NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NME NDA
Application Number(s)	NDA 212994
Priority or Standard	Standard
Submit Date(s)	03/02/2020
Received Date(s)	03/02/2020
PDUFA Goal Date	03/02/2021
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience
Review Completion Date	03/02/2021
Established/Proper Name	Serdexmethylphenidate chloride (SDX Cl) & Dexmethylphenidate hydrochloride (d-MPH HCL)
(Proposed) Trade Name	Azstarys
Pharmacologic Class	Stimulant (Drugs for Minimal Brain Dysfunction)
Code name	N/A
Applicant	Commave Therapeutics SA
Dosage form	26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg (expressed as SDX/d-MPH free base) capsules (for reference, in parts of this review and others, sometimes the doses are also expressed in chloride salt form as 28/6 mg; 42/9 mg; and 56/12 mg respectively)
Applicant proposed Dosing Regimen	26.1 mg/5.2 mg once daily in the morning. The dose may be increased weekly in increments of 13.1 mg/2.6 mg per day to a maximum of 52.3 mg/10.4 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in patients ages 6 years and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	406506008
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of ADHD in patients ages 6 to 12 years
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	406506008
Recommended Dosing Regimen	26.1/5.2 mg once daily in the morning, may be increased weekly in increments of 13.1/2.6 mg per day with a maximum of 52.3/10.4 mg

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DEPI=Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

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Glossary

ADHD	Attention-Deficit/Hyperactivity Disorder
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
d-MPH	dexmethylphenidate
DP	Division of Psychiatry
DPT-N	Division of Pharmacology/Toxicology for Neuroscience
DPMH	Division of Pediatrics and Maternal Health
DSM-5	Diagnostic and Statistical Manual (5^{th} edition)
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ITT	intent to treat
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRHD	maximum recommended human dose
MTD	maximum tolerated dose
NDA	new drug application
NME	new molecular entity
NOAEL	no adverse effect level
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act

PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDX	serdexmethylphenidate
TEAE	treatment emergent adverse event
TK	toxicokinetics

1 Executive Summary

1.1. Product Introduction

KP415 is a combination drug product consisting of two components: 1) serdexmethylpenidate (SDX), which is an inactive prodrug of dexmethylphenidate (d-MPH), and 2) immediate-release d-MPH. SDX is converted to d-MPH in the gastrointestinal tract, a process which gradually produces d-MPH in the systemic circulation, with peak concentrations approximately 8 hours after ingestion. The immediate-release d-MPH component produces therapeutic blood levels of d-MPH during the first few hours after administration.

Dexmethylphenidate is the d-isomer of racemic d,l-methylphenidate. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of the monoamines into the extraneuronal space, with the d-isomer being more pharmacologically active than the l-isomer. Methylphenidate was first FDA-approved for the treatment of ADHD in 1955 and it, or its d-isomer, is the active ingredient in several currently marketed products for the treatment of patients with ADHD.

KP415 capsules are available in three strengths (expressed in mg of free base):

1. 26.1 mg SDX/5.2 mg d-MPH (equivalent to 28/6 mg as a salt and a total d-MPH dose of 20 mg).
2. 39.2 mg SDX/7.8 mg d-MPH (equivalent to 42/9 mg as a salt and a total d-MPH dose of 30 mg).
3. 52.3 mg SDX/10.4 mg d-MPH (equivalent to 56/12 mg as a salt and a total d-MPH dose of 40 mg).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The conclusion on efficacy of KP415 relies on: 1) the established efficacy of the Listed Drug (LD), Focalin XR; 2) the pharmacokinetic (PK) bridge to the LD, demonstrated by Studies KP 415.105, KP415.107 and KP415.110; and 3) the demonstration of efficacy in children, ages 6 to 12 years, in Study KP415.E01. These data are sufficient to support a claim for the treatment of patients, 6 years of age and older, with ADHD.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

KP415 is a combination stimulant-class drug product consisting of two components: 1) serdexmethylpenidate (SDX), which is an inactive prodrug of dexmethylphenidate (d-MPH), and 2) immediate-release d-MPH. SDX is converted to d-MPH in the gastrointestinal tract and then eventually in the systemic circulation. The immediate-release d-MPH component produces therapeutic blood levels of d-MPH during the first few hours after administration. While various formulations of methylphenidate have been marketed in the United States since 1955 for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), for regulatory purposes FDA considers KP415 a combination product with a new molecular entity (NME) for the SDX portion in combination with the d-MPH IR portion. The d-MPH IR portion is relying upon 505(b)(2) bridging with the listed drug Focalin XR (NDA 021802, approved in 2005) which is a bimodal-release version of d-MPH. The Applicant plans to market three strengths of KP415 (26.1/5.2, 39.2/7.8, 52.3/10.4 mg) equivalent to a total d-MPH dose of 20, 30, and 40 mg respectively.

The Applicant conducted one new pediatric efficacy and safety study (KP415.E01) for this NDA submission utilizing a double-blind, dose-optimized, randomized lab classroom design in 150 patients (74 on KP415 and 76 on placebo) ages 6 to 12 with a 3-week open-label treatment period and 1-week placebo-controlled double-blind phase with lab classroom comparison only on Day 28. The efficacy of KP415 relies on: 1) the established efficacy of the Listed Drug (LD), Focalin XR; 2) the pharmacokinetic (PK) bridge to the LD, demonstrated by Studies KP415.105, KP415.107, and KP415.110; and 3) the demonstration of efficacy in children, ages 6 to 12, in Study KP415.E01. These data are sufficient to support a claim for the treatment of patients, age 6 years and older, with ADHD. There was also an open-label long-term (12-month) pediatric safety study KP415.S01 as an extension from Study KP415.E01 and additional safety data from other phase 1 studies.

Together with PK bridging to the LD, we agree that statistically significant results on an established endpoint (the SKAMP) in one novel study (KP415.E01) is sufficient to establish the efficacy of KP415 for the treatment of ADHD in patients age 6 years and older. There were disagreements with the Applicant on which statistical analysis to include [redacted] (b) (4); the Applicant preferred a post-hoc analysis utilizing a new baseline timepoint (morning of Day 28 instead of Day 21) that our team felt would not be as scientifically sound as the original prespecified one and potentially misrepresented the drug's effects relative to placebo. [redacted] (b) (4) [redacted] (b) (4). The effective daily doses in children were 39.2 mg SDX/7.8 mg d-MPH and 52.3 mg SDX/10.4 mg d-MPH (with more than half requiring the higher dose), and the maximum dose the Applicant has proposed for KP415 labeling is 52.3 mg SDX/10.4 mg d-MPH. Extrapolation of efficacy to adolescents and adults is based on the finding of equal or higher d-MPH concentrations, consistently at all time points, after KP415 52.3 mg SDX/10.4 mg d-MPH/day at steady state compared to single dose Focalin XR 20 mg in adults. Downward extrapolation from adults to adolescents is reasonable based on the similarity of d-MPH PK between adults and adolescents. Because evidence

of efficacy in adults and adolescents at KP415 dosages of 26.1 mg SDX/5.2 mg d-MPH and 39.2 mg SDX/7.8 mg d-MPH/day is not available, the recommended daily dose for adolescents and adults is 52.3 mg SDX/10.4 mg d-MPH.

