration

Table 17 shows the results from the primary analysis

Table 17: Results from the primary analysis on Drug Liking Emax (n=30) - IV

# of Completers 30	TRT	d-MPH	KP415	P		
	Mean	84.3	56.6	53.8		
	StdErr	2.5	2.2	1.5		
Comparisons	Mean /Med Diff	StdErr /(Q1, Q3)	Test value	P-value	95% CI	
					LCL	UCL
d-MPH vs P	30.5	2.7	15	<0.0001	25.9	Infy
d-MPH vs KP415	27.7	3.5	10	<0.0001	21.8	Infy
KP415 vs P	0.0	(-1, 8)	11	0.0040	-Infy	1.0

The results show that for Drug Liking Emax:

The mean difference between 15 mg d-MPH API and placebo was significantly larger than 15 points ($p < 0.0001$), thus, validating the primary analysis in the Completers Population. 30 mg SDX API produced a significantly smaller mean than d-MPH API 15 mg with a test margin of 10 points ($p < 0.0001$). The median difference between SDX API 30 mg and placebo was significantly smaller than 11 points ($p = 0.0040$).

Secondary analysis:

The prespecified key secondary endpoint was Take Drug Again Emax. This measure was evaluated on a unipolar visual analog scale in this study. **Table 18** summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 3 treatments in the study for Take Drug Again Emax.

Table 18: Summary statistics for Take Drug Again Emax (N=30) - IV

TRT	Mean	SD	Min	Q1	Med	Q3	Max
d-MPH	63.3	36.9	0	29.25	72.5	100	100
KP415	19.6	33.3	0	0	0	37.75	100
P	14.4	32.9	0	0	0	1.5	100

Table 19 shows the results from the analysis on Take Drug Again Emax.

Table 19: Results from the secondary analysis on Take Drug Again Emax- IV

# of Completers 30	TRT	d-MPH	KP415	P		
	Mean	63.2	20.0	14.0		
	StdErr	6.1	6.1	6.1		
Comparisons	Mean	StdErr	Test value	P-value	95% CI	
					LCL	UCL
d-MPH vs P	49.1	8.3	15	<.0001	35.2	Infy
d-MPH vs KP415	43.1	8.3	10	0.0001	29.2	Infy
KP415 vs P	6.0	8.3	11	0.2750	-Infy	19.9

The results show that for Take Drug Again Emax:

15 mg d-MPH API produced a mean significantly greater than placebo with a test margin of 15 points ($p < 0.0001$).

15 mg d-MPH API produced a mean significantly greater than 30 mg SDX API with a test margin of 10 points ($p = 0.0001$).

The mean difference between 30 mg SDX API and placebo was not significantly less than 11 points ($p = 0.2750$).

Descriptive statistics for secondary endpoints

Secondary endpoints considered were Emax scores for Bad Effects VAS, Good Effects VAS, High VAS, Overall Drug Liking VAS, ARCI-A, and ARCI-BG. Pre-dose responses were collected for High VAS. For High VAS, Emax scores were calculated based on change from pre-dose response. **Tables 20 and 21** show the summary statistics for these endpoints, which all, except Bad Effects VAS, supported the findings from the primary analysis.

Table 20: Summary Statistics of the secondary endpoints (n=30) - IV

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Bad effects VAS	d-MPH	16.9	26.8	0	0	4	21	91
	KP415	3.7	14.4	0	0	0	0	72
	P	4.9	18.5	0	0	0	1	90
Good Effects VAS	d-MPH	82.1	19.6	17	68.5	85	100	100
	KP415	15.5	27.8	0	0	0	13.5	76
	P	13.3	28.2	0	0	0	3.25	91
High VAS	d-MPH	77.4	20.8	6	67.25	79	97.5	100
	KP415	14.5	26.2	0	0	0	15.25	73
	P	11.2	25.7	0	0	0	2.5	86
Overall Drug Liking Emax	d-MPH	72.4	22.2	11	50	74	91.25	100
	KP415	55.2	12.2	45	50	50	52.25	100
	P	53.8	10.9	50	50	50	50	95

Table 21: Summary statistics for Emax scores of ARCI A and ARCI BG group (n=30)- IV

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
ARCI Amphetamine Group Emax	d-MPH	3.1	2.8	-2	0.75	3	5.25	8
	KP415	0.9	1.9	0	0	0	1	9
	P	0.1	1.3	-2	0	0	1	4
ARCI Benzedrine Group Emax	d-MPH	2.5	3.3	-4	0	2	6	11
	KP415	0.6	1.8	-2	0	0	1	9
	P	0.3	1.3	-2	0	0	1	5

Table 22 shows the results of the analysis of High Emax.

Table 22: Results from the analysis on High Emax (n=30)- IV administration

Comparisons	Med Diff	(Q1, Q3)	Test value	P-value	95%/90% CI	
					LCL	UCL
d-MPH vs P	74.0	(58, 86)	0	<0.0001	60.0	81.0
d-MPH vs KP415	72.5	(40, 87)	0	<0.0001	56.0	86.0
KP415 vs P	0.0	(-2.0, 11)	0	0.7353	0.0	1.0

The results show that for High Emax,

the median difference between 15 mg d-MPH API and placebo was significantly greater than zero

the median difference between 15 mg d-MPH API and 30 mg SDX API was significantly greater than zero

the median difference between 30 mg SDX API and placebo was not significantly different from zero

The test results were consistent with those from the primary analysis.

Pharmacokinetic Results:

Mean plasma d-MPH concentrations over time are presented graphically for both d-MPH API 15 mg and KP415 prodrug (SDX) API 30 mg in **Figure 6** (Applicant Figure 7). Plasma d-MPH concentrations rose rapidly after IV administration of d-MPH API 15 mg and reached a mean peak of 56.0 ng/mL at 15 minutes post-dose. Plasma d-MPH concentrations declined in a monophasic manner thereafter, with most subjects having plasma concentrations less than 0.5 ng/mL by 36 hours post-dose.

Plasma d-MPH concentrations were much lower following administration of KP415 prodrug (SDX) API 30 mg compared with d-MPH API 15 mg, with a mean peak concentration of 12.8 ng/mL at 5 minutes post-dose. Plasma d-MPH concentrations declined steadily over time and most subjects had plasma concentrations below 0.5 ng/mL by 24 hours post-dose.

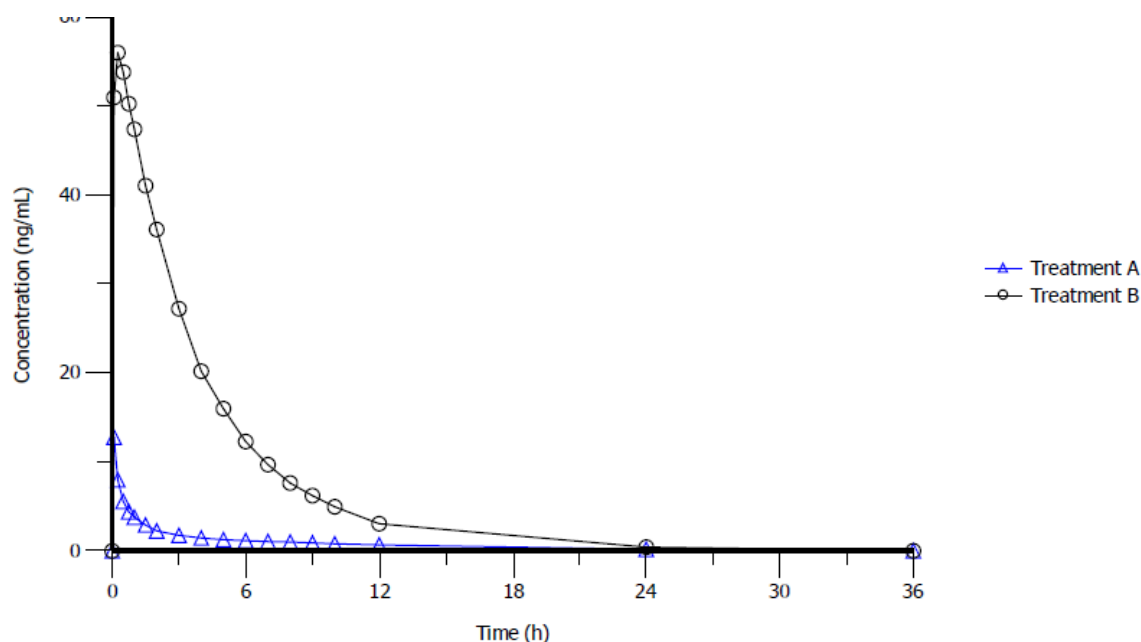


Figure 6 (Applicant Figure 7): Mean Plasma d-Methylphenidate Concentrations over Time (Completers Population) Treatment A=KP415 prodrug (SDX) API 30 mg; Treatment B=d-MPH API 15 mg

Abuse-related adverse events:

Table 23 displays the abuse-related AEs observed in Study KP415 A03. This table was compiled from the AE tables submitted by the Applicant. Euphoric mood and hypervigilance were reported to a greater extent with d-MPH API than KP415 prodrug (SDX) API.

Table 23: Abuse-related Adverse events - Study KP415 A03 (n%)

	KP415 prodrug (SDX) API (N=31)	d-MPH API (N=30)	Placebo (N=31)
Energy increased	2 (6.5)	1 (3.3)	1 (3.2)
Feeling abnormal	1 (3.2)	2 (6.7)	0
Feeling jittery	0	2 (6.7)	0
Feeling of relaxation	0	1 (3.3)	2 (6.5)
Somnolence	1 (3.2)	4 (13.3)	0
Anxiety	0	1 (3.3)	1 (3.2)
Change in attention	0	2 (6.7)	0
Emotional disorder	0	1 (3.3)	0
Euphoric mood	4 (12.9)	17 (56.7)	2 (6.5)
Hypervigilance	4 (12.9)	10 (33.3)	2 (6.5)
Logorrhea	0	1 (3.3)	0
Hyperhidrosis	1 (3.2)	4 (13.3)	0

Comments on Study design This was a randomized, double-blind, placebo-controlled, crossover study, which is an appropriate design for a HAP study so that each subject may act as their control. The positive control (d-MPH API) in this study was appropriate, as it belongs to the same class (stimulants) as the test drug. A reinforcing IV dose of the positive control was appropriately determined in Part A of the study, and this dose (15 mg) was utilized in the Treatment Phase along with a molar equivalent dose of SDX. Wash out times were appropriate representing approximately five times or more the half-lives of the tested drugs (half-life: SDX: 5 hours, d-MPH: 3.5 hours).

Summary and Conclusions:

- Plasma d-MPH concentrations rose rapidly after IV administration of d-MPH API 15 mg and reached a mean peak of 56.0 ng/mL at 15 minutes post-dose. Plasma d-MPH concentrations were much lower following administration of SDX API 30 mg compared with d-MPH API 15 mg, with a mean peak concentration of 12.8 ng/mL at 5 minutes post-dose.
- The mean difference in maximum liking between 15 mg d-MPH API and placebo was significantly greater than 15 points ($p < 0.0001$). Thus, the study was validated.
- The primary analysis demonstrated that the mean of Drug Liking Emax scores produced by 30 mg SDX API was significantly smaller than that by 15 mg d-MPH API with a test margin of 10 points ($p < 0.0001$); and the median difference in maximum liking between 30 mg SDX API and placebo was significantly smaller than 11 points ($p = 0.0040$).
- The key secondary endpoint, Take Drug Again Emax was evaluated on a unipolar visual analog scale. The secondary analysis demonstrated that, for Take Drug Again Emax, the mean produced by 30 mg SDX API was significantly smaller than that by 15 mg d-MPH with a test

margin of 10 points ($p=0.0001$). For Take Drug Again Emax, SDX failed to show no difference from placebo with a test margin of 11 points ($p=0.2750$).

- The results of High VAS supported the findings on the primary analysis.
- Descriptive statistics on secondary measures Good Effects VAS, Overall Drug Liking VAS, ARCI-A, and ARCI-BG and on their Emax scores all supported the findings from the primary analysis.
- Euphoric mood was reported to a greater extent with d-MPH API than KP415 prodrug (SDX) API.

In conclusion, Study KP415.A03 demonstrated that, with IV administration, 30 mg KP415 prodrug (SDX) API has less abuse potential than 15 mg d-MPH API and did not have abuse potential compared to placebo.

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, 3-Way Crossover Study to Determine the Abuse Potential and Pharmacokinetics of 80 mg SDX API Compared with 40 mg of d-Methylphenidate API after Intranasal Administration in Healthy, Nondependent, Recreational Stimulant Users KP415.A02

The main purpose of this study was to assess the human abuse potential (HAP) and PK of KP415 prodrug (SDX) API relative to d-MPH API and placebo when administered intranasally in healthy, nondependent, individuals who recreationally use stimulants.

Primary Objectives

- To assess the abuse potential of KP415 prodrug (SDX) API relative to d-MPH API when administered intranasally in healthy, nondependent, individuals who recreationally use stimulants
- To assess the PK of SDX, and KP415 prodrug (SDX)-derived d-MPH after a single IN dose of SDX) API in healthy, nondependent, individuals who recreationally use stimulants

Secondary Objectives

- To assess the safety and tolerability of a single IN dose of SDX API

The study was a Phase 1, randomized, double-blind, single-dose, active-and placebo-controlled, 3-treatment, 3-period, 6-sequence crossover study evaluating the abuse potential and PK of 80 mg SDX API, 40 mg d-MPH API, and placebo, after intranasal administration in healthy, nondependent, individuals who recreationally use stimulants with intranasal insufflation experience. The study consisted of a Screening Period, an in-clinic Drug Discrimination Phase, a Treatment Phase, and a Follow-up visit.

Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria were met:

- Subject must have been an individual who recreationally used stimulants and who had ≥ 10 lifetime experiences with any stimulant (e.g., amphetamines, cocaine, and/or MPH)
- Subject must have used CNS stimulants by nasal insufflation more than once within 12 weeks prior to the Screening visit
- Subject must have used any stimulant for non-therapeutic purposes at least 5 times within the last 6 months prior to the Screening visit
- Subject must have been between 18 and 55 years of age (inclusive) at Screening

Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria were met:

- Substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition Text
- Revision (DSM-IV-TR) and/or had ever participated or planned to participate in a substance or alcohol rehabilitation program to treat their substance or alcohol dependence
- Heavy smoker (≥ 20 cigarettes per day) and/or was unable to abstain from the use of prohibited nicotine containing products
- Subject had a positive urine screen for drugs of abuse (amphetamines/methamphetamines, barbiturates, benzodiazepines, cocaine, oxycodone, and/or other opiates) or MPH, or a positive breath alcohol test, on Day -1, excluding cannabinoids and tetrahydrocannabinol (THC)
- Subject was unable to refrain from smoking or using tobacco products for up to 6 hours: subjects were not allowed to smoke or use tobacco products from 2 hours prior to dosing to 4 hours post-dosing with the study drug

Drug Discrimination Phase: Subjects who successfully completed the screening period returned to the clinic to complete the Drug Discrimination Phase. The Drug Discrimination test ensured that subjects were able to differentiate between the effects of a single dose of d-MPH API and placebo administered intranasally. Subjects who successfully completed the Drug Discrimination Phase remained as inpatients to enter the Treatment Phase. The Drug Discrimination Phase was a double-blind, IN, single-dose, 2-treatment, 2-period, 2-sequence, randomized, crossover design. Subjects received single IN doses of the following treatments separated by a 48-hour washout period:

- Treatment X: 40 mg d-MPH API mixed with 40 mg microcrystalline cellulose (MCC)
- Treatment Y: 80 mg matching placebo powder

All subjects were required to fast for at least 8 hours prior to each dose until approximately 4 hours after each dose. Drug Liking scores and other HAP PD measures in the Drug Discrimination Phase were used to determine whether subjects could discriminate between d-MPH API and placebo, and, in combination with safety and tolerability data, whether subjects were eligible to continue in the Treatment Phase, according to the following criteria:

- Peak score (Emax) of at least 65 points for d-MPH API on the Drug Liking visual analog scale (VAS) and at least 15 points higher in response to d-MPH API vs placebo response (so that subjects have a minimal response to d-MPH API, outside the placebo response range).

- Placebo response was in the range of 40 to 60 points (inclusive) on the Drug Liking VAS (so that subjects neither endorsed liking nor disliking of placebo).
- Subject was able to insufflate at least 95% of the drug product (d-MPH API and placebo).

The washout period between the last dose of the study drug in the Drug Discrimination Phase and the first dose of study drug in the Treatment Phase was approximately 70 to 72 hours.

Treatment Phase: After subjects completed and passed the Drug Discrimination Phase, they were eligible to enter into the Treatment Phase. The Treatment Phase was a double-blind, IN, single-dose, 3-treatment, 3-period, 6-sequence, randomized, crossover design separated by a minimum 96-hour washout period, with the following treatments:

- Treatment A: 80 mg KP415 prodrug (SDX) API
- Treatment B: 40 mg d-MPH API
- Treatment C: matching placebo powder

All subjects were required to fast for at least 8 hours prior to each dose until approximately 4 hours after each dose. Abuse potential measures and PK were collected at different times after the administration of study drug. Safety assessments were performed throughout and at the end of the Treatment Phase. In order to maintain the blind, the drug was administered with a straw from an amber container.

The dose of 80 mg SDX API was expressed in terms of SDX chloride and contains an equivalent amount as compared to 40 mg d-MPH HCl API. The doses of 80 mg SDX API and 40 mg d-MPH API, therefore, contain molar-equivalent amounts of d-MPH.

Single IN doses of 20, 40, and 60 mg d-MPH were evaluated in Study KP415.DR1 that was conducted in healthy, nondependent individuals who recreationally use CNS stimulants, and, based on the results from this study, the optimal IN dose of d-MPH API was selected to be 40 mg. The optimal IN d-MPH API dose was defined as a dose that produces significant positive psychostimulant effects (e.g., Drug Liking) while minimizing potentially aversive effects that are associated with higher doses of CNS stimulants and that can increase ratings of negative effects and potentially confound the assessment of rewarding effects. The IN SDX API dose in the current HAP study was 80 mg, which is the molar-equivalent dose to the 40 mg d-MPH API IN dose used as the positive control.

The following compliance parameters were assessed:

- Percent of Dose Insufflated (% of dose by weight insufflated): The percent of dose insufflated was calculated using the weights recorded of drug presented for insufflation and drug that was not insufflated
- The time needed to complete the IN administration
- Post-dose assessments of the absence or presence of study drug in the nostrils (as part of the nasal cavity assessment)
- Incidence and timing of post-dose sneezing or nose blowing up to 1 hour post-dose.

Subject-reporting assessments to measure the ease of nasal insufflation were completed within 5 minutes after the completion of each IN drug administration during the Treatment Phase. The question was scored using a 0-to-100-point unipolar VAS anchored on the left with “Very Easy” (score of 0) and anchored on the right with “Very Difficult” (score of 100).

Completers Population: This population consisted of all subjects in the Safety Population who received all study treatments and completed all treatment periods of the Treatment Phase regardless of whether or not they had protocol deviations. Subjects must have had at least one response on the VAS for Drug Liking within 2 hours of T_{max} for each treatment. This population served as the primary population for the PK and PD analyses. The Completers Population included 45 of 49 subjects in the Safety Population who completed all treatment periods in the Treatment Phase and had at least one Drug Liking VAS score.

Pharmacodynamic Endpoints

- Primary Endpoint: Drug Liking E_{max}
- Secondary Endpoints:
 - take drug again (TDA) E_{max}
 - overall drug liking (ODL) E_{max}
- Exploratory Endpoints:
 - E_{max} for High, Good Effects, Bad Effects, Any Effects, and Drowsiness/Alertness VAS scores, and for ARCI-A and ARCI-BG scores
 - Ease of Nasal Insufflation VAS (score at post-dose assessment)
 - T_E_{max} and area under the effect curves (AUEs) for Drug Liking

Results: Fifty subjects successfully met all the qualification criteria. Of the 50 qualifiers, 49 subjects were randomized to the Treatment Phase while 1 subject was not randomized due to an episode of syncope and sinus bradycardia with pause. Four of the 49 randomized subjects discontinued from the Treatment Phase: One subject due to AEs of anxiety and claustrophobia and three subjects withdrew consent. A total of 45 subjects completed the study. Overall, the majority of subjects in the Randomized Population were white (59.2%), non-Hispanic (93.9%) males (73.5%). Subjects had a mean age of approximately 36 years, ranging from 20 to 53 years.

Results for Drug Liking VAS E_{max} in the Drug Discrimination Phase is summarized in **Table 24 (Applicant Table 13)**

Table 24: (Applicant Table 13): Summary of Drug Liking VAS Emax in Drug Discrimination Phase (Completers Population)

	Placebo (n=45)	40 mg d-MPH API (n=45)
Mean (SE)	50.7 (0.120)	95.8 (1.230)

The following notations for the treatments were used in the Biometrics reviewer's analyses:

- KP415 – 80 mg KP415 prodrug (SDX) API
- d-MPH – 40 mg d-MPH API
- P – matching placebo powder

Descriptive statistics and individual Ease of Insufflation VAS scores at 5 minutes post-dose for each treatment are summarized in **Table 25 (Applicant Table 28)**. At 5 minutes after dosing, mean scores for KP415 prodrug (SDX) API were markedly higher than for d-MPH API and placebo, suggesting greater difficulty in snorting the study drug.

All subjects were able to completely insufflate the study treatments.

Table 25 (Applicant Table 28): Ease of insufflation at 5 minutes post dose (Completers Population)

	Placebo (n=45)	40 mg d-MPH API (n=45)	KP415 Prodrug (SDX) API (n=45)
Mean (SE)	6.90 (2.81)	18.1 (3.50)	65.8 (4.77)

The following tables and figures are obtained from the Biometrics review unless otherwise stated.

Pharmacodynamic Results.

Primary analysis

Table 26 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 3 treatments in the study for the primary endpoint Drug Liking Emax and Drug Liking TEmax.

Table 26: Summary statistics for Drug Liking Emax and Drug Liking TE max (n=45) -IN

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Emax	d-MPH	93.2	10.4	58	89.5	100	100	100
	KP415	71.0	18.5	50	51.5	71	83.5	100
	P	51.1	1.4	50	50.5	51	51	59
TEmax	d-MPH	0.7	0.8	0.25	0.25	0.5	0.875	4
	KP415	1.7	2.5	0.25	0.38	0.98	1.5	12
	P	3.0	4.4	0.25	0.25	1	5	24

The mean and median of TEmax were 0.7 hours and 0.5 hours for 40 mg d-MPH API and 1.7 hours and 0.98 hours for 80 mg SDX prodrug API, respectively.

Figure 7 shows the mean time course profiles by treatment for Drug Liking VAS. The peak mean response produced by 80 mg KP415 prodrug (SDX) API was 59.5 at 0.5 hours, while the peak mean response produced by 40 mg d-MPH API was 86.8 at 0.75 hours. At hours 0.5 and 1, the means produced by 40 mg d-MPH API were 85.8 and 86.1, respectively.

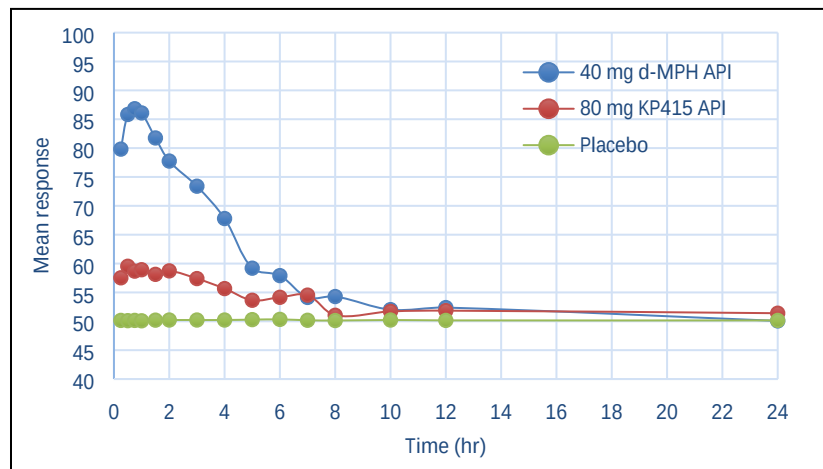


Figure 7: The mean time course profiles by treatment for Drug Liking VAS (n=45) – intranasal administration

Table 27 lists the results from the primary analysis.

Table 27: Results from the primary analysis on Drug Liking Emax (n=45)- IN

# of Completers 45	TRT	d-MPH	KP415	P		
	Mean	93.2	71.0	51.1		
	(StdErr)	(1.6)	(2.8)	(0.2)		
Comparisons	Mean /Med Diff	StdErr /(Q1, Q3)	Test value	P-value	95% CI	
					LCL	UCL
d-MPH vs P	48.0	(40, 49)	15	<0.0001	44.0	Infty
d-MPH vs KP415	22.3	3.0	10	<0.0001	17.3	Infty
KP415 vs P	21.0	(0, 30)	11	0.9980	-Infty	24.0

The results from the primary analysis show that for Drug Liking Emax:

- The median difference between 40 mg d-MPH API and placebo was significantly larger than 15 points ($p < 0.0001$), thus, the study was validated
- 80 mg SDX API produced a significantly smaller mean than 40 mg d-MPH API with a test margin of 10 points ($p < 0.0001$)
- The median difference between 80 mg SDX API and placebo was not significantly smaller than 11 points ($p = 0.9980$)

Secondary Analysis

The secondary endpoints were Overall Drug Liking Emax and Take Drug Again Emax in this study.

Table 28 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 3 treatments in the study for the secondary endpoints.

Table 28: Summary statistics for Overall Drug Liking Emax and Take Drug Again Emax (n=45)- IN

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Overall Drug Liking Emax	d-MPH	81.0	23.8	1	73	90	100	100
	KP415	61.8	24.2	0	50	58	80	100
	P	50.3	0.5	50	50	50	51	52
Take Drug Again Emax	d-MPH	80.3	28.1	0	70.5	95	100	100
	KP415	60.0	27.9	0	50	56	80.5	100
	P	49.2	7.5	0	50	50	51	52

Based on prespecified analysis, all the tests for the secondary endpoints were two-sided with a margin of zero. **Table 29** displays the analysis for the secondary endpoints.

Table 29: Results from the secondary analysis on Overall Drug Liking Emax and Take Drug Again Emax- IN

Endpoint	# of Completers	TRT	d-MPH	KP415	P		
----------	-----------------	-----	-------	-------	---	--	--

	45	Mean	81.0	61.8	50.3		
		StdErr	3.5	3.6	0.1		
Overall Drug Liking Emax	Comparisons	Mean /Med Diff	StdErr /(Q1, Q3)	Test value	P-value	95%/90% CI	
						LCL	UCL
	d-MPH vs P	40.0	(23, 49)	0	<0.0001	26.0	47.0
	d-MPH vs KP415	19.3	5.2	0	0.0006	8.8	29.8
	KP415 vs P	11.5	3.6	0	0.0027	5.4	17.5
Endpoint	# of Completers 45	TRT	d-MPH	KP415	P		
		Mean	80.3	60.0	49.2		
		StdErr	4.2	2.2	1.1		
Take Drug Again Emax	Comparisons	Mean /Med Diff	StdErr /(Q1, Q3)	Test value	P-value	95%/90% CI	
						LCL	UCL
	d-MPH vs P	44.0	(22, 49)	0	<.0001	34.0	49.0
	d-MPH vs KP415	20.3	6.2	0	0.0021	7.8	32.9
	KP415 vs P	10.8	3.942	0	0.0091	4.1	17.4

The results from the secondary analysis show that for both Overall Drug Liking Emax and Take Drug Again Emax:

- The median difference between 40 mg d-MPH API and placebo was significantly greater than zero.
- 40 mg d-MPH API produced a mean value significantly greater than 80 mg KP415 prodrug (SDX) API.
- 80 mg KP415 prodrug (SDX) API produced a mean value significantly greater than placebo.