Safety findings in KP415.E01 and the other open-label studies were generally comparable to existing approved methylphenidate products. The only unusual findings were some laboratory values indicating higher than expected coagulation times and proteinuria rates on drug; neither concern is a known issue for MPH-related drugs. After reviewing additional Applicant data and consulting our pediatric reviewers, our team felt there was no conclusive safety signal related to the drug. We also remain concerned that we do not have sufficient placebo-controlled safety data from the submitted studies, even for the age 6 to 12 range, given that SDX is still technically an NME. Accordingly, we will recommend that the Sponsor conduct an efficacy and safety parallel-group, placebo-controlled study for children ages 4 to 12 years (as we also will require similar data for the preschool age population per our division's guidance on ADHD drug development). Because d-MPH exposures in adolescents and adults are only approximately 50% of those in children, it is reasonable to assess safety in adolescents and adults based on the safety evaluation of KP415 in children.

Overall, we note that KP415 administered once daily is effective and safe for the treatment of ADHD in patients age 6 years and older and recommend approval for this indication. However, because 1) ADHD is prevalent in children, ages 4 and 5 years, and there are no PK, safety, or efficacy data in those patients; and 2) there are no placebo-controlled safety data in children 6 to 12 years of age, the Applicant will be required, as Postmarketing Requirements (PMRs), to conduct 1) a randomized, placebo-controlled study of safety and efficacy in patients 4 to 12 years of age with ADHD, that includes sparse PK sampling in children 4 to less than 6 years of age; and 2) a 12 month, open-label safety study in children 4 to less than 6 years of age to assess effects on growth.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of about 11%. It typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior. These symptoms cause significant impairment in academic and social functioning during critical years of development, unless treated.	ADHD is a very prevalent condition in children and adolescents. ADHD symptoms can substantially compromise childhood academic and social development without treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are several products that have demonstrated safety and effectiveness in the treatment of ADHD over the past 65 years. Most of these products contain amphetamine salts or methylphenidate. More recently approved products contain atomoxetine or guanfacine. These products display some differences in time to therapeutic onset and/or duration of action because of different pharmacokinetic profiles. Thus, some require more than one dose per day because of a short duration of action. Also, products have been developed as different formulations (tablets, capsules, or oral suspensions) which allow for different modes of oral administration (sprinkling on food, chewing, swallowing whole pills).	KP415 offers no distinct advantage over currently approved methylphenidate products.
Benefit	Study KP415.E01 and data from the approval of Focalin XR together provide substantial evidence of the efficacy of KP415 in the treatment of children (ages 6 to 12 years) with ADHD. In Study KP415.E01, the average change from baseline in the SKAMP-C score on the laboratory classroom day in the KP415-treated patients was statistically significantly greater than that in the placebo-treated patients. The Agency required only one efficacy trial because the effectiveness of d-MPH has already been established for the LD, Focalin XR. Efficacy in adolescent and adult patients with ADHD is inferred via a PK bridge to the LD, Focalin XR.	The Applicant has provided substantial evidence of the efficacy of KP415 in the treatment of patients, age 6 years and older, with ADHD.
Risk and Risk Management	Adverse events (AEs) after KP415 administration in phase 3 trials were generally the same as those observed with other MPH products, e.g., decreased appetite, mood changes, insomnia, abdominal pain, headache, and behavioral changes. Possible hypersensitivity reactions to KP415 were bronchospasm, rash, and pruritus. There was a modest increase from baseline in blood pressure and pulse rate during KP415 treatment. During the 12-month safety trial, there was an appreciable	The clinical review identified no findings that suggest a new risk that is reasonably attributable to KP415. Possible hypersensitivity reactions will be described in Section 4 (Contraindications) of labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	decrease in the rate of weight gain during the trial, with a mean sex- and gender-adjusted z-score change from baseline to month 12 of -0.20 standard deviations (SDs) among study completers. There was also a lower than expected increase in height, after adjustment for sex and age, with a mean z-score change from baseline to month 12 of -0.21 SDs among study completers. Laboratory abnormalities included proteinuria and increased activated partial thromboplastin time (aPTT), which were not clearly associated with AEs and not clearly attributable to KP415 treatment. A source of uncertainty in the safety review was the evaluation of the causal relationship between KP415 and AEs. Given that d-MPH is the only active moiety produced by KP415 treatment, and that the safety profile of d-MPH is well-established, and no unexpected clinically important AEs were reported with KP415, this uncertainty should not preclude approval of this application.	Because of the limitation in evaluating causality of AEs, class risks will be described in labeling and the Medication Guide as opposed to AE incidence data from the phase 3 trials. Safety in adolescent and adult patients with ADHD is assessed from the safety evaluation in children, ages 6 to 12 years, based on the finding that exposure in adolescents and adults is approximately 50% of that in children.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1.1
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of about 11%. ADHD typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior. The clinical presentation may be primarily inattentive, hyperactive/impulsive, or combined. These symptoms cause significant impairment in academic and social functioning during critical years of development, unless treated. Although symptoms often attenuate during adolescence and early adulthood, some patients continue to experience the full disorder or some symptoms of the disorder into mid-adulthood, when symptoms can cause substantial impairment in occupational functioning. Pharmacologic treatments for ADHD have had a significant impact on the well-being and functioning of patients with this disorder.

2.2. Analysis of Current Treatment Options

Several products have demonstrated safety and efficacy in the treatment of patients with ADHD over the last 65 years. Most of these products contain amphetamine salts or methylphenidate, and are associated with abuse potential, decreased appetite, and insomnia. These products display some differences in time to therapeutic onset and/or duration of action because of different PK profiles. Thus, some require more than one dose per day because of a short duration of action. Also, products have been developed as different formulations (tablets, capsules, or oral suspensions) which allow for different modes of oral administration (sprinkling on food, chewing, swallowing whole pills) to meet the needs of individual patients.

More recently approved products contain atomoxetine or guanfacine. Atomoxetine is a selective presynaptic norepinephrine reuptake inhibitor that has no known abuse potential, but is associated with nausea and decreased appetite. Guanfacine is a central alpha$_{2A}$ adrenergic receptor agonist that is approved for monotherapy or as adjunctive therapy to stimulants in the treatment of patients with ADHD. Guanfacine has no known abuse potential, but is associated with hypotension, bradycardia, syncope, and somnolence.

KP415 capsules can be administered once daily, based on a duration of action up to 10 hours after dosing. Also, KP415 can be either swallowed whole or opened, with the entire contents sprinkled onto applesauce or added to water. Because other marketed d-MPH products have these features, KP415 offers no distinct advantage over the existing treatment armamentarium.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

MPH products have been approved and used in the United States to treat ADHD for several decades and have a well-established safety and efficacy profile.

KP415 contains a new molecular entity (NME), SDX, which is a prodrug of d-MPH. Originally, the Applicant intended to develop a product (b) (4) with the expectation of marketing a treatment for ADHD that had reduced abuse liability via non-oral routes, such as nasal insufflation, based on the fact that SDX requires conversion to d-MPH in the gastrointestinal tract. However, after PK data with SDX showed that peak blood levels of d-MPH are not achieved until about 8 hours after dosing, the Applicant decided (b) (4) (b) (4) that KP415 would provide a therapeutic effect from the first hour post-dose throughout the day. Thus, as for other MPH products, the Drug Enforcement Administration will likely designate KP415 as a Schedule II product under the Controlled Substances Act.

KP415 has not been marketed in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

KemPharm, Inc. has developed KP415 for the treatment of ADHD. This 505(b)(2) application for KP415 is relying on Focalin XR (NDA 21802) as the LD to bridge to prior findings of safety and efficacy for a once daily d-MPH drug product.

The Agency provided advice to the Applicant under IND 130463 on several occasions during the development of KP415:

- Pre-IND Written Response Only (WRO) comments, dated July 1, 2016, provided advice on nonclinical studies, the design of the initial phase 1 oral bioavailability study, and the 505(b)(2) pathway to approval. Also, the Controlled Substances Staff (CSS) advised the Applicant that the abuse potential of SDX alone must be evaluated, because it is not currently scheduled as a controlled substance.

- The Applicant submitted an IND application on September 6, 2016 and the Agency issued a "May Proceed" letter on November 2, 2016.

- The Agency denied a September 6, 2016, request for Fast Track designation because the Applicant did not demonstrate that an unmet medical need existed. The Agency denied a second request for Fast Track designation on May 15, 2018 for the same reason.

- The Agency held an End-of-Phase 1 meeting on June 14, 2017. The Agency advised the Applicant that additional animal studies may be needed to qualify SDX and any other major human metabolites. Other discussion topics included 1) the potential need to conduct additional PK studies, 2) the design of a PK bridging study, 3) extrapolation of efficacy from children to adolescents, 4) the design of a pivotal efficacy trial in children, and 5) studies to evaluate human abuse potential (HAP).

- The Agency held an End of Phase 2 (EOP2) meeting on November 14, 2017. The Agency indicated that SDX alone is a new molecular entity (NME) that is not rapidly metabolized to d-MPH and, therefore, SDX itself required adequate assessment for toxicity in animals. Other issues that were discussed included 1) the need to compare PK data across child, adolescent, and adult age ranges to support safety and efficacy in patients age 6 years and older, 2) feedback from CSS on proposed HAP studies, and 3) the need to evaluate the potential for alcohol-induced dose dumping. It should be noted that the Applicant asked if their efficacy and safety findings in children (6 to 12 years) from Study KP415.E01) could support safety and efficacy in all patients 6 years of age and older. We informed them that this will be a matter of review after they submit the results of these studies and provide justification why safety and efficacy can be inferred for adolescents and adults based on the available data in children ages 6 to 12 years.

- The Agency issued an Agreed initial Pediatric Study Plan (iPSP) on August 2, 2018.

- Written Response Only (WRO) comments, dated October 10, 2018, addressed concerns regarding the protocol-specified analysis of data supporting therapeutic onset and duration of effect claims from the pivotal efficacy study (Study KP415.E01). The baseline time point specified in the protocol (first day of randomized treatment) differed from that usually implemented in similar laboratory classroom studies (predose assessment on the day of the laboratory classroom study) and yielded results which the Applicant felt did not reflect the true magnitude of onset and duration of therapeutic effect. A post-hoc analysis was claimed to be more accurate. The Division advised the Applicant to discuss this issue within the NDA. The Division's decision on the acceptability of the post-hoc analysis will be a matter for review.

- The Agency held a pre-NDA meeting on April 10, 2019. The Agency informed the Applicant that Study KP415.E01 appears to be adequate to assess the efficacy of SDX/d-MPH in the treatment of ADHD in children 6 to 12 years of age. The Agency also informed the Applicant that the October 2018 justification for the post hoc analysis appeared to be reasonable but the acceptability of this analysis (b) (4) will be a matter for review. The Division noted that, in the post hoc analysis, the mean changes from baseline in the SKAMP-C at 12 and 13 hours post-dose indicated worsening ADHD symptoms in the SDX/d-MPH-treated patients compared to baseline, although the changes were statistically superior to

those in placebo-treated patients. Thus, (b) (4) (b) (4) these findings should be addressed in the NDA application. The Applicant stated that one possible reason for deterioration of efficacy at the end of the day is fatigue at the end of the laboratory classroom day. Additionally, we informed the Applicant that the extrapolation of efficacy from children (ages 6 to 12 years) to adolescents (ages 13 to 17 years) and to adults (18 years and older) will be a matter for review.

The Applicant submitted NDA 212994 on March 2, 2020. At that time, the study report for Study KP415.S01, a 12-month, open-label safety study in children 6 to 12 years of age, was not complete; only an interim clinical study report (CSR) was submitted, with the full report to be submitted as part of the 120-Day Safety Update Report (SUR) for this application. The Agency agreed with this plan at the pre-NDA meeting. The application was filed on May 11, 2020.

The Applicant submitted the 120-Day SUR for this application on June 18, 2020. This submission included the final study report for Study KP415.S01.

The Agency concluded that the first proposed proprietary name, (b) (4) was conditionally acceptable on May 29, 2020. The Applicant withdrew the name on July 30, 2020, and requested review of a new proprietary name, Azstarys, on that same date. The Agency found the name Azstarys to be conditionally acceptable on October 28, 2020.

The Agency held a Mid-Cycle teleconference with the Applicant on August 13, 2020. Significant issues for discussion were 1) abnormal laboratory findings in phase 3 trials (proteinuria and increased coagulation parameters), 2) unexpected efficacy findings from Study KP415.E01, 3) the choice of the baseline time point for the primary efficacy analysis, and 4) the proposed dosing recommendations for labeling.

The Agency held a Late-Cycle teleconference with the Applicant on December 1, 2020. Minor issues for discussion were 1) the PK bridging strategy to support extrapolation of efficacy from children (6 to 12 years of age) to adolescents (13 to 17 years of age) and adults (18 years and older) and 2) the choice of the baseline time point for the primary efficacy analysis. The Agency agreed to advise the Applicant on a Postmarketing Requirement (PMR) to assess PK, safety, and efficacy in 4- and 5-year olds with ADHD after internal Agency discussion, to be conducted in January 2021.

The Division of Psychiatry (DP) conferred with team staff at the Office of Neuroscience (ON) level on February 18, 2021, regarding the limitation of the approved population age range to patients 6 to 12 years of age. After in-depth discussion of this issue and further discussion within DP the next day, DP decided to expand the approved age range to patients age 6 years and older. The rationale for this decision is provided in Section 8.1.2 of this review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Due to the COVID-19 pandemic restricting travel, OSI could not complete on-site clinical inspections for this NDA. Based on our preliminary analyses of the sites and studies involved, we did not feel these inspections were mission-critical for our regulatory decision-making process for this NDA.