Exploratory endpoints

Table 30 displays the results of the statistical testing for High Emax, which was an exploratory endpoint.

Table 30: Results from the analysis on High Emax- IN

# of Completers 45	TRT	d-MPH	KP415	P		
	Mean	87.8	43.3	2.5		
	SD	14.6	34.9	10.5		
Comparisons	Mean /Med	StdErr	Test	P-value	95%/90% CI	

	Diff	/(Q1, Q3)	value		LCL	UCL
d-MPH vs P	88.0	(78, 100)	0	<0.0001	81.0	98.0
d-MPH vs KP415	44.5	5.3	0	<0.0001	33.9	55.1
KP415 vs P	40.8	5.4	0	0.0027	31.7	49.8

The results from the analysis on High Emax show that:

- The median difference between 40 mg d-MPH API and placebo was significantly greater than zero ($p < 0.0001$).
- 40 mg d-MPH API produced a mean value significantly greater than 80 mg SDX API ($p \leq 0.0001$).
- 80 mg SDX API produced a mean value significantly greater than placebo ($p = 0.0027$).

The results are consistent with those from analyses on the primary and the key secondary endpoints.

Other exploratory endpoints considered were Emax scores for Bad Effects VAS, Good Effects VAS, ARCI-A and ARCI-BG groups. **Tables 31 and 32** show the summary statistics for these endpoints. The results are consistent with those from analyses on the primary and the key secondary endpoints.

Table 31: Summary statistics of the exploratory endpoints (n=45)- IN

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Bad effects VAS	d-MPH	18.6	28.6	0	0	2	30.5	100
	KP415	14.9	23.4	0	0	1	23.5	100
	P	1.6	3.9	0	0	0	1	20
Good Effects VAS	d-MPH	90.6	11.9	57	80	97	100	100
	KP415	44.9	38.2	0	6.5	42	78	100
	P	0.7	1.1	0	0	0	1	5

Table 32: Summary statistics for Emax scores of ARCI-A and ARCI-BG group (n=45) -IN

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
ARCI Amphetamine Group Emax	d-MPH	5.1	3.4	-4	2.5	5	8.5	10
	KP415	2.5	2.9	-1	0	2	5	10
	P	0.1	0.8	-2	0	0	0	2
ARCI Benzedrine Group Emax	d-MPH	4.1	3.3	-2	1	4	7	10
	KP415	1.9	2.6	-1	0	1	3	10

	P	0.1	0.8	-2	0	0	0	2
--	---	-----	-----	----	---	---	---	---

Pharmacokinetic results:

Mean plasma d-MPH concentrations were greater for the active comparator (d-MPH API) than KP415 prodrug (SDX) API as shown in **Figure 8 (Applicant Figure 15)**. Following IN administration of d-MPH API, plasma d- MPH concentrations rose rapidly, achieving peak mean concentration of 46.3 ng/mL at 2 hours post-dose. After administration of SDX API, mean plasma d-MPH concentrations rose rapidly to 6.19 ng/mL by 0.25 hours post-dose, then declined and plateaued at ~3–4 ng/mL from 1.5 to 10 hours post-dose

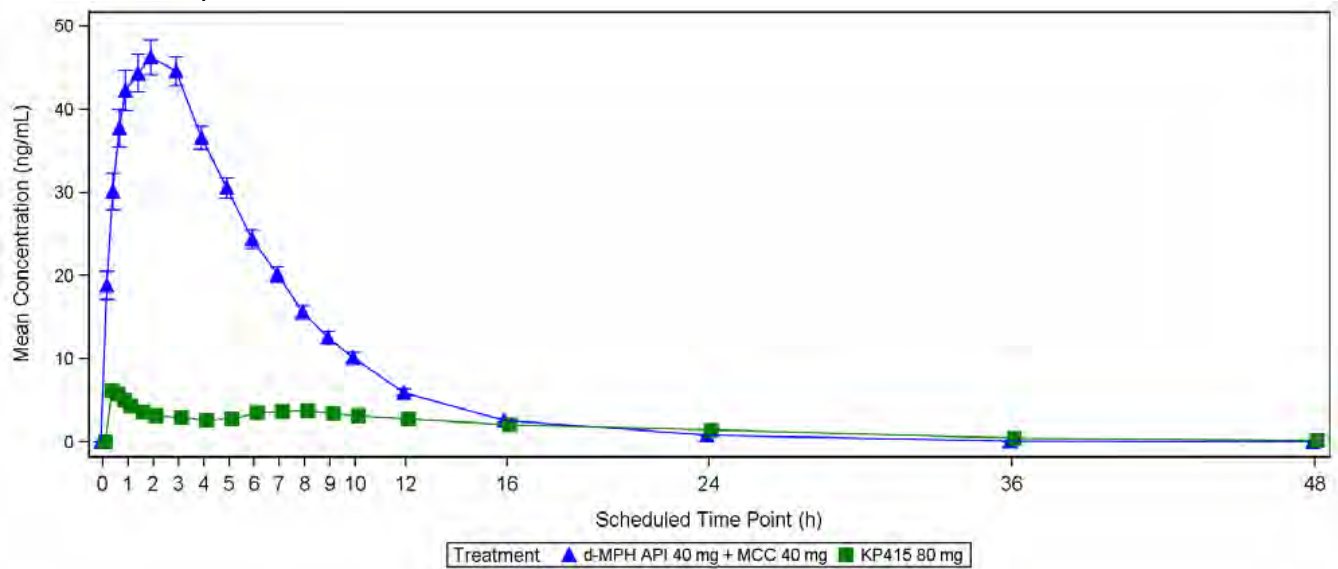


Figure 8 (Applicant Figure 15): Mean (±SD) d-MPH Plasma Concentration vs Time (PK Population)

Adverse Events

According to the Applicant, mean values for blood pressure (systolic and diastolic) and heart rate were elevated following dosing with d-MPH API. There was a marked increase in mean changes from baseline, particularly for heart rate, immediately after insufflation of d-MPH API up to 4- or 6-hours post-dose, but these parameters gradually declined thereafter. There was also a rapid increase in mean values for these parameters after IN administration of KP415 prodrug (SDX) API; however, the effects were transient, as mean changes from baseline declined after 0.25 hours post-dose.

Table 33 displays the abuse-related AEs reported in Study KP 415.A02. Euphoric mood and hypervigilance were reported to a greater extent with d-MPH API than with KP 415 prodrug (SDX). KP415 prodrug (SDX) treated subjects reported euphoric mood and hypervigilance to a greater extent than placebo-treated subjects. Nasal discomfort and congestion were reported to the greatest extent in KP415 prodrug (SDX) treated subjects.

Table 33: Abuse-related adverse events KP415.A02 n (%)

	Placebo n=48	d-MPH API 40 mg n=46	SDX 80 mg n=46
Euphoric mood	0	29 (63)	9 (19.6)
Hypervigilance	0	16 (34.8)	6 (13)
Anxiety	0	2 (4.3)	1 (2.2)
Restlessness	0	2 (4.3)	0
Agitation	0	0	1 (2.2)
Change in sustained attention	0	1 (2.2)	0
Irritability	0	0	1 (2.2)
Nasal discomfort	0	3 (6.5)	13 (28.2)
Nasal congestion	0	1 (2.2)	10 (21.7)
Somnolence	0	2 (4.3)	1 (2.2)
Energy increased	0	2 (4.3)	0
Feeling of relaxation	0	0	2 (4.3)
Hyperhidrosis	0	3 (6.5)	2 (4.3)

Comments on Study design: This was a randomized, double-blind, placebo-controlled, crossover study, which is an appropriate design for a HAP study so that each subject may act as their control. The positive control (d-MPH API) in this study was appropriate, as this belongs to the same class (stimulants) as the test drug. A reinforcing IN dose of the positive control was appropriately determined in Study KP415.DR1, and this dose (40 mg) was utilized in the Treatment Phase along with a molar equivalent dose of KP415 prodrug (SDX). Wash out times were appropriate representing approximately five times or more the half-lives of the tested drugs (half-life SDX: 9.4 hours, d-MPH: 4.3 hours).

Summary and Conclusions:

Pharmacokinetic results:

Mean plasma d-MPH concentrations were greater for the active comparator (d-MPH API) than KP415 prodrug (SDX) API. Following IN administration of d-MPH API, plasma d- MPH concentrations rose rapidly, achieving a peak mean concentration of 46.3 ng/mL at 2 hours post-dose. After administration of KP415 prodrug (SDX) API, mean plasma d-MPH concentrations rose rapidly to 6.19 ng/mL by 0.25 hours post-dose, then declined and plateaued at ~3–4 ng/mL from 1.5 to 10 hours post-dose.

Pharmacodynamic Results:

Primary analysis:

- For Drug Liking Emax, the median difference between 40 mg d-MPH API and placebo was significantly greater than 15 points, thus validating the study.

- The mean difference between 40 mg d-MPH API and 80 mg SDX API was significantly larger than 10 points.
- The study failed to demonstrate a median difference between 80 mg SDX API and placebo significantly smaller than 11 points.

Secondary analysis for both Overall Drug Liking Emax and Take Drug Again Emax:

- The median difference between 40 mg d-MPH API and placebo was significantly greater than zero.
- The mean difference between 40 mg d-MPH API and 80 mg SDX API was significantly greater than zero.
- The median difference between 80 mg SDX API and placebo was significantly greater than zero.

Exploratory endpoints:

- The statistics for the exploratory measures (Good Effects VAS, High VAS, ARCI-A and ARCI-BG) and their Emax scores supported the findings from the primary and secondary analyses.

Adverse Events:

- Euphoric mood and hypervigilance were reported to a greater extent with d-MPH API than with SDX. SDX treated subjects reported euphoric mood and hypervigilance to a greater extent than placebo-treated subjects.
- Nasal discomfort and congestion were reported to the greatest extent in SDX-treated subjects.

In conclusion, Study KP415.A02 demonstrated that, with intranasal administration, 80 mg SDX API had less abuse potential than 40 mg d-MPH API and had greater abuse potential compared to placebo.

4.2 Adverse Event Profile Through all Phases of Development

The Applicant conducted Phase 1 and Phase 3 studies as part of the clinical development program for SDX/d-MPH. All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description and analysis of abuse-related AEs reported during different phases of clinical development.

Phase 1 Studies:

Phase 1 Studies with SDX alone: **Table 34** displays the abuse-related AEs in Phase 1 studies that evaluated SDX alone, without d-MPH.

Table 34: Abuse-related adverse events in Phase 1 studies with SDX alone

Study	Test products	Abuse-related AEs n/N(%)
KP415.102	SDX 20, 40, and 60 mg	Somnolence 2/24 (8.3%)
KP415.108	SDX 60 mg	None (N=14)

KP415.101	SDX 32 mg, Concerta (MPH) 36mg	None (N=24)
KP415.106	SDX 6 mg and 60 mg	Somnolence 1/6 (16.7%)
KP415.111	SDX 60 mg	None (N=8)

Phase 1 single dose studies with SDX/d-MPH: **Table 35** displays the abuse-related AEs in Phase1 single-dose studies of SDX/d-MPH.

Table 35: Abuse-related adverse events in single-dose Phase 1 studies of SDX/d-MPH

Study	Population	Test Products	Abuse-related AEs n/N (%)
KP415.104	Healthy volunteers	SDX 56mg/ MPH 12 mg	Hyperhidrosis 1/30 (3.3%); Anxiety 1/30 (3.3%); Bruxism 1/30 (3.3%); Agitation 3/30 (10%); Energy increased 4/30 (13.3%)
KP415.107	Healthy volunteers	SDX 56mg/ MPH 12 mg (total MPH=40 mg) vs Focalin (d-MPH) 40 mg	SDX/d-MPH: Energy increased 1/30 (3.3%) Focalin: Energy increased 1/29 (3.4%)
KP415.105	Children and adolescents with ADHD	SDX 56mg/ MPH 12 mg SDX 28mg/ MPH 6 mg	None (N=31)

Study KP415.110: This was a Phase 1 single-dose (SDX/MPH 28 mg/6 mg, 42 mg/9 mg, and 56 mg/12 mg) and multiple-dose (SDX 56 mg/ MPH 12 mg) Phase 1 study in healthy volunteers. The abuse-related adverse events are displayed in **Table 36**.

Table 36: Abuse-related adverse events Study KP415.110 n (%)

	SDX/MPH 28mg/6mg (N=23)	SDX/MPH 42mg/9mg (N=24)	SDX/MPH 56mg/12mg single dose (N=23)	SDX/MPH 56mg/12mg multiple doses (N=23)
Somnolence	0	0	1(4.3)	2 (8.7)
Disturbance in attention	0	0	0	1 (4.3)
Agitation	0	1 (4.2)	0	0
Irritability	0	0	1 (4.3)	0
Mood swings	0	0	0	1 (4.3)
Mood altered	0	0	0	2 (8.7)
Anxiety	0	0	0	1 (4.3)
Euphoric mood	0	0	0	1 (4.3)
Feeling jittery	0	0	0	3 (13.0)

Study KP415.109: This was a Phase 1 multiple-dose PK study in healthy volunteers evaluating different doses of SDX/d-MPH and Concerta (MPH). The abuse-related AEs are displayed in **Table 37**.