4.2. Product Quality

CMC recommends approval of this application based on drug substance, drug product, process/facilities, and biopharmaceutics reviews.

The data provided by the Applicant support the proposed 24-month shelf-life when stored at 20°–25° (68°–77° F).

See the CMC/OPQ review for more details.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This application submitted by Commave Therapeutics SA is a 505(b)(2) NDA for KP415 (serdexmethylphenidate and dexmethylphenidate) for the treatment of Attention Deficit Hyper Activity Disorder (ADHD) in patients ages 6 years and older. KP415 is a combination of a new molecular entity (NME), serdexmethylphenidate (SDX), and a previously approved product, dexmethylphenidate (d-MPH). SDX is a prodrug of d-MPH. The proposed maximum recommended human dose (MRHD) is 52.3/10.4 mg SDX/d-MPH (56/12 mg of SDX Cl/d-MPH Cl). The Applicant is partially relying on the Agency's previous findings of safety for Focalin XR (d-MPH; NDA 021802), a central nervous system (CNS) stimulant, approved in 2005 for the same indication proposed for KP415. The submitted nonclinical package contains studies to support approval of SDX, which is also referred to in these studies as KP415. It should be noted that KP415 in the non-clinical section refers only to the prodrug SDX and not to the combination of SDX with d-MPH.

SDX did not show significant binding to the human transporters for dopamine, norepinephrine, and serotonin, or to 68 other molecular targets examined.

There are substantial species differences in pharmacokinetics (PK) and toxicokinetics (TK) for SDX and the active metabolite, d-MPH. After single and repeat dosing with SDX, rodents (rats and mice) have greater plasma exposures (AUC and C_{max}) to d-MPH compared to SDX, while dogs and rabbits have lower plasma exposures to d-MPH compared to SDX. In addition, rabbits reach maximum plasma concentration (C_{max}) for d-MPH the slowest after single and repeat doses of SDX (approximately 2 to 4 hours in rabbits compared to 0.5 to 1.2 hours in rats and 0.5 to 2 hours in dogs).

SDX has minimal distribution or binding to red blood cells. [^{14}C]SDX-related radioactivity widely distributed in rat tissues with the highest radioactivity concentrations observed in eye uvea, kidney cortex and medulla, liver, gastric mucosa of stomach, and small intestine. SDX was extensively metabolized in a rodent mass balance study where only trace amounts of SDX were detected in plasma and feces. The active metabolite d-MPH was only detected in plasma and the inactive metabolite ritalinic acid was detected in plasma, urine, and feces. SDX is thought to release d-MPH by hydrolysis at the serine moiety (producing the intermediate SDX-des-Ser) or at the carbamate group (producing the intermediate nicotinoyl-L-Ser). SDX-des-Ser was identified at low levels (1.33% of total dose) in feces of humans in a mass balance study but was not observed in rats or dogs. The low level of this metabolite in human feces is not of a safety concern. Nicotinoyl-L-Ser was present in pooled plasma samples from rats and dogs but not in any human matrix. Release of d-MPH from SDX is predicted to result in the release of formaldehyde and the final products of SDX metabolism are L-Ser and niacin. These amounts are either found endogenously and/or obtained in the diet at levels greater than what will be

released at the MRHD and are not of a safety concern. No unique metabolites of d-MPH were observed.

All findings from safety pharmacology studies of SDX were consistent with known effects for d-MPH. In rat and dog single- and repeat-dose toxicology studies of up to 28-day duration of oral SDX with d-MPH as a comparator, the dose-limiting toxicities were clinical signs consistent with a CNS stimulant [including increased activity, excessive licking or grooming (which could lead to self-mutilation), and/or increased respiration] and decreases in body weight gain or body weight loss. All findings in SDX dose groups were similar to findings in the d-MPH comparator group for both 28-day studies; therefore, no unique SDX toxicity was observed that could be attributed to either the parent or the unique metabolites of SDX. For rats, the exposures at the no adverse effect level (NOAEL) for stimulant-related findings (25 mg/kg) was less than the human exposure at the MRHD. For dogs, the NOAEL for stimulant-related findings was not established because the NOAEL is less than the lowest dose tested.

Because SDX is an NME that is not rapidly metabolized to d-MPH in humans (half-life of SDX is ~5.7 hours) and will be used chronically, SDX needed to be adequately assessed for toxicity. In order to use the species with the highest SDX exposure compared to humans in the pivotal embryo-fetal development study and the 6-month juvenile animal study, a cross-species analysis was conducted, and the rabbit was determined to be the most appropriate species.

In the embryo-fetal development study in rabbits, there were no findings of maternal or fetal development toxicity at exposures up to 49 times (400 mg/kg) the MRHD. Because of the large exposure multiple, the high dose was considered adequate for the embryo-fetal development study even though it was not the maximum tolerated dose (MTD). In a dose range-finding study in juvenile rabbits, adverse clinical signs (including excessive licking, grooming, and scratching that resulted in self-mutilation) were observed at doses ≥400 mg/kg and the MTD was considered 300 mg/kg. In the pivotal 6-month juvenile animal study in rabbits, clinical signs consistent with a stimulant were mild and not considered adverse at all doses tested. The NOAEL (300 mg/kg) in juvenile rabbits is 50-times the MRHD for juveniles based on body surface area (no human plasma levels at MRHD in juveniles were available). Of note, d-MPH exposures after a single-dose of 400 mg/kg SDX Cl in juvenile rabbits was 3-times the d-MPH exposures after a single-dose of 400 mg/kg SDX Cl in pregnant rabbits which might account for the observance of adverse clinical signs in juvenile rabbits but no clinical signs in pregnant rabbits.

SDX was not genotoxic in an appropriate valid battery of assays. After a positive prediction of mutagenicity by QSAR for an impurity (chloro-substituted SDX, Cl-SDX or Cl-KP415), a valid Ames assay determined that Cl-SDX was negative for mutagenicity.

There are no novel excipients in the drug product. Drug substance impurity and drug product degradant specifications and elemental impurities risk assessment are consistent with ICH guidelines.

Although SDX is technically a new molecular entity and circulating levels of SDX can be detected in humans at levels comparable to the active d-MPH, during development, the Division agreed to consider an abbreviated nonclinical drug development program if adequate data were provided to support the conclusion that the toxicological profile of SDX is comparable to d-MPH and there are no unique toxicities derived from the parent or the unique metabolic byproducts released during prodrug metabolism to d-MPH. The Division agreed to review 28-day repeat-dose toxicology data in two species, an embryo-fetal development study in the rabbit, and 6-month juvenile rabbit study to support this position. Upon review, it was concluded that additional nonclinical studies are not needed for SDX because there were no unique, adverse findings for SDX compared to d-MPH in 28-day repeat-dose toxicology studies in rat and dog, embryo-fetal development study in rabbits, and 6-month juvenile animal study in rabbits, the unique metabolic by products do not raise any safety concerns, and further studies would not provide any additional data not already characterized via referenced data for d-MPH. In addition, carcinogenicity studies in mice or rats, fertility and early embryonic development in rats, embryofetal development in rats, and prenatal and postnatal development study in rats would not be informative because of species differences in pharmacokinetics for SDX (see review for more details).

Recommendation: The Applicant has provided sufficient nonclinical safety information on serdexmethylphenidate to support approval for the treatment of ADHD in patients ages 6 years and older from a Pharmacology/Toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA 021802 for Focalin XR (d-MPH)

5.3. Pharmacology

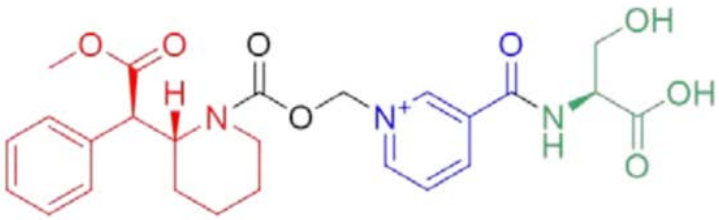
Serdexmethylphenidate (SDX; KP415) is a prodrug of d-methylphenidate hydrochloride (d-MPH). SDX contains a molecule of d-MPH connected to a nicotinoyl-L-serine (nicotinoyl-L-Ser) by a carboxymethylene linker (Figure 1). (b) (4)

(b) (4)

(b) (4)

See Figure 22, page 128 in Appendix for the proposed metabolic pathway. Although the Applicant did not measure plasma exposures for formaldehyde, L-Ser, and niacin in humans and animals after SDX administration; this is not of a safety concern because they are either found endogenously in humans (formaldehyde and L-Ser), are found in foods (formaldehyde, L-Ser, and niacin), in dietary supplements (L-Ser and niacin), or approved drug products (niacin) at levels above those found in SDX (see Table 43, page 123 in Appendix). Therefore, this review of SDX safety will not further discuss formaldehyde, L-Ser, and niacin.

Figure 1: Serdexmethylphenidate Chemical Structure



Molecular Components
red = d-methylphenidate
black = carboxymethylene linker
blue = niacin
green = L-serine

Serdexmethylphenidate (SDX)

Source: Applicant's Figure, Nonclinical Overview, p. 4

Primary and Secondary Pharmacology

In a primary pharmacology in vitro radioligand receptor binding assay (Study No. AB54825); SDX at concentrations from 0.03 to 10 µM did not show significant binding to the human dopamine transporter (DAT), norepinephrine transporter (NET), or serotonin transporter (SERT; IC_{50} > 10 µM for all three transporters). Of the three human transporters, SDX appeared to have higher affinity for DAT and inhibited 33% and 44% of ligand binding at 3 and 10 µM, respectively (Table 1). The validity of this assay was confirmed with reference compounds which generated IC50 values comparable to historical control values. In a secondary pharmacology radioligand binding screening assay with 68 primary molecular targets including CNS targets (Study No. AB54826), SDX at 10 µM showed limited affinity for the targets investigated (<25% inhibition). Notably, at 10 µM, SDX had 41% inhibition of radioligand binding to DAT, consistent with the value from primary pharmacology study confirming that there is minimal activity at the DAT. In addition, no significant binding was observed with the nicotinoyl-L-Ser (10 µM) moiety in a radioligand binding screening assay with 68 molecular targets (Study No. AB54826).

Table 1: In Vitro SDX Binding Affinity for Human DAT, NET, and SERT

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC_{50}*	K_i	n_H	R
Compound: KP415, PT #: 1200798										
220320	Transporter, Dopamine (DAT)	388899	hum	2	10 µM	44	>10.0 µM			
			hum	2	3 µM	33				
			hum	2	1 µM	17				
			hum	2	0.3 µM	13				
			hum	2	0.1 µM	-1				
			hum	2	0.03 µM	-9				
204410	Transporter, Norepinephrine (NET)	388899	hum	2	10 µM	31	>10.0 µM			
			hum	2	3 µM	9				
			hum	2	1 µM	10				
			hum	2	0.3 µM	7				
			hum	2	0.1 µM	7				
			hum	2	0.03 µM	-3				
274030	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	388846	hum	2	10 µM	8	>10.0 µM			
			hum	2	3 µM	6				
			hum	2	1 µM	-6				
			hum	2	0.3 µM	9				
			hum	2	0.1 µM	5				
			hum	2	0.03 µM	8				

Source: Applicant's Table, Report No. AB54825, p. 6

Safety Pharmacology

SDX was evaluated in a standard battery of safety pharmacology studies which included the comparator d-MPH (CNS study No. 0200RK19.001, hERG assay study No. CYP1555-R3, cardiovascular study No., and respiratory study No. 1275RK19.001). All findings for SDX were typical of a CNS stimulant (including dilated pupil, increased activity, increased heart rate and blood pressure, and increased respiratory rate) and all findings were generally comparable for SDX and a comparative dose of d-MPH. In the hERG assay, the IC_{50} for SDX was considered >25 µM.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
(Study Nos. 0841MK19.001, KP415-ROPK-001, KP415-ROPK-004, 0832DK19.004,	There are substantial species differences in PK for SDX (Table 2) and the active metabolite, d-MPH (Table 3). Rodents (rats and mice) have the largest exposure to d-MPH and dogs and rabbits have the lowest exposures to d-MPH after SDX administration (Table 4). After SDX administration, C_{max} for d-MPH release is slowest in rabbits

Type of Study	Major Findings
0852LK19.001, and DCN 4005904)	compared to other species. A cross-species comparison of mean plasma concentration-time curves of SDX following single oral doses of SDX (Figure 20) and of d-MPH following single oral doses of SDX or d-MPH (Figure 21) are shown on page 124 in the Appendix.

Table 2: PK of SDX in Mice, Rats, Dogs, and Rabbits after a Single Oral Administration of SDX Cl

Parameter	Mice[a]	Rats[b]	Dogs[c]	Rabbits[d]
AUC_{last}^ (h.ng/mL)	33	8.3	110	93
C_{max} (ng/mL)	41	9.5	89	65
T_{max} (h)	0.5	0.3	0.4	0.75
$T_{1/2}$ (h)	0.63	--	--	0.69

[a]dose = 75 mg/kg; [b]dose = 4.75 mg/kg; [c]dose = 4.59 mg/kg; [d]dose = 15 mg/kg; ^AUC_{last} was calculated for up to 4 hours in rats and 8 hours in mice, dogs, and rabbits; AUC: area under the curve; C_{max}: maximum plasma concentration; T_{max}: time to maximum plasma concentration; $T_{1/2}$: terminal elimination half-life

Table 3: PK of d-MPH in Mice, Rats, Dogs, and Rabbits after a Single Oral Administration of SDX Cl or d-MPH Cl

Parameter	Test Article	Mice[a]	Rats[b]	Dogs[c]	Rabbits[d]
AUC_{last}^ (h.ng/mL)	SDX	3756	80	36	48
	d-MPH	3442	79	50	41
C_{max} (ng/mL)	SDX	3270	65	20	13
	d-MPH	4080	97	47	17
T_{max} (h)	SDX	0.5	1.2	0.8	2
	d-MPH	0.25	0.4	0.3	0.5
$T_{1/2}$ (h)	SDX	0.94	--	--	1.83
	d-MPH	0.68	--	--	2.32