Table 37: Abuse-related adverse events Study KP415.109 n (%)

	SDX/MPH 64mg/8mg N=12	SDX/MPH 56mg/12mg N=12	SDX/MPH 48mg/16mg N=12	Concerta 54 mg N=12
Somnolence	0	0	1 (8.3)	0
Anxiety	0	1 (8.3)	3 (25)	1 (8.3)
Disturbance in attention	0	1 (8.3)	1(8.3)	0
Euphoric mood	2 (16.6)	1 (8.3)	2 (16.6)	1 (8.3)

Phase 1 Studies Conclusions:

Studies evaluating SDX alone, without MPH, did not reveal any abuse-related AEs at doses up to 60 mg.

Studies that evaluated a combination of SDX/MPH revealed the abuse-related adverse events consistent with stimulants of agitation, feeling jittery, increased energy, and euphoric mood. Increased energy occurred at a similar frequency as Focalin. SDX/MPH at a 40 mg equivalent MPH dose displayed a similar frequency of euphoric mood as 54 mg Concerta.

Thus, SDX alone did not produce abuse-related AEs and SDX/MPH produced rates of abuse-related AEs similar to other stimulants.

Phase 3 studies:

A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled, Parallel Efficacy Laboratory Classroom Study with KP415 in Children with Attention-Deficit/Hyperactivity Disorder KP415.E01 Phase 3

The primary objective of this study was to determine the efficacy of SDX/d-MPH capsules compared with placebo in treating children 6 to12 years old with ADHD in a laboratory classroom setting. The secondary objectives of this study were to determine the onset and duration of the clinical effect of SDX/d-MPH capsules and to determine the safety and tolerability of SDX/d-MPH capsules in treating children 6 to12 years old with ADHD in a laboratory classroom setting.

This was a multicenter, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy laboratory classroom study. The study consisted of a Screening Period, an Open-Label Dose Optimization Phase, a Double-Blind Treatment Phase, and a Follow-Up Visit.

The number of subjects enrolled in the Open-Label Dose Optimization and Double-Blind Treatment Phase were 155 and 150, respectively. Subjects were titrated with SDX/d-MPH capsules during the Open-Label Dose Optimization Phase for 3 weeks. During the Double-Blind Treatment Phase, subjects received single daily doses of SDX/d-MPH capsules or placebo for 7 days.

The abuse-related adverse events may be difficult to evaluate in children who may not be able to express feelings of euphoria, relaxation, etc. However, **Table 38** displays adverse events of mood, affect, etc. that may be associated with abuse potential.

Table 38: Abuse-related AEs Study KP415.E01 n (%)

	Dose Optimization Phase Open Label N=155	Randomized Subjects SDX/d-MPH N=74	Randomized Subjects Placebo N=76
Affect lability	18 (11.6)	1 (1.4)	1 (1.3)
Irritability	12 (7.7)	0	0
Anxiety	3 (1.9)	0	0
aggression	2 (1.3)	0	0
Defiant behavior	2 (1.3)	0	0
Emotional disorder	2 (1.3)	0	0
Logorrhea	2 (1.3)	0	0
Tearfulness	2 (1.3)	0	0
Agitation	1 (0.6)	0	0
Anger	1 (0.6)	0	0
Blunted affect	1 (0.6)	0	0
Constricted affect	1 (0.6)	0	0
Depressed mood	1 (0.6)	0	0
Emotional distress	1 (0.6)	0	0
Mood altered	1 (0.6)	0	0
Nervousness	1 (0.6)	0	0
Psychomotor hyperactivity	1 (0.6)	0	0
Somnolence	1 (0.6)	0	0
Feeling jittery	1 (0.6)	0	0

A Multicenter, Dose-Optimized, Open-Label Safety Study with SDX/d-MPH in Children with Attention-Deficit/Hyperactivity Disorder KP415.S01 Phase 3

The primary objective of this study was to determine the safety and tolerability of SDX/d-MPH in treating children (6-13 years of age) with attention-deficit/hyperactivity disorder (ADHD).

The study was a multicenter, multiple-dose, dose-optimized, open-label safety study with SDX/d-MPH administered orally in children with ADHD. The study consisted of a Screening Phase, a Dose-Optimization Phase, a Treatment Phase, and a Follow-up Visit.

The abuse-related adverse events may be difficult to evaluate in children who may not be able to express feelings of euphoria, relaxation, etc. However, **Tables 39 and 40** display adverse events of mood, affect, etc. that may be associated with abuse potential. The 120-day safety update reported no further abuse-related AEs.

Table 39: Treatment Phase abuse-related AEs Study KP415.S01 n (%)

	SDX/d-MPH N=238
Irritability	16 (6.7)

Affect Lability	5 (2.1)
Flat Affect	3 (1.3)
Tearfulness	3 (1.3)
Anxiety	3 (1.3)
Depression	1 (0.4)
Emotional disorder	1 (0.4)
Visual hallucination	1 (0.4)
Hypnagogic Hallucination	1 (0.4)
Nervousness	1 (0.4)
Suicidal ideation	1 (0.4)
Overdose	1 (0.4)
Mental impairment	1 (0.4)
Sedation	1 (0.4)
Depersonalization/Derealization Disorder	1 (0.4)
Somnolence	1 (0.4)

Table 40: Abuse-related AEs in Dose optimization Phase Study KP415.S01 n (%)

	SDX/d-MPH N=208
Irritability	14 (6.7)
Affect lability	6 (2.9)
Emotional disorder	3 (1.4)
Nervousness	2 (1.0)
Tearfulness	2 (1.0)
Agitation	1 (0.5)
Depressed mood	1 (0.5)
Hallucination Visual	1 (0.5)
Psychotic disorder	1 (0.5)
Psychomotor hyperactivity	1 (0.5)
Somnolence	1 (0.5)
Energy increased	1 (0.5)
Aggression	1 (0.5)

Phase 3 Study Conclusions:

The Phase 3 studies were not useful for determining abuse potential of SDX/d-MPH because they were conducted in children with ADHD, who typically have mood, behavioral, and affect abnormalities. In addition, one study was an open-label study without a placebo group, which limited assessment of AEs. In the other study, no significant abuse-related AEs were noted during the double-blind phase, and the assessment of AEs was limited during the open-label phase, which did not have a placebo group.

4.3 Safety Profile

Abuse of SDX/d-MPH may result in more severe adverse events than those that are typically seen with therapeutic doses of stimulants. Based on accumulated data from other methylphenidate products, the common adverse reactions are decreased appetite, insomnia, nausea, vomiting, dyspepsia, abdominal

pain, headache, aggression, agitation, decreased weight, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increase. Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials.

Instances of abuse were not an issue during the Phase I studies because study staff administered all doses.

There were no reports of overdose in Study KP415.E01.

There were 11 overdosage occurrences in Study KP415.S01, most of which were considered accidental, involving only 1 to 2 additional capsules. In most instances, this involved multiple family members providing capsules to the patient or a parent's misunderstanding of the dosing regimen. A single case of potential abuse was reported in Study KP415.S01, which involved another prescription stimulant. Two possible cases of diversion were noted: The mother of a subject dispensed 1 capsule of 42/9 mg SDX/d-MPH to the subject's sibling; another subject provided study drug to a friend. During study drug accounting, it was determined that the subject had taken one additional 56/12 mg SDX/d MPH capsule and had provided one capsule (56/12 mg) to a friend. The subject was discontinued from the study because of this event and previous reports of compliance greater than 100%. Fifteen subjects had deviations associated with incomplete drug returns, 3 of whom had 2 incidents, and 52 subjects failed to return study drug to the study site after withdrawing from the study or being lost to follow-up.

Thus, although details of subjects not returning the study drug are not known, there does not appear to be significant abuse, misuse, or diversion during the clinical trials.

4.5 Tolerance and Physical Dependence Studies in Humans

No dedicated study evaluating physical dependence was conducted with SDX. The Applicant states that SDX is an inactive prodrug while intact and the only role of SDX is to provide a mechanism to gradually deliver active d-MPH to the patient. SDX has no discernible pharmacology or interactions with metabolizing enzymes or transporters, therefore, the potential of development of dependence to intact SDX does not seem to be a relevant consideration.

Withdrawal symptoms occur after abrupt cessation following prolonged high dosage administration of CNS stimulants, however, these AEs were not observed after abrupt cessation of SDX/d-MPH treatment in clinical studies KP415.E01 and KP415.S01.

Withdrawal symptoms following abrupt cessation of CNS stimulants are described in Section 9.3, Dependence, of the proposed labeling.

5. Regulatory Issues and Assessment

- Based on the oral human abuse potential study, which showed that serdexmethylphenidate (SDX) had lower abuse potential than Focalin (schedule II), similar abuse potential to phentermine (schedule IV), and greater abuse potential than placebo, we have recommended in an eight-factor analysis that SDX be placed in schedule IV of the Controlled Substances Act (CSA).
- Since the drug product SDX/dexmethylphenidate (d-MPH) contains d-MPH, a schedule II substance, the product formulation, if approved, will be controlled as schedule II.
- Labeling negotiations are ongoing with the Applicant at the time of this writing, however, specifics of the (b) (4) (b) (4) (b) (4) remaining abuse-related information in the labeling is based on the reference product's labeling with updates to the language to reflect current approaches to labeling this class of products.

III. References

Ghosh, A. K. and M. Brindisi (2015). "Organic carbamates in drug design and medicinal chemistry." J Med Chem **58**(7): 2895-2940.

Holzer, P. (2009). "Opioid receptors in the gastrointestinal tract." Regul Pept **155**(1-3): 11-17.

Janssen (2019). "Janssen Pharms, Product Label, Ultram (tramadol hydrochloride) tablets , NDA 20281." Access at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020281s045lbl.pdf.

Pennick, M. (2010). "Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine." Neuropsychiatr Dis Treat **6**: 317-327.

Zhao, L. (2019). "Quantitative Analysis of Opioid ADF PK/PD- Presentation at the 2019 American Society for Clinical Pharmacology and Therapeutics." Access at <https://www.ascpt.org/Meetings/Past-Future-Annual-Meetings/ASCPT-2019/Friday-March-15-Presentations>.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHALINI M BANSIL
02/16/2021 05:39:00 PM

SILVIA N CALDERON
02/16/2021 07:03:51 PM

JOSHUA M LLOYD
02/17/2021 09:12:01 AM

DOMINIC CHIAPPERINO
02/17/2021 10:18:04 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: February 2, 2021

To: Gregory Dubitsky, M.D., Clinical Reviewer
Division of Psychiatry (DP)

Bill Bender, RPh, Regulatory Project Manager, (DP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for AZSTARYS (serdexmethylphenidate and dexamethylphenidate) capsules, for oral use, CII

NDA: 212994

In response to DP's consult request dated April 10, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for AZSTARYS (serdexmethylphenidate and dexamethylphenidate) capsules, for oral use, CII.

PI: OPDP's comments on the proposed labeling are based on the draft labeling downloaded from DP's SharePoint on February 2, 2021, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on January 26, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor via the eCTD on October 14, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

26 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOMENIC G DALESSANDRO
02/02/2021 01:49:45 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 26, 2021

To: William Bender, RPh.
Regulatory Project Manager (RPM)
Division of Psychiatry (DP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Domenic D'Alessandro, PharmD, MBA, CDE
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): AZSTARYS (serdexmethylphenidate and dexmethylphenidate)

Dosage Form and Route: Capsules, for oral use, CII

Application Type/Number: 212994

Applicant: KemPharm, Inc. (KemPharm) on behalf of Commave Therapeutics SA

1 INTRODUCTION

On March 2, 2020, KemPharm, Inc. (KemPharm) on behalf of Commave Therapeutics SA, submitted for the Agency's review an original New Drug Application (NDA) for AZSTARYS (serdexmethylphenidate and dexamethylphenidate) capsules, for oral use, CII, for the proposed indication of use for the treatment of attention-deficit hyperactivity disorder (ADHD) in patients age six years and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on April 24, 2020 and April 10, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for AZSTARYS (serdexmethylphenidate and dexamethylphenidate) capsules, for oral use, CII.

2 MATERIAL REVIEWED

- Draft AZSTARYS (serdexmethylphenidate and dexamethylphenidate) MG received on March 2, 2020 and received by DMPP and OPDP on January 22, 2021.
- Draft AZSTARYS (serdexmethylphenidate and dexamethylphenidate) Prescribing Information (PI) received on March 2, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 22, 2021.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHAWNA L HUTCHINS
01/26/2021 02:01:17 PM

DOMENIC G DALESSANDRO
01/26/2021 02:03:32 PM

LASHAWN M GRIFFITHS
01/26/2021 02:08:11 PM

LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 22, 2021
Requesting Office or Division:	Division of Psychiatry
Application Type and Number:	NDA 212994
Product Name and Strength:	Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, and 52.3 mg/10.4 mg ^a
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Commave Therapeutics SA (Commave)
FDA Received Date:	March 2, 2020 and October 14, 2020
OSE RCM #:	2020-459
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

^a The serdexmethylphenidate strengths have been changed (from (b) (4) to 26.1 mg, 39.2 mg, and 52.3 mg, respectively) per recommendation from the Office of Pharmaceutical Quality to correct the serdexmethylphenidate strength to one decimal accuracy.

1 PURPOSE OF REVIEW

As part of the approval process for Azstarys^b (serdexmethylphenidate and dexamethylphenidate) capsules, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, and 52.3 mg/10.4 mg, the Division of Psychiatry (DP) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 BACKGROUND/REGULATORY HISTORY

NDA 212994 for Azstarys (serdexmethylphenidate and dexamethylphenidate) capsules is a 505(b)(2) submission. The listed drug product (Focalin XR, NDA 021802), was approved in May 2005.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Table 2 below includes the identified medication error issues with the submitted container labels, DMEPA's rationale for concern, and the proposed recommendations to minimize the risk for medication error. We note that we contacted the Office of Prescription Drug Promotion to see if they had any promotional concerns with how the proprietary name is presented on the container labels as it relates to the red font and graphic containing a star figure. They stated that they have no objections.