SDX: [a]dose = 75 mg/kg; [b]dose = 4.75 mg/kg; [c]dose = 4.59 mg/kg; [d]dose = 15 mg/kg; d-MPH: [a]dose = 37.5 mg/kg; [b]dose = 2.39 mg/kg; [c]dose = 2.31 mg/kg; [d]dose = 7.5 mg/kg; ^AUC was calculated for up to 4 hours in rats and 8 hours in mice, dogs, and rabbits; AUC: area under the curve; C_{max}: maximum plasma concentration; T_{max}: time to maximum plasma concentration; $T_{1/2}$: terminal elimination half-life

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Table 4: Exposure Ratio between d-MPH and SDX after SDX Cl Administration
<table>
<tr><td rowspan="2">Species</td><td colspan="2">Exposure Ratio (d-MPH:SDX)</td></tr>
<tr><td>AUC</td><td>Cmax</td></tr>
<tr><td>Mice</td><td>114</td><td>80</td></tr>
<tr><td>Rats</td><td>10</td><td>7</td></tr>
<tr><td>Dogs</td><td>0.3</td><td>0.2</td></tr>
<tr><td>Rabbits</td><td>0.5</td><td>0.2</td></tr>
</table></td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>(Study Nos. CY1555-R2, CYP1555-R5, and 437N-1701)</td><td>SDX and d-MPH moderately bound to human plasma protein (56% and 47.3%, respectively). SDX has minimal distribution or binding to red blood cells [mean blood-to-plasma concentration ratio (C_b/C_{pl}) = 0.59; mean red blood cell partition coefficient ($K_{RBC/PL}$) = 0.01].

[^{14}C]KP415-related radioactivity was widely distributed in rat tissues with peak radioactive concentration in blood and most tissues 1-hour postdose. Quantifiable concentrations of radioactivity were present in most tissues through 48 hours post dose with half-life ranging from <10 hours (22 of 42 tissues sampled) to >50 hours (eye uvea, thyroid, kidney cortex, and liver). The half-life in blood was 4.7 hours. The highest radioactivity concentrations were found in eye uvea, kidney cortex, liver, kidney medulla, stomach (gastric mucosa), and small intestine.</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>In Vitro (Study Nos. 437D-1601, CYP1555-R1, CYP1555-R4, CYP1555-R6, CYP1555-R7A, CYP1555-R7D, CYP1555-R7E, CYP1555-R7F, andCYP1555-R7G)</td><td>SDX was slowly metabolized in human whole blood, plasma, simulated intestinal fluid (SIF), simulated gastric fluid (SGF), human kidney S9 fractions, human liver S9 fractions, human intestinal S9 fractions, and human lung S9 fractions. In blood, the amount of SDX after 90 minutes of incubation was 73.8%. d-MPH was first observed at 45 mins after incubation with whole blood and plasma, at 90 mins with SIF, and was not detected in SGF.

SDX did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 at concentrations up to 30 μM and did not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 at concentrations up to 100 μM. SDX did not induce CYP1A2, CYP2B6, and CYP3A4 at concentrations up to 100 μM. SDX was not found to be metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, CYP2A6, CYP2 E1, UGT1A1, UGT1A3,</td></tr>
</table>

Type of Study	Major Findings
	UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15, aldehyde oxidase, xanthine oxidase, and monoamine oxidase.
In Vivo (Study No. 4001435, KP415-MP-001, and 4006354)	Thirty-four putative metabolites of SDX were identified from plasma collected from rats dosed with 114.87 mg/kg SDX. Four metabolites resulted from hydrolysis at the serine moiety [M25 (SDX-des-Ser)], the carbamate moiety [M1 (nicotinoyl-L-Ser) and M2a (d-MPH)], and at the methyl ester [M33 (SDX acid). Twenty-six reflect metabolism of d-MPH via oxidation, reductive elimination, or hydrolysis, and four appear to be glucuronide conjugates of oxidized d-MPH. Results from a rodent mass balance study, rats orally dosed with 75 mg/kg (184.5 µCi/kg) [^{14}C]-SDX Cl, confirmed that SDX is extensively metabolized in rats (Table 44, page 125 in Appendix). Trace amounts of SDX were detected in plasma and feces. The active metabolite, d-MPH was only detected in plasma. The inactive metabolite RA was detected in plasma, urine, and feces. In rats and dogs; nicotinoyl-L-Ser, SDX acid, and ritalinic acid (RA; M3a, a known metabolite of MPH) were present in pooled plasma after a single oral and 28-day oral repeat dose of SDX, while SDX-des-Ser (M25) was below the level of quantification at both time points. In humans who received 32 mg oral SDX, only ritalinic acid was present in pooled plasma samples. See Table 45, page 127 in Appendix for PK data. The proposed metabolic pathway of SDX is shown in Figure 22, page 128 in Appendix.
Excretion	
(Study No. 437N-1701)	The primary route of excretion in rat was urine with some elimination in feces. After administration of a single oral dose of 75 mg/kg [^{14}C]KP415 in male rats, 64.9% of radioactivity was measured in urine and 30.3% of radioactivity was measured in feces. Approximately 94% of the radioactivity was recovered within 24 h post dose.
TK data from general toxicology studies	
Rat: 28-day oral gavage (Study No. 0436RK19.003) • NOAEL is 25 mg/kg	Dose proportionality: SDX and d-MPH generally increased more than dose-proportional. Sex differences: Females had similar or higher exposures to SDX and d-MPH compared to males with a greater difference for d-MPH (up to 5-fold higher at the high dose).

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>d-MPH- to SDX-AUC ratio: ~4 for males; ~10 for females

Table 5: TK of SDX in Rats on Day 28 of Oral Daily Administration of SDX Cl
<table>
<tr><th>Parameter</th><th>Sex</th><th>25 mg/kg</th><th>50 mg/kg</th><th>75 mg/kg</th></tr>
<tr><td rowspan="2">AUC_{last} (ng.h/mL)</td><td>M</td><td>47.28</td><td>208.8</td><td>240.6</td></tr>
<tr><td>F</td><td>69.55</td><td>203.8</td><td>542.2</td></tr>
<tr><td rowspan="2">C_{max} (ng/mL)</td><td>M</td><td>56.9</td><td>149</td><td>284</td></tr>
<tr><td>F</td><td>112</td><td>243</td><td>460</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>M</td><td>0.25</td><td>1</td><td>0.25</td></tr>
<tr><td>F</td><td>0.25</td><td>0.25</td><td>1</td></tr>
<tr><td rowspan="2">$T_{1/2}$ (h)</td><td>M</td><td>0.53</td><td>1.26</td><td>NE</td></tr>
<tr><td>F</td><td>0.56</td><td>4.74</td><td>NE</td></tr>
</table>
NE: Not estimable