^b The proposed proprietary name, Azstarys, was found conditionally acceptable in the following review: Holmes, L. Proprietary Name Review for Azstarys (serdexmethylphenidate and dexamethylphenidate) NDA 212994. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 27. RCM No.: 2020-41769544.

Additionally, we noted discrepancies between the administration instructions in Section 2.2 *General Dosing Information* and Section 17 *Patient Counseling Information* in the Full Prescribing Information and we provided a recommendation to address our concern. We note that during internal labeling discussions, Section 2.2 was revised and our concern addressed.

Table 2: Identified Issues and Recommendations for Commave (entire table to be conveyed to Applicant)

Container Labels			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	A (b) (4) font color and a (b) (4) in the proprietary name, from the other letters which are in a lighter green font color.	The (b) (4) font color and the (b) (4) draw attention away from important information on the principal display panel.	Consider presenting the proprietary name in a single color without highlighting any portion of the name. Typically, methods used to highlight a portion of the name are reserved for tallman lettering when we have identified a safety concern. (b) (4)
2.	The NDC numbers on the container labels differ from the NDC numbers in the Prescribing Information (e.g., 70040-228-01 versus 70040-0228-1, respectively).	The inconsistency of the NDC numbers presentation may cause confusion or errors with product identification.	Ensure that the correct NDC numbers are in the Prescribing Information and on the container labels. Revise as needed to ensure consistency across the labels and labeling.
3.	The controlled substance symbol appears twice on the principal display panel (adjacent to the proprietary name and the Medication Guide statement).	The presence of two controlled substance symbols is duplicative, clutters the principal display panel, and is unnecessary.	Ensure that the control substance symbol on the labels is clear and large enough to afford easy identification of the schedule of the controlled substance upon inspection without removal from the dispenser's shelf (per 21 CFR 1302.04). Delete one of the controlled substance symbols.

4.	The “Rx Only” statement is too prominent due to its size and bold font.	Due to its prominence, the “Rx Only” statement distracts from important information on the principal display panel.	Decrease the size of the “Rx Only” statement and unbold the font.
5.	The net quantity statement is too prominent due to its bold font.	Due to its prominence, the net quantity statement distracts from important information on the principal display panel.	Unbold the net quantity statement font.
6.	The storage statement is not consistent with the storage statement in the Prescribing Information. The sentence “Protect from moisture” is not present on the container labels but it is present in the Prescribing Information.	Inconsistency between the storage statement on the container labels and in the Prescribing Information may lead to confusion.	Add the sentence “Protect from moisture” to the storage statement on the container labels.
7.	The Medication Guide (MG) statement states (b) (4)	There is no carton labeling proposed so, therefore, it is not clear how the MG is actually supplied (b) (4).	Please explain how the MG is supplied. (b) (4) consider revising the statement to read “accompanying”, “attached” or use a similar term, as appropriate, to describe how the MG is supplied.

5 CONCLUSION

Our evaluation of the proposed container labels and Prescribing Information identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to Commave so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Azstarys that Commave submitted on March 2, 2020, and the listed drug (LD).

Table 3. Relevant Product Information for Focalin XR (Listed Drug) and Azstarys		
Product Name	Focalin XR	Azstarys
Initial Approval Date	05/26/2005	N/A
Active Ingredient	dexmethylphenidate hydrochloride	serdexmethylphenidate and dexmethylphenidate
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older
Route of Administration	Oral	Oral
Dosage Form	Extended-release capsules	Capsules
Strengths	5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg	26.1 mg/5.2 mg, 39.2 mg/7.8 mg, and 52.3 mg/10.4 mg ^c
Dose and Frequency	<u>Patients New to Methylphenidate</u> The recommended starting dosage of Focalin XR for patients who are not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate are: - Pediatric patients: Start with 5 mg orally once daily in the morning with or without food. - Adult patients: Start with 10 mg orally once daily in the morning with or without food.	Given orally once daily in the morning with or without food. The recommended starting dose for patients 6 years and older is (b) (4) mg once daily in the morning. The dose may be titrated weekly in increments of 13/2 6 mg (b) (4) (b) (4)

^c The serdexmethylphenidate strengths have been changed (from (b) (4) to 26.1 mg, 39.2 mg, and 52.3 mg, respectively) per recommendation from the Office of Pharmaceutical Quality to correct the serdexmethylphenidate strength to one decimal accuracy.

	<u>Patients Currently on Methylphenidate</u> • The recommended starting dose of Focalin XR for patients currently using methylphenidate is half (1/2) the total daily dose of racemic methylphenidate. • Patients currently using Focalin (dexmethylphenidate) immediate-release tablets may be given the same daily dose of Focalin XR. <u>Titration Schedule</u> The dose may be titrated weekly in increments of 5 mg in pediatric patients and 10 mg in adult patients. The dose should be individualized according to the needs and response of the patient. Daily doses above 30 mg in pediatrics and 40 mg in adults have not been studied and are not recommended.	
How Supplied	100-count bottles	100-count bottles
Storage	Store at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F to 86°F) [See USP Controlled Room Temperature].	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from moisture.
Container Closure	Info N/A	(b) (4)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Azstarys labels and labeling submitted by Commave on March 2, 2020 and October 14, 2020.

- Container label received on October 14, 2020
- Prescribing Information (Image not shown) received on March 2, 2020 (no image)

F.2 Label and Labeling Images (not to scale)

Container Labels



^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LORETTA HOLMES
01/22/2021 12:00:04 PM

SEVAN H KOLEJIAN
01/22/2021 12:02:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine (ORPURM)
Office of New Drugs Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Psychiatry (DP)
Office of Neuroscience (ON), OND

Subject: Review of safety data regarding the occurrence of
proteinuria in clinical trials of Azstarys

Applicant: Commave Therapeutics, SA

Drug: Azstarys (serdexmethylphenidate chloride (SDX) and
dexamethylphenidate hydrochloride (d-MPH))¹

¹ This review will refer to the drug product as “SDX/d-MPH”

Proposed Indication: Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)

Proposed Dosage Form: Capsules

Proposed Dosage Strength (SDX/d-MPH): 28 mg/6 mg, 42 mg/9 mg, and 56 mg/12 mg

Consult Request:

DP requested DPMH review the urinalysis data from Study KP415.S01 to assess the clinical significance of the occurrence of proteinuria in the subset of the study subjects in which it was documented.

Materials Reviewed:

- The following documents were entered into DARRTS under NDA 212994
 - o Clinical Study Report for Study KP415.E01, Module 5.3.5.1 (eCTD #1)
 - o Clinical Study Report for Study KP415.S01, Module 5.3.5.2 (eCTD #1)
 - o Summary of Clinical Safety, Module 2.7.4 (eCTD #1)
 - o Individual Patient Urinalysis Data Listing, Listing 16.2.8.1.3, Module 5.3.5.2 (eCTD #1)

I. Background: Proteinuria

The detection of protein by urine dipstick is accomplished thru a calorimetric reaction in which a tetrabromophenol indicator dye on the urine dipstick changes color due to a pH change from negatively charged amine groups on proteins, especially high molecular weight anionic proteins such as albumin that carry many such amine groups. A urine dipstick detects the concentration of protein, primarily albumin, in a urine sample based on a progressive change in color. The protein concentration may be detected as trace (15-30 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1000 mg/dL), or 4+ (> 1000 mg/dL). False positive tests for protein on urine dipstick can occur with concentrated urine specimens (e.g. high specific gravity), an alkaline urine sample (e.g. elevated urine pH), and contamination of the urine with antiseptic agents or iodinated radiocontrast agents.^{2,3} Due to the urine dipstick's reliance on measuring the concentration of proteins in the urine, urine dipstick positivity for protein which correlates best with a true elevation in urine protein is one in which there is ≥ 100 mg/dL

² Viteri B, Reid-Adam J. Hematuria and Proteinuria in Children. *Pediatr Rev.* 2018;39(12):573-587.

³ Morcos SK, el-Nahas AM, Brown P, Haylor J. Effect of iodinated water soluble contrast media on urinary protein assays. *BMJ.* 1992;305(6844):29.

(e.g. 2+) of protein in a concentrated urine specimen (e.g. specific gravity > 1.015) or ≥ 30 mg/dL (e.g. 1+) in a more dilute specimen (e.g. specific gravity is ≤ 1.015).⁴

Due to the inherent limitations in urine dipstick analysis of protein, detection of 1+ or greater protein by dipstick should prompt quantification of the protein in a urine sample to confirm “true” abnormal excretion of protein in the urine. This is normally accomplished by assaying a first morning urine sample for protein and creatinine concentrations in mg/dL and then calculating the urinary protein to creatinine ($U_{P/C}$) ratio. This is expressed as mg of urine protein per mg of creatinine. This quantification approximates the 24-hour urine protein excretion, in grams of protein with mild to moderate elevations.^{5,6} For instance, a $U_{P/C}$ of 1 is approximately equivalent to the excretion of 1 gram of protein in the urine per 24 hours. A $U_{P/C}$ of < 0.2 is considered normal in children older than 24 months of age with mature kidney function.⁷

Proteinuria may be classified as transient, orthostatic, or persistent. Transient proteinuria is often detected as 1+ or greater protein by urine dipstick on one occasion with subsequent detection of trace to negative protein on repeat urine dipstick testing. Transient proteinuria may occur after fever, exercise, stress, seizure, urinary tract infection or due to the presence of vaginal mucous.⁸ Orthostatic proteinuria is characterized by the presence of 1+ or greater protein by urine dipstick and an elevated $U_{P/C}$ when the patient is in an upright position that is not present in urine made when the patient is in a recumbent position.⁹ Orthostatic proteinuria is diagnosed by detection of a normal $U_{P/C}$ of < 0.2 in a first morning urine sample but the presence of an elevated $U_{P/C}$, generally between 0.2 and 1, in a mid-day urine. Both transient and orthostatic proteinuria are not associated with an increased risk of chronic kidney disease above that in the general population.¹⁰ On the other hand, persistent proteinuria may be the initial sign of underlying kidney disease which may be due to congenital or acquired etiologies.

⁴ Makihara N, Yamasaki M, Morita H, Yamada H. A dipstick test combined with urine specific gravity improved the accuracy of proteinuria determination in pregnancy screening. *Kobe J Med Sci*. 2011;56(4):E165-E172.

⁵ Houser M. Assessment of proteinuria using random urine samples. *J Pediatr*. 1984;104(6):845-848.

⁶ Chen YT, Hsu HJ, Hsu CK, et al. Correlation between spot and 24h proteinuria: Derivation and validation of equation to estimate daily proteinuria. *PLoS One*. 2019;14(4):e0214614.

⁷ Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). *Pediatrics*. 2000;105(6):1242–1249.

⁸ Hogg RJ. Adolescents with proteinuria and/or the nephrotic syndrome. *Adolesc Med Clin*. 2005;16(1):163-172

⁹ Ibid

¹⁰ Levitt JI. The prognostic significance of proteinuria in young college students. *Ann Intern Med*. 1967;66(4):685-696

Persistent proteinuria is characterized by the presence of a $U_{P/C}$ persistently greater than 0.2 in a first morning urine sample.

II. Brief Synopsis of the Protocol for Study KP415.S01

Study KP415.S01 is an ongoing multicenter, dose-optimization, open-label safety study of serdexmethylphenidate/d-methylphenidate (SDX/d-MPH) in patients between 6 and 13 years of age (inclusive) with attention-deficit/hyperactivity disorder (ADHD). The study is being conducted at 18 study sites within the U.S.

Eligible patients included those who successfully completed Study KP415.E01, a multicenter, double-blind, randomized, placebo-controlled parallel efficacy study and rolled-over to receive the 1st dose of SDX/d-MPH within 45 days of the last dose in this study or new patients who did not participate in Study KP415.E01 or completed the last dose from this study more than 45 days before the 1st dose for Study KP415.S01.

New patients underwent screening, dose-optimization, treatment, and follow-up phases of the study while patients who rolled-over from Study KP415.E01 underwent screening, treatment, and follow-up phases. The screening phase of the study lasted up to 30 days. The dose-optimization and treatment phases in which patients received SDX/d-MPH lasted up to 23 days and 380 days respectively. Patients were not eligible to participate if:

- 1) The patient had any clinically significant chronic medical condition that, in the judgment of the investigator, could interfere with their ability to participate in the study.
- 2) The patient had any clinically significant unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality, including the renal system, that may interfere with drug absorption, distribution, metabolism, or excretion of SDX/d-MPH.

However, a history of renal disease was not a pre-specified exclusion criterion for participation.

The study protocol included collection of a urinalysis (consisting of urine dipstick and urine microscopic evaluation) and clinical laboratory tests at screening, at approximately 6 months (Visit 11), and one year (Visit 17), but the protocol did not include parameters to fully assess for the presence of persistent proteinuria. Specifically, the study protocol did not require urine samples to be collected as first morning voids and did not contain any parameters for when urine protein and creatinine should be quantified based on the urine dipstick results. A urinalysis was also performed at the early termination visit if patients withdrew or were withdrawn from the study during the treatment phase. Clinical laboratory tests were performed with patients fasting, but the time of urine collection was neither pre-specified nor recorded on the case report forms. Urinalyses were performed at

a central lab and, if positive for blood, protein, and/or nitrites, a microscopic examination was performed.

III. KP415.S01 Study Safety Endpoint Results: Proteinuria

Study KP415.S01 enrolled 282 patients of whom 254 received treatment with SDX/d-MPH and 183 subsequently completed 12 months of treatment. The trial targeted enrollment of at least 250 patients with the projection that 200 patients would complete 12 months of treatment with SDX/d-MPH. Thirty-five percent (99/282) of patients prematurely discontinued before Visit 11 (e.g. end of treatment).