Table 6: TK of SDX Metabolite d-MPH in Rats on Day 28 of Oral Daily Administration of SDX Cl or 37.5 mg/kg d-MPH Cl
<table>
<tr><th>Parameter</th><th>Sex</th><th>25 mg/kg</th><th>50 mg/kg</th><th>75 mg/kg</th><th>d-MPH</th></tr>
<tr><td rowspan="2">AUC_{last} (ng.h/mL)</td><td>M</td><td>210.8</td><td>689.6</td><td>1017</td><td>941.5</td></tr>
<tr><td>F</td><td>775</td><td>2112</td><td>5185</td><td>6654</td></tr>
<tr><td rowspan="2">C_{max} (ng/mL)</td><td>M</td><td>121</td><td>328</td><td>447</td><td>432</td></tr>
<tr><td>F</td><td>628</td><td>992</td><td>2070</td><td>1260</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>M</td><td>1</td><td>1</td><td>1</td><td>0.25</td></tr>
<tr><td>F</td><td>0.5</td><td>0.5</td><td>1</td><td>0.25</td></tr>
<tr><td rowspan="2">$T_{1/2}$ (h)</td><td>M</td><td>NE</td><td>1</td><td>1.12</td><td>1.14</td></tr>
<tr><td>F</td><td>0.59</td><td>NE</td><td>2.57</td><td>3.15</td></tr>
</table>
NE: Not estimable</td></tr>
<tr><td><u>Dog</u>: 28-day oral gavage (Study No. 0436DK19.004)
• NOAEL is <10 mg/kg</td><td>Dose proportionality: SDX and d-MPH generally increased dose-proportionally or more than dose-proportional.
Sex differences: Generally, exposures were similar except at the mid dose where C_{max} and AUC exposures were greater for females (up to 3-fold).
d-MPH- to SDX-AUC ratio: ~0.2</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>

Table 7: SDX TK in Dogs on Day 28 of Oral Daily Administration of SDX Cl

Parameter	Sex	10 mg/kg	20 mg/kg	30 mg/kg
AUC_{last} (ng.h/mL)	M	582.5	1073	5259
	F	694.6	2947	6360
C_{max} (ng/mL)	M	424	617	2360
	F	396	1330	2800
T_{max} (h)	M	0.42	0.5	0.6
	F	0.67	0.67	0.65
$T_{1/2}$ (h)	M	2.54	1.55	1.96
	F	0.8	2.19	1.66

Table 8: SDX Metabolite d-MPH TK in Dogs on Day 28 of Oral Daily Administration of SDX Cl or 10 mg/kg d-MPH Cl

Parameter	Sex	10 mg/kg	20 mg/kg	30 mg/kg	d-MPH
AUC_{last} (ng.h/mL)	M	135.5	257.6	940	1206
	F	155.4	385.3	745.4	1311
C_{max} (ng/mL)	M	53.2	77.3	291	697
	F	45.2	107	177	823
T_{max} (h)	M	0.5	1	1.20	0.4
	F	1.33	1.67	1.90	0.5
$T_{1/2}$ (h)	M	9.13	6.60	5.44	3.77
	F	5.4	4.54	3.64	3.98

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<tr><td>

TK data from reproductive toxicology studies
Rabbit: embryo-fetal development (Study No. 8381422)
- NOAEL is 400 mg/kg

</td><td>

Dose proportionality: SDX and d-MPH generally increased more than dose-proportional.
d-MPH- to SDX-AUC ratio: ~0.03

Table 9: SDX TK after SDX Cl Administration in Pregnant Rabbits

Dose Level	100 mg/kg/day	200 mg/kg/day	400 mg/kg/day
Parameter			
$AUC_{0\text{-}24}$ (h*ng/mL) - GD7/19	1317/2867	3161/7576	10750/11690
C_{max} (ng/mL) - GD7/19	902/1190	1290/3670	5730/4110
T_{max} (h) - GD7/19	0.33/0.50	0.50/0.58	0.33/0.58

Source: Applicant's Table, Study No. 8381422, p. 23

</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Table 10: SDX Metabolite d-MPH TK after SDX Cl Administration in Pregnant Rabbits
<table>
<tr><th>Dose Level</th><th>100 mg/kg/day</th><th>200 mg/kg/day</th><th>400 mg/kg/day</th></tr>
<tr><td>Parameter</td><td></td><td></td><td></td></tr>
<tr><td>$AUC_{0\text{-}24}$ (h*ng/mL) - GD7/19</td><td>43.49/57.55</td><td>121.5/161.0</td><td>418.5/374.5</td></tr>
<tr><td>C_{max} (ng/mL) - GD7/19</td><td>11.8/7.8</td><td>18.7/21.3</td><td>47.8/38.0</td></tr>
<tr><td>T_{max} (h) - GD7/19</td><td>2.50/0.83</td><td>2.50/2.00</td><td>3.33/2.50</td></tr>
</table>
Source: Applicant's Table, Study No. 8381422, p. 23</td></tr>
<tr><td>TK data from juvenile animal studies
Rabbit: dose-range finding study oral gavage (Study No. 20144933)
• The mid dose was reduced from 400 mg/kg to 300 mg/kg on Day 4 because of clinical signs and mortality.
• MTD is 300 mg/kg</td><td>Dose proportionality: SDX and d-MPH generally increased greater than dose proportional
Sex differences: Generally, exposures were similar
d-MPH- to SDX-AUC ratio: ~0.14

Table 11: SDX TK in Juvenile Rabbits after a Single Dose of SDX Cl
<table>
<tr><th>Parameter</th><th>Sex</th><th>200 mg/kg</th><th>400 mg/kg</th><th>800 mg/kg</th></tr>
<tr><td rowspan="2">$AUC_{0\text{-}t}$ (ng.h/mL)</td><td>M</td><td>2306</td><td>5101</td><td>13,020</td></tr>
<tr><td>F</td><td>2137</td><td>4487</td><td>18,130</td></tr>
<tr><td rowspan="2">C_{max} (ng/mL)</td><td>M</td><td>1480</td><td>2790</td><td>5130</td></tr>
<tr><td>F</td><td>805</td><td>1810</td><td>8950</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>M</td><td>0.25</td><td>0.5</td><td>0.5</td></tr>
<tr><td>F</td><td>0.5</td><td>0.25</td><td>0.5</td></tr>
<tr><td rowspan="2">$T_{1/2}$ (h)</td><td>M</td><td>1.22</td><td>1.62</td><td>1.75</td></tr>
<tr><td>F</td><td>1.25</td><td>1.80</td><td>2.23</td></tr>
</table>
Table 12: SDX Metabolite d-MPH TK in Rabbits after a Single Dose of SDX Cl
<table>
<tr><th>Parameter</th><th>Sex</th><th>200 mg/kg</th><th>400 mg/kg</th><th>800 mg/kg</th></tr>
<tr><td rowspan="2">AUC_{last} (ng.h/mL)</td><td>M</td><td>189</td><td>1201</td><td>2809</td></tr>
<tr><td>F</td><td>236</td><td>1297</td><td>2951</td></tr>
<tr><td rowspan="2">C_{max} (ng/mL)</td><td>M</td><td>66</td><td>308</td><td>607</td></tr>
<tr><td>F</td><td>76</td><td>233</td><td>840</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>M</td><td>2</td><td>2</td><td>2</td></tr>
<tr><td>F</td><td>2</td><td>4</td><td>2</td></tr>
<tr><td rowspan="2">$T_{1/2}$ (h)</td><td>M</td><td>NE</td><td>NE</td><td>NE</td></tr>
<tr><td>F</td><td>NE</td><td>NE</td><td>NE</td></tr>
</table>
NE: Not estimable</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Rabbit: 6-month oral gavage (Study No. 2144952)
• NOAEL is 300 mg/kg</td><td>Dose proportionality: SDX and d-MPH generally increased greater than dose proportional except for AUC of SDX from mid to high dose in males and AUC of d-MPH from low to mid dose in males which increased less than dose proportional.
Sex differences: Generally, exposures were similar except low dose males had greater exposures to SDX (~2-fold) and high dose females had greater exposures to d-MPH (~2-fold)
d-MPH- to SDX-AUC ratio: ~0.02