A total of 42 study patients had urine dipstick positivity of trace or greater for protein either at baseline or during the study period, but none of these patients underwent urine protein quantification at any point during the trial. The trial itself was designed to detect proteinuria only qualitatively by urinary dipstick with no plan for urine protein quantification to confirm the presence of true proteinuria based on positive urine dipstick test for protein.

- 15 patients had proteinuria at the baseline screening study visit prior to study medication exposure. All of these patients had 1+ protein on urine dipstick with all but one with a specific gravity ≥ 1.024 , suggesting that the possibility of a falsely positive urine dipstick for protein due to their concentrated urine sample that cannot be confirmed without quantification of urine protein in these samples. Of these patients, 4 continued to have 1+ proteinuria at subsequent study visits with all urinalyses having a specific gravity > 1.015 . One subject developed increasing proteinuria to 3+ at Visit 17 associated with leukocytes and bacteria in the urinalysis. This subject was a 9-year old female without a past medical history of kidney disease and was not taking concomitant medications known to be associated with the development of proteinuria.
- Twenty-seven patients with no baseline proteinuria developed protein $\geq 1+$ while on study treatment at study Visit 11, Visit 17, or at the early termination visit.
 - Ten patients developed proteinuria at study Visit 11 of whom 8 had 1+ protein and 2 had 2+ protein on the urinalysis. All urinalyses at study Visit 11 had specific gravities > 1.020 , again suggesting the possibility of a falsely positive urinalysis for protein due to their concentrated urine sample that cannot be confirmed without quantification of urine protein in these samples.
 - Two patients continued to have proteinuria at Visit 17. One patient had 1+ protein on a concentrated urine specimen with a specific gravity of 1.027 associated with hematuria and calcium oxalate crystals in the urine and the other patient had persistence of 2+ protein with bacteria noted in the urine. This patient was an 8-year

old female without a past medical history of kidney disease. She was receiving amoxicillin for a tooth abscess at the time of the initial discovery of proteinuria at Visit 11. At Visit 17, she was no longer on concomitant medications with persistence of 2+ protein on her urinalysis.

- o 17 patients developed protein $\geq 1+$ which was first noted at study Visit 17. All but 2 of these study patients had 1+ proteinuria on concentrated urine specimens with specific gravities ≥ 1.020 . Two patients developed 2+ protein on urinalysis. One patient was a 12-year old male with a prior chronic medical history of dyssomnia and asthma who had no protein on a dilute screening visit urine specimen (e.g., specific gravity of 1.007) and trace protein in the urine at Visit 11 visit. Along with the 2+ protein on a concentrated urine specimen (e.g. specific gravity of 1.035), he had spermatozoa present in the urine at Visit 17. He was not taking concomitant medications at the time of the Visit 17 urinalysis. The other patient was a 12-year old female with a prior chronic medical history of eczema, insomnia, and seasonal allergies but not renal disease. She was not taking concomitant medications at the time proteinuria was discovered at study Visit 17. She had bacteria and calcium oxalate crystals in the urine along with 2+ protein at that study visit. Her screening visit urinalysis was clear, and she had trace protein and large blood with confirmation of greater than 25 red blood cells per high powered field on urine microscopy in the urine at Visit 11.

IV. Summary and Conclusions:

Approximately 15% (42/282) of patients enrolled in Study KP415.S01 had urine dipstick positivity of 1+ or greater for protein at least once during the trial, and 2% (8/282) had persistent urine dipstick abnormalities for protein. No conclusions can be made with regards to the proteinuria detected in these patients because the trial itself was not designed to allow further assessment as to whether the proteinuria detected either at baseline or during the course of the trial was due to transient causes, orthostatic changes, or persistent.

Protein detected in the urinalyses in study KP415.S01 does not appear to be of clinical significance for the majority of patients with this finding. Neither active ingredient of SDX/d-MPH is known to be associated with the development of kidney injury nor proteinuria. The mechanism of action for this drug product does not target the kidneys or any components of the nephron that would suggest proteinuria is a drug-related safety concern. Ultimately, without repeated urine quantification of protein excretion on a 1st morning (e.g. recumbent) urine specimen, it is not possible to definitively exclude the

presence of persistent proteinuria for patients on study treatment. If proteinuria continues to be a potential concern for this drug product, future study protocols should include provisions for submitting 1st morning urine specimens for urinalysis with subsequent formal quantification of urine protein to creatinine ratios in the case of greater than “trace” results for protein detected by urine dipstick.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHAMIR TUCHMAN
12/17/2020 05:17:16 PM

MONA K KHURANA
12/18/2020 10:14:48 AM

JOHN J ALEXANDER
12/18/2020 11:32:17 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Use Review**

Date: October 23, 2020

Reviewer: Nilar Iorio, RPh
Drug Utilization Data Analyst
Division of Epidemiology II

Acting Team Lead: Tracy Pham, PharmD
Drug Utilization Team Lead (Acting)
Division of Epidemiology II

Deputy Division Director: Rajdeep Gill, PharmD
Deputy Division Director for Drug Utilization
Division of Epidemiology II

Subject: Outpatient Retail Utilization of Focalin XR and Generic
Dexmethylphenidate XR Products, Cotempla XR-ODT,
Jornay PM, and Quillivant XR

Drug Groups: Dexmethylphenidate (Focalin XR and generic)
Methylphenidate (Cotempla XR-ODT, Jornay PM, and
Quillivant XR)

Application Type/Number: NDA 212994

Applicant/sponsor: Commave Therapeutics SA

OSE RCM #: 2020-1185

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology. ****

CONTENTS

EXECUTIVE SUMMARY	1
1 INTRODUCTION	1
1.1 Background	1
1.2 Product Information	2
2 METHODS and MATERIALS.....	3
2.1 Data Sources.....	3
3 RESULTS	3
3.1 Primary Setting of Care - Manufacturer Sales Data.....	3
3.2 Patient data	3
4 DISCUSSION	4
5 CONCLUSION.....	5
6 APPENDICES	6
6.1 APPENDIX A: Tables	6
6.2 APPENDIX B: Drug Use Database Descriptions	11

EXECUTIVE SUMMARY

This review from DEPI II (Division of Epidemiology II) provides annual drug use trends for the selected extended-release/long-acting (ER/LA) stimulants (Focalin XR and generic dexamethylphenidate XR products, Cotempla XR-ODT, Jornay PM, and Quillivant XR) in children and adults from 2016 through 2019. The drug use data will assist OCP (Office of Clinical Pharmacology) in their assessment on the approvability of a new drug application (NDA) 212994 (b)(4) (dexamethylphenidate and serdexmethylphenidate) for the proposed indication for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older.

We examined U.S. outpatient pharmacy claims data for the selected ER/LA stimulants from 2016-2019, annually. In 2019, an estimated total of (b)(4) patients received prescriptions dispensed for the selected ER/LA stimulants. Of these patients, (b)(4)% received prescriptions dispensed for Focalin XR and generic dexamethylphenidate XR products. The majority of use of the selected ER/LA stimulants were in patients ages 6-11 years, followed by 12-16 years and 17-64 years. The most commonly dispensed drug strengths among these three patient age groups were 10mg of Focalin XR or generic dexamethylphenidate XR products, Cotempla ODT-XR 17.3 mg, and Jornay PM 20 mg.

1 INTRODUCTION

OCP (Office of Clinical Pharmacology) is evaluating a new drug application (NDA) 212994 (b)(4) (dexamethylphenidate and serdexmethylphenidate) with a proposed indication for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older. Hence, OCP requested DEPI II (Division of Epidemiology II) to provide annual drug use trends for the selected extended release/long acting (ER/LA) stimulants (Focalin XR and generic dexamethylphenidate XR products, Cotempla XR-ODT, Jornay PM, and Quillivant XR) in children and adults from 2016 through 2019. The drug use data will assist OCP in understanding the extent of use of the selected ER/LA stimulants currently marketed in U.S., and serve as a background for their assessment on the approvability of this NDA for the proposed indication.

1.1 BACKGROUND

Commave Therapeutics SA submitted and requested approval of a new drug application (NDA) 212994 (b)(4), an oral, once-daily, extended-release product that contains dexamethylphenidate (d-MPH) and serdexmethylphenidate (SDX). The proposed indication is for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older. The proposed dosage formulations are capsules containing 28/6mg, 42/9mg, and 56/12mg of SDX and d-MPH, respectively, in which the Applicant claims to correspond to total molar equivalent doses of 20mg, 30mg, and 40mg of d-MPH, respectively.

Dexamethylphenidate and methylphenidate (MPH) products are approved for use in pediatric patients six years and older for ADHD. These products are usually prescribed in a wide dose range to treat ADHD and patients in different age groups may need different

doses to obtain optimal responses. Hence, OCP (Office of Clinical Pharmacology) requested drug utilization data for the selected ER/LA stimulants to assist in determining the approvability of (b) (4) for the proposed indication for the treatment of ADHD in patients 6 years and older.

1.2 PRODUCT INFORMATION

Molecule and Trade Name	NDA Approval Date	Dosage Form and available strengths	FDA-Labeled Indications <i>Pediatric Information</i>
Dexmethylphenidate			
Focalin XR and generics	NDA 021802 May 26, 2005	Extended-release oral capsule 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg	➤ Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged six years and older. ➤ https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021802lbl.pdf
Methylphenidate			
Cotempla XR-ODT	NDA 205489 June 19, 2017	Extended-release orally disintegrating tablet 8.6mg, 17.3mg, 25.9mg	➤ Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age ➤ https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205489s000lbl.pdf
Methylphenidate			
Jornay PM	NDA 209311 August 8, 2018	Extended-release oral capsule 20mg, 40mg, 60mg, 80mg, 100mg	➤ Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older ➤ https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209311s000lbl.pdf
Quillivant XR	NDA 202100 September 27, 2012	Extended-release oral suspension 5mg/ml	➤ Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) ➤ https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202100lbl.pdf

Prescribing Information obtained from U.S. Food and Drug Administration: Drugs@FDA. Accessed October 2020. Available at www.accessdata.fda.gov/scripts/cder/drugsatfda			

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these concurrency analyses. Detailed descriptions and limitations of the databases are included in Appendix B.

2.1 DATA SOURCES

We used the IQVIA, National Sales Perspectives™ (NSP) database to determine the primary setting of care based on the volume of Focalin XR and generic dexamethylphenidate XR products, Cotempla XR-ODT, Jornay PM, and Quillivant XR products sold from manufacturers to the various U.S. channels of distribution in 2019.

We used the Symphony Health, Metys™ database to obtain the annual estimated number of unique patients who received dispensed prescriptions for Focalin XR or generic dexamethylphenidate XR products, Cotempla XR-ODT, Jornay PM, or Quillivant XR from U.S. outpatient retail pharmacies, stratified by product, drug strength and patient age groups (0-1, 2-5, 6-11, 12-16, 17-64, and 65+ years) from 2016 through 2019.

3 RESULTS

3.1 PRIMARY SETTING OF CARE - MANUFACTURER SALES DATA

In 2019, sales data showed approximately (b) (4) % of total bottles of Focalin XR and generic dexamethylphenidate XR products, Cotempla XR-ODT, Jornay PM, and Quillivant XR were distributed to the outpatient retail pharmacies.^a As a result, only outpatient retail pharmacy utilization patterns were examined for these products in this review.

3.2 PATIENT DATA

Tables 1-5 in Appendix A provide the estimated number of patients who received dispensed prescriptions for the selected ER/LA stimulants (Focalin XR and generic dexamethylphenidate XR products, Quillivant XR, Cotempla XR-ODT, and Jornay PM) from U.S. outpatient retail pharmacies, from 2016 through 2019, yearly.

In 2019, an estimated total of (b) (4) received dispensed prescriptions for the selected ER/LA stimulants. Of these patients, Focalin XR and generic dexamethylphenidate XR products accounted for (b) (4) % (b) (4) followed by Quillivant XR at (b) (4) % (b) (4) Cotempla XR-ODT at (b) (4) % (b) (4) and

^a IQVIA National Sales Perspectives™, 2019. Data Extracted October 2020. File: NSP MPH ER_LA products 2019.xlsx

Jornay PM at (b) (4)% (b) (4)). The number of patients with dispensed prescriptions for Focalin XR or generic dexamethylphenidate XR products increased approximately (b) (4)% from (b) (4) in 2016 to (b) (4) in 2019. Meanwhile, utilization of Quillivant XR decreased by (b) (4)% from (b) (4) in 2016 to (b) (4) in 2019. (**Table 1** in Appendix A).

Throughout the study time-period, the highest proportion of use of the selected ER/LA stimulants was among patients ages 6-11 years, 12-16 years, and 17-64 years. The use of the selected ER/LA stimulants in patients ages younger than 6 years, and 65 years and older was infrequent. In 2019, most of patients receiving dispensed prescriptions for Focalin XR or generic dexamethylphenidate XR products were ages 6-11 years (b) (4), followed by 12-16 years (b) (4) and 17-64 years (b) (4). During the same year, most of patients receiving dispensed prescriptions for Cotempla XR-ODT were ages 6-11 years (b) (4), followed by 12-16 years (b) (4) and 17-64 years (b) (4). Similarly, most patients receiving dispensed prescriptions for Jornay PM in 2019 were ages 6-11 years (b) (4), followed by 12-16 years (b) (4) and 17-64 years (b) (4). Furthermore, most patients receiving dispensed prescriptions for Quillivant XR in 2019 were ages 6-11 years (b) (4), followed by 12-16 years (b) (4).

Among patients who received prescriptions dispensed for Focalin XR or generic dexamethylphenidate XR products in 2019, the 10mg (b) (4), 5mg (b) (4), and 15mg (b) (4) capsules accounted for the highest proportion of patients ages 6-11 years, respectively. Meanwhile, the 20mg (b) (4), 10mg (b) (4) and 15mg (b) (4) capsules accounted for the highest proportion of patients ages 12-16 years and 17-64 years, respectively. (**Table 2** in Appendix A).

Among patients who received prescriptions dispensed for Jornay PM in 2019, the 20mg (b) (4) followed by 40mg (b) (4) and 60mg (b) (4) capsules accounted for the highest proportion of patients ages 6-11 years, 12-16 years, and 17-64 years, respectively. (**Table 3** in Appendix A). Among patients who received prescriptions dispensed for Cotempla XR-ODT in 2019, the most frequently dispensed drug strength to patients ages 6-11 years (b) (4), 12-16 years (b) (4), and 17-64 years (b) (4) was 17.3mg. (**Table 4** in Appendix A).

4 DISCUSSION

This review provides drug utilization trends for the selected ER/LA stimulants to further assist OCP with their assessment on the approvability of NDA 212994 (b) (4). The selected ER/LA stimulants are Focalin XR and generic dexamethylphenidate XR products, Jornay PM, Quillivant XR, and Cotempla XR-ODT.

Analysis of U.S. outpatient retail pharmacy claim data from 2016 through 2019 suggest the most widely used products among the selected ER/LA stimulants were Focalin XR and generic dexamethylphenidate XR products (b) (4). Moreover, the selected ER/LA stimulants were most widely used among patient ages 6-11 years, followed by 12-16 years and 17-64 years during the examined period. The use of the selected ER/LA stimulants among patients ages younger than 6 years, and 65 years and older was very low throughout the review period.

Prescription claim data indicate that Focalin XR and generic dexamethylphenidate XR 10mg capsules were mostly used in patients ages 6-11 years whereas 20mg capsules were mostly used in patients 12-16 years and 17-64 years. Additionally, Jornay PM 20mg capsules and Cotempla XR-ODT 17.3mg tablets were most commonly used among these three age groups.

The drug utilization findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that selected ER/LA stimulants were distributed primarily in the outpatient retail pharmacy settings, based on the IQVIA™ National Sales Perspectives database. As such, we focused our analyses on utilization data generated from outpatient retail pharmacy prescription claims. Therefore, these estimates may not apply to other settings of care in which these products are used, such as hospitals, physician offices, clinics, mail-order or specialty pharmacies.

The patient estimates are nationally projected based on a sample of prescriptions claims from outpatient retail pharmacies, and should be interpreted with caution, particularly for the pediatric population as they are based on a small sample size. Certain estimates may be a result of errors; however, medical charts were not available for validation. Summarization of the projected estimates across patient age groups, time periods, and/or products may lead to differences in patient counts due to rounding attributable to the projection methodology utilized. Moreover, summarization of patient estimates across patient age groups, time periods, and/or products may double count patients due to patients aging or switching products during the study period. No statistical tests were performed on these estimates to determine statistically significant changes over time.

5 CONCLUSION

Outpatient retail pharmacy claims data show that among the selected ER/LA stimulants, Focalin XR and generic dexamethylphenidate products were the most widely used products during the review period. The majority of use of the selected ER/LA stimulants were in patients ages 6-11 years, followed by 12-16 years and 17-64 years. The most commonly dispensed strengths among these three patient age groups were 10mg of Focalin XR or generic dexamethylphenidate XR products, Cotempla ODT-XR 17.3 mg, and Jornay PM 20 mg.

5 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives (NSP) is the industry standard for measuring pharmaceutical spending because it captures ~90% of the total pharmaceutical market in the United States. NSP measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are estimated based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. NSP reports sales from 388 indirect suppliers and direct sales reported from ~100 manufacturers. IQVIA processes ~1.5 billion transactions per year. The universe for the retail channel consists of chain pharmacies, food stores with pharmacies, mail service pharmacies, mass merchandisers and independent pharmacies. The universe for the non-retail channel consists of non-federal hospitals, clinics, federal facilities, HMOs, long-term care (LTC) facilities, home healthcare, prisons and universities. NSP captures ~86% of the sales within the retail channel and ~97% of the sales within the non-retail channel.

Metys™ from Symphony Health

Metys™ is the only completely integrated solution in the market that is specifically engineered for pharmaceutical market measurement. Powered by IDV® (Integrated Dataverse), Metys is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data along with non-retail invoice activity and is accessible through one single access point -- all while delivering insights faster than any other tool in the industry.

The dispensed prescriptions in the sample represent approximately 93% of all U.S. retail prescriptions (cash, Medicaid, commercial), 72% of all U.S. mail order prescriptions and 50% of all U.S. Long Term Care prescriptions. The retail, mail order and long-term care prescriptions are projected to the national level. The database has over 280 million unique patients with an average of 5 years of prescription drug history. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NILAR Z IORIO
10/28/2020 09:23:04 AM

TRACY M PHAM
10/28/2020 09:44:48 AM

RAJDEEP K GILL
10/28/2020 10:09:49 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 212994
Submission Number	001
Submission Date	3/2/2020
Date Consult Received	3/17/2020
Drug Name	(b) (4) (serdexmethylphenidate chloride [SDX Cl]) and dexmethylphenidate hydrochloride
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older
Therapeutic dose	Recommended starting dose for patients 6 years and older is (b) (4) (base equivalent) once daily (QD) in the morning, with or without food. Dosage may be increased weekly in increments of 13/2.6 mg per day. Daily dosage above (b) (4)/10.4 mg is not recommended.
Clinical Division	DP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 3/17/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 130463 ([link](#)) dated 07/16/2019 in DARRTS;
- [Waiver justification](#) (IND 130463, Submission 0059);
- [Study KP415-A02 report](#) (Submission 0001);
- [QT evaluation report](#) (Submission 0001);
- Sponsor's [response](#) to Information Request (Submission 0003);
- [Proposed label](#) (Submission 0001);
- [Highlights of clinical pharmacology and cardiac safety](#) (IND 130463, Submission 0059)

1 SUMMARY

No significant QTc prolongation effect of serdexmethylphenidate chloride (SDX Cl) was detected in this QT assessment.

The effect of SDX Cl was evaluated in study KP415.A02, a randomized, double-blind, 3-treatment, crossover, human abuse potential study comparing 80 mg SDX Cl, 40 mg d-MPH HCl, and placebo after intranasal administration in 46 healthy subjects. The 80 mg dose of SDX Cl provides more than 40-fold exposure margin for the therapeutic dose of (b) (4) (b) (4)/10.4 mg base equivalent, QD oral) and therefore supports waiving the requirement for a positive control per ICH E14 Q&A (R3) 5.1. The data were analyzed

using exposure-response analysis as the primary analysis, which did not suggest that SDX Cl is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2), by-time analysis (section 4.3), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)
QTcF	(b) (4) (b) (4)/10.4 mg base, QD)	41.7	0.6	(-1.7, 3.0)

Study KP415.A02 does not include ECGs at Tmax (around 0.3 hours) or at 24 hours postdose to detect potential delayed effect. Despite this limitation in the ECG recording schedule, the data from this study are interpretable for the following reasons:

- 1) ECG were collected at 1 hour post-dosing where the mean (90% CI) $\Delta\Delta\text{QTc}$ was 0.9 msec (90% CI: -2.5 to 4.3 msec) (reviewer's by time point analysis). At this time point the mean concentrations of SDX Cl was 1745 ng/mL which provides a 42-fold exposure margin of the therapeutic exposure of (b) (4).
- 2) Based on the sponsor's analysis, in studies that included a SDX Cl dose at or above the maximum recommended dose and included an ECG measurement at 24-hour postdose in ≥ 20 subjects, the mean of ΔQTcF at 24-hour postdose ranged from 0.66–7.7 msec and the standard deviation ranged from 7-11 msec (KP415.104, KP415.107, and KP415.110). These data do not appear to suggest a delayed effect on the QTc interval.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

This review focuses on the effect of SDX Cl on the QTc interval. This review is not intended to evaluate the effect of MPH on the QTc interval.

- Systemic exposure of MPH after repeated dosing of SDX Cl / d-MPH hydrochloride capsule (KP415 capsule) was reported to be 20.0 ng/mL at the highest recommended dose. The exposure of MPH is not higher than that with Focalin XR, and is covered in a previous TQT study for Focalin XR.
- In the TQT study, clinically relevant QT prolonging effect was not detected after a single dose of Focalin XR at 40 mg dose level and there was no evident-exposure response relationship.
- In the 40 mg d-MPH HCl treatment arm in Study KP415.A02, the arithmetic mean (SD) concentration of MPH was 42.3 (16.3) ng/mL, 36.6 (9.5) ng/mL, and 15.6 (5.5) ng/mL at 1, 4, and 8 hours postdose, respectively. This treatment arm provided coverage of the therapeutic exposure of MPH for KP415 capsule in the current application. However, the study design and the exposure margin are not adequate to detect potential delayed effect or to support an evaluation of MPH effect at the highest clinically relevant exposure.

- Because the overall findings are consistent with previous QT assessment of MPH and because there is no additional data to supplement the previous QT assessment of MPH, we do not propose QT language related to MPH in the proposed product label.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the proposed label in Submission 0001. We proposed the following language for the Division's consideration.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of serdexmethylphenidate on QTc interval was evaluated in a randomized, double-blind, placebo-controlled, human abuse potential study (intranasal administration) in 46 healthy subjects. At a mean concentration 40 times the C_{max} for the highest dose of (b) (4) (b) (4)/10.4 mg base equivalent), serdexmethylphenidate does not prolong the QT interval to any clinically relevant extent.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Serdexmethylphenidate is a prodrug of d-threo-methylphenidate (d-MPH). The sponsor is developing SDX Cl / d-MPH hydroxychloride capsule (KP415 capsules) for the treatment of ADHD in patients 6 years and older. The sponsor is seeking approval under the 505(b)(2) route relying in part on Focalin XR (NDA 021802).

After oral administration, SDX is rapidly converted to MPH with a T_{max} about 1.5-2 hrs and T_{1/2} of 4.8 hours. There is minimal accumulation with repeated daily dosing. SDX is not a substrate of CYP450 enzymes or major transporters. Renal impairment or hepatic impairment is not expected to increase SDX PK. Food decreases SDX exposure. The highest study-mean SDX C_{max} across all pharmacokinetic studies was 46.5 ng/mL (observed in Study KP415.110); this value is referenced as the highest exposure scenario in this QT assessment.

Previously the IRT reviewed the sponsor's request to waive a thorough QT study based on nonclinical and clinical cardiac safety data, as well as a QT assessment using data cross multiple clinical trials, focusing on a concentration-QTc analysis based on study KP415.A02. Even though ECG quality in study KP415.A02 was not ideal for QT assessment, the study provided a large exposure margin (approximately 40-fold) for the therapeutic exposure of SDX at the maximum recommended dose of KP415 capsules ((b) (4)/10.4 mg base equivalent). Therefore, the IRT recommended the sponsor to submit

the QT assessment report for review. Whether the data would be adequate to exclude a small mean effect on the QTc interval was considered a review issue.

In the current submission, the sponsor provided the QT assessment report based on nonclinical data with SDX, and clinical studies with SDX Cl or SDX/d-MPH. The primary analysis is concentration-QTc modeling of $\Delta QTcF$ using data from KP415.A02. Study KP415.A02 is a Phase 1, randomized, double-blind, 3-treatment, crossover, human abuse potential study comparing 80 mg SDX Cl, 40 mg d-MPH HCl, and placebo after intranasal administration in 46 healthy subjects. Singular 12-lead ECGs were measured at pre-dose, and at 1 h and 8 h post-dose. An ECG measurement was saved at 4 h postdose at the end of the protocol-specified continuous cardiac telemetry. All ECG data were derived from automatic measurements. The sponsor also provided descriptive statistics of the ECG parameters and conducted outlier analysis across 15 clinical trials.

3.1.2 Nonclinical Safety Pharmacology Assessments

HEK293 cells expressing the hERG potassium channel were dispensed onto chips and hERG tail currents were measured by whole cell voltage clamping in Study CYP1555-R3. The highest concentration of SDX tested in vitro (25 μM) represents a more than 300-fold exposure margin over the mean SDX C_{max} observed (41.7 ng/mL) at steady state in humans receiving the maximum recommended therapeutic dose (56 mg SDX Cl per day; Study KP415.110). The maximum % inhibition was 2.8% at 25 μM .

The oral administration of SDX Cl (10, 20 or 40/30 mg/kg) or d-MPH HCl (10 mg/kg) for 28 days did not have any biologically relevant effects on cardiac rhythm, ECG morphology and quantitative ECG variables (including QTc interval) in conscious male or female telemetered dogs, at daily SDX AUC exposure up to 24x the daily AUC exposure after oral administration of the highest clinical dose in humans.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis was based on exposure-response analysis. Please see section 3.2.3 for additional details.

The sponsor presented summary statistics such as mean, SD, minimum, median and maximum for each time points without confidence intervals in $\Delta QTcF$ across clinical studies with SDX or SDX/d-MPH ([link](#)). No large $\Delta QTcF$ increase was observed in those studies at 24-hour post-dosing timepoint.

FDA reviewer used Mixed Effect Model Repeat Measurement (MMRM) to analyze the $\Delta QTcF$ only in study KP415.A02. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

Reviewer's comment: All ECG measurements in study KP415.A02 were automatic, which removes concerns for measurement bias.

3.2.2 Categorical Analysis

The sponsor presented outlier tables on QTcF and Δ QTcF across clinical studies with SDX Cl or SDX/d-MPH ([link](#)). 1 subject treated with 56 mg SDX Cl + 12 mg d-MPH HCl in KP415.109 had QTcF > 500 msec. 1 subject treated with 56 mg SDX Cl + 12 mg d-MPH HCl in KP415.109 and 1 subject treated with SDX/d-MPH in KP415.S01 had Δ QTcF > 60 msec.

Reviewer's comment: FDA reviewer performed categorical analysis for HR, PR and QRS for study KP415.A02 study only. Please see section 4.4 for additional details.

3.2.3 Exposure-Response Analysis

The relationship between Δ QTcF and the plasma concentration of SDX was modelled with a repeated-measures linear mixed effect model (LME, Proc Mixed in SAS). The dependent variable in the model was Δ QTcF. The model has a random intercept effect within-subject and an unconstructed variance between period. The fixed effect parameters were SDX concentration effect (slope), baseline (centered baseline effect), treatment (SDX=1 or placebo=0), and time post-dose (1, 4, and 8 h). An unstructured variance between period accounted for the design element of subjects having multiple records per period.

Most fixed effects in the linear model, including the slope and intercept, were not statistically significant at $\alpha=0.1$. The model predicted Δ QTcF was 0.236 msec (90% CI: -2.88 to 3.35 msec) at 46.5 ng/mL (highest exposure scenario defined in this QT assessment) and 2.039 msec (90% CI: -2.28 to 6.35 msec) at 3005 ng/mL (overall C_{max} in study KP415.A02).

Reviewer's comment: The reviewer's analysis results are similar to the sponsor's results.

3.2.4 Cardiac Safety Analysis

Of the 49 subjects who were randomized in the Treatment Phase, 45 subjects completed all treatment periods and each subject received single IN doses of 80 mg SDX Cl prodrug API, 40 mg d-MPH API, and placebo.

No deaths or SAEs occurred during the study. One subject (Subject (b) (6)) discontinued from the study due to mild AEs of anxiety and claustrophobia.

The incidence of cardiac disorders was notably higher with administration of d-MPH (42%) relative to SDX Cl prodrug API (4.3%) and placebo (2.1%). Palpitations (23.9%), sinus tachycardia (15.2%), tachycardia (17.4%), and ventricular extrasystoles (4.3%) occurred in at least 2 subjects after IN d-MPH API. These TEAEs were not observed following IN SDX Cl prodrug API except for palpitations, which occurred in 4.3% of subjects.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. $|\text{mean}| < 10$ bpm) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Paper ECGs were submitted.

4.2.2 QT Bias Assessment

Not applicable. All ECG measurements in study KP415.A02 were automatic.

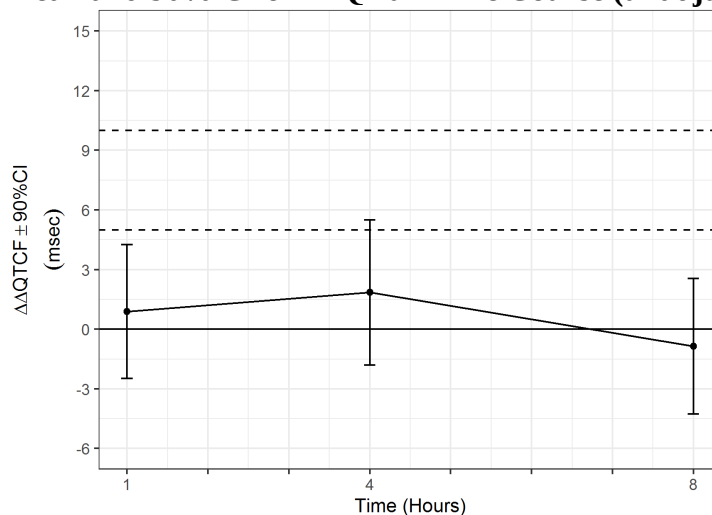
4.3 BY TIME ANALYSIS

This reviewer used Mixed Effect Model Repeat Measurement (MMRM) to analyze the ΔQTcF based on 80 mg SDX Cl and placebo data from KP415.A02 study. The model includes treatment, sequence, time, and time and treatment interaction as fixed effect, and baseline values as a covariate. All figures display times at 1 h, 4 h and 8 h post-dose.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for SDX Cl 80 mg.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time Course (unadjusted CIs).



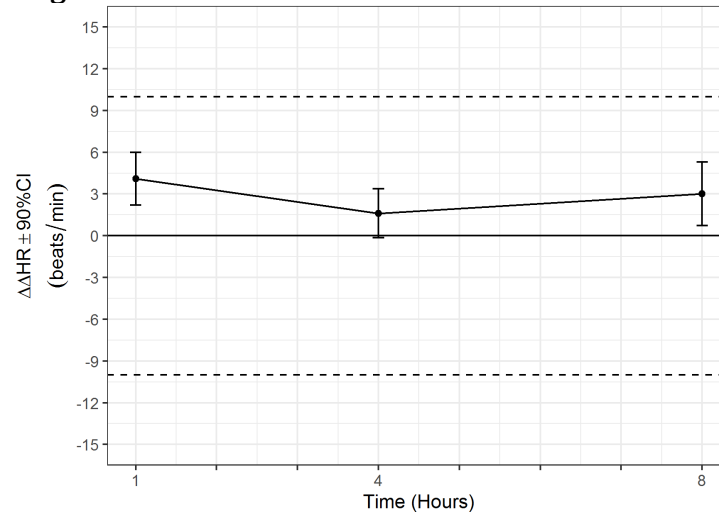
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for SDX Cl 80 mg.

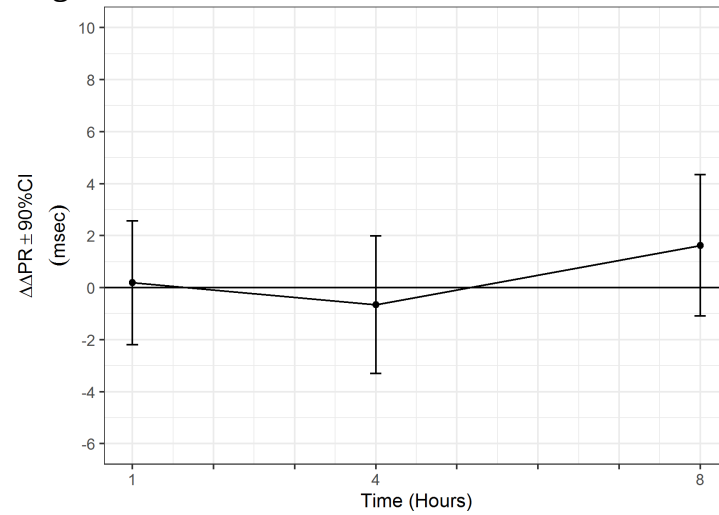
Figure 2: Mean and 90% CI of $\Delta\Delta\text{HR}$ Time Course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ for SDX CI 80 mg.

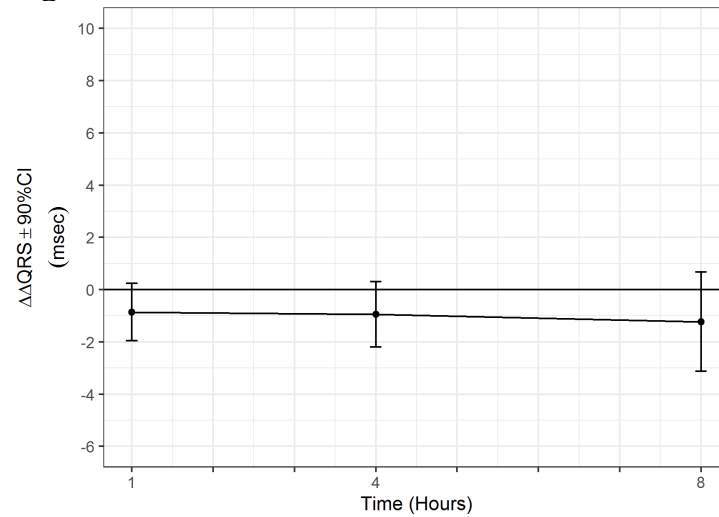
Figure 3: Mean and 90% CI of $\Delta\Delta\text{PR}$ Time Course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta\text{QRS}$ for SDX CI 80 mg.

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis were performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs in study KP415.A02.

4.4.1 QTc

No subject had QTcF > 450 msec nor Δ QTcF > 60 msec.

4.4.2 HR

No subject had HR > 100 beat/min.

4.4.3 PR

None of the subjects experienced PR > 220 msec with > 25% increase over baseline in SDX Cl 80 group.

4.4.4 QRS

None of the subjects experienced QRS > 120 msec with > 25% increase over baseline in SDX chloride 80 group.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK in study KP415.A02 study.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and $\Delta\Delta$ QTc and 3) presence of non-linear relationship.

Figure 2 shows the time-course of $\Delta\Delta\text{HR}$, which shows an absence of significant $\Delta\Delta\text{HR}$ changes. Figure 5 evaluates the time-course of drug-concentration and $\Delta\Delta\text{QTc}$. Systemic exposure of SDX decrease by approximately 8-fold from 1-8 hours postdose, but there is no apparent change in the time course of $\Delta\Delta\text{QTc}$. Because ECG sampling schedule does not capture maximum drug exposure after the intranasal dosing (median T_{max} : 0.29 hrs; range: 0.267-0.8 hrs), we cannot detect the presence of hysteresis. That being said, considering that SDX concentration at 1 hr postdose and 4 hr postdose are 40-fold and 10-fold higher than the maximum concentration after oral administration, it is unlikely that dose-dependent or exposure-dependent QTc effect would be undetected. Figure 6 shows the relationship between SDX concentration and ΔQTc and supports the use of a linear model.

Figure 5: Time course of SDX concentration (top) and QTc (bottom)

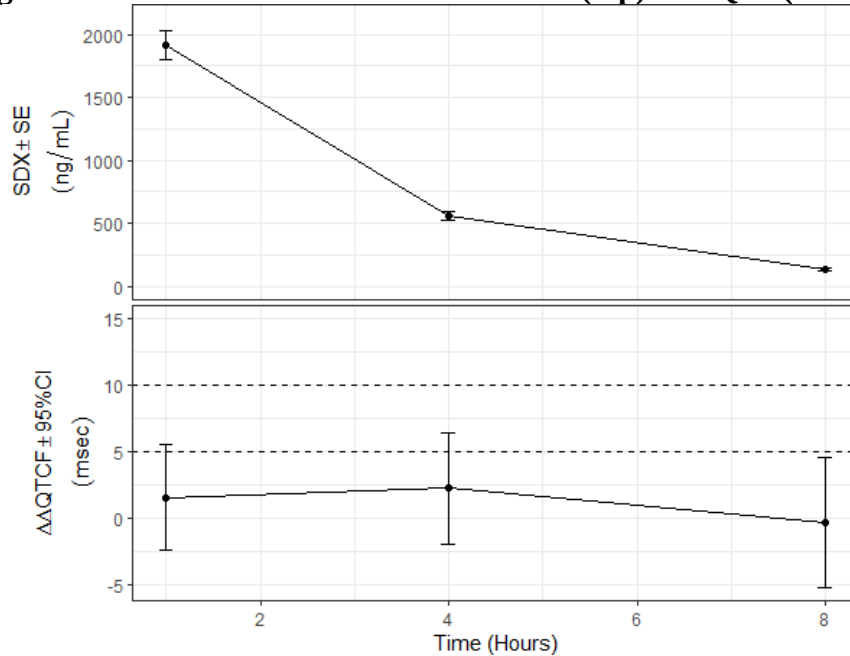
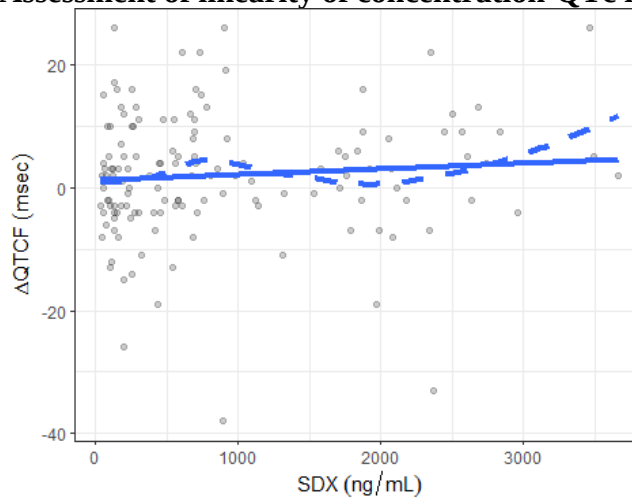
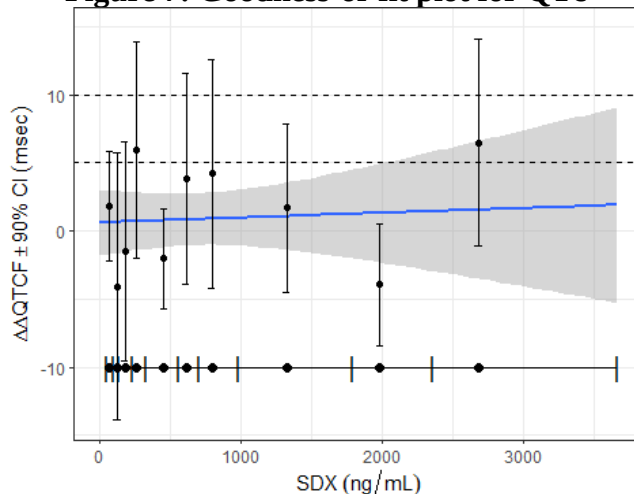


Figure 6: Assessment of linearity of concentration- QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. The data does not suggest a significant exposure-response relationship within the studied concentration range. Predictions from the concentration-QTc model are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc



We derived similar conclusions in a sensitivity analysis based on 1-hour and 8-hour postdose data only.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAN ZHENG
05/21/2020 08:46:40 AM

MOH JEE NG
05/21/2020 09:43:15 AM

FERDOUSE BEGUM
05/21/2020 09:46:32 AM

DALONG HUANG
05/21/2020 09:47:25 AM

MICHAEL Y LI
05/21/2020 09:55:39 AM

LARS JOHANNESSEN
05/21/2020 09:58:32 AM

CHRISTINE E GARNETT
05/21/2020 10:25:05 AM