Table 13: SDX TK in Juvenile Rabbits on Day 196 of Oral Daily Administration of SDX Cl
<table>
<tr><th>Parameter</th><th>Sex</th><th>75 mg/kg</th><th>150 mg/kg</th><th>300 mg/kg</th></tr>
<tr><td rowspan="2">AUC_{last} (ng.h/mL)</td><td>M</td><td>2440</td><td>6690</td><td>9030</td></tr>
<tr><td>F</td><td>1340</td><td>4510</td><td>10800</td></tr>
<tr><td rowspan="2">C_{max} (ng/mL)</td><td>M</td><td>1690</td><td>3680</td><td>6240</td></tr>
<tr><td>F</td><td>804</td><td>2050</td><td>5480</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>M</td><td>0.3</td><td>0.4</td><td>0.4</td></tr>
<tr><td>F</td><td>0.35</td><td>0.8</td><td>0.35</td></tr>
<tr><td rowspan="2">$T_{1/2}$ (h)</td><td>M</td><td>1.24</td><td>1.49</td><td>2.70</td></tr>
<tr><td>F</td><td>1.75</td><td>1.51</td><td>1.66</td></tr>
</table>
Table 14: SDX Metabolite d-MPH TK in Rabbits on Day 196 of Oral Daily Administration of SDX Cl or 75 mg/kg d-MPH Cl
<table>
<tr><th>Parameter</th><th>Sex</th><th>75 mg/kg</th><th>150 mg/kg</th><th>300 mg/kg</th><th>d-MPH</th></tr>
<tr><td rowspan="2">AUC_{last} (ng.h/mL)</td><td>M</td><td>35.9</td><td>59.4</td><td>123</td><td>170</td></tr>
<tr><td>F</td><td>21.4</td><td>76.3</td><td>280</td><td>586</td></tr>
<tr><td rowspan="2">C_{max} (ng/mL)</td><td>M</td><td>14.1</td><td>16.5</td><td>30.8</td><td>131</td></tr>
<tr><td>F</td><td>9.06</td><td>19.4</td><td>56.7</td><td>474</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>M</td><td>2</td><td>1.7</td><td>1.1</td><td>0.35</td></tr>
<tr><td>F</td><td>1.7</td><td>2</td><td>2</td><td>0.3</td></tr>
<tr><td rowspan="2">$T_{1/2}$ (h)</td><td>M</td><td>NC</td><td>NC</td><td>NC</td><td>1.09</td></tr>
<tr><td>F</td><td>5.38</td><td>NC</td><td>NC</td><td>0.9</td></tr>
</table>
NC: Not calculated</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

A 28-Day Oral Toxicity Study with KP415 in Rats Followed by a 14-Day Recovery Period/Study No. 0436RK19.003:

- A dose-dependent increase in severity and/or incidence of clinical signs consistent with a stimulant, including increased activity, biting and licking of the home cage, excessive grooming, and head twitching.
- Decreased body weight gain (up to 20% for males and 33% for females) at the end of dosing consistent with a stimulant.
- Findings in SDX dose groups were similar to findings in the d-MPH comparator group.
- The NOAEL is 25 mg/kg based on the moderate to severe clinical signs at 100/75 mg/kg and decreased body weight gain at doses ≥50 mg/kg, which is less than the human exposure at the MRHD ($AUC_{24hr,ss}$ = 241 ng.h/mL).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle control), 25 (LD), 50 (MD), 100/75 (HD)^ mg/kg/day SDX (KP415) Cl and 50/37.5 mg/kg/day d-MPH Cl Once daily for 28 days
Route of administration:	Oral gavage
Formulation/Vehicle:	Solution/deionized water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	15/sex/group for control, HD, and d-MPH (5/sex/group recovery group); 10/sex/group for LD and MD
Age:	7 - 8 weeks
Satellite groups/ unique design:	9/sex/dose group and d-MPH (TK) No unique study design
Deviation from study protocol affecting interpretation of results:	Yes

LD: low dose; MD: mid dose; HD: high dose
^Because of adverse clinical signs, the doses were lowered for the SDX high-dose group from 100 to 75 mg/kg and d-MPH comparator group from 50 to 37.5 mg/kg on Day 3 for males and Day 2 for females.

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were no test article-related deaths. There were 2 d-MPH related deaths (1 male from the d-MPH TK group was found dead on Day 5 and one female from the d-MPH TK group was euthanized because of clinical signs on Day 1).
Clinical Signs	Test article- and d-MPH-related clinical signs including increased activity, biting and licking of the home cage, excessive grooming, swollen or missing digits (probably from self-mutilation), scabs on various locations on the body (which were often accompanied by red substance), and head twitching were observed. The severity and/or incidence generally occurred in a dose-dependent manner with moderate to severe findings at the HD. No clinical signs were noted during the recovery period.
Body Weights	There were test article- and d-MPH related decreases in body weight gain over the dosing period consistent with a stimulant (% of control gain: 99.6 LDM, 80 MDM, 82 HDM, 75 d-MPHM, 91 LDF, 78 MDF, 67 HDF, 79 d-MPHF). During the recovery period, HD and d-MPH males and females had the same amount of body weight gain or increased body weight gain compared to controls, but HD and d-MPH males still weighed less than the control group at the end of the recovery period.
Ophthalmoscopy	There was no test article- or d-MPH-related findings.
Hematology	A small, but significant decrease in mean white blood cell (↓~20%), absolute neutrophil (↓~30%), and absolute monocyte (↓~37%) counts were seen on Day 29 for HDM and d-MPH comparators compared to controls. Neutrophil and monocyte counts were also decreased for MDM compared to controls (↓28% and 35%, respectively). There was no difference after the recovery period.
Clinical Chemistry	A dose-related increase in mean glucose (up to ↑29%) and sodium (up to ↑2%) was observed on Day 29 for males and females and for d-MPH comparator. Increase in mean total bilirubin (up to ↑ 18%) for MDM, HDM (not statistically significant) and d-MPHM observed on Day 29. Increase in mean alkaline phosphatase for d-MPHM (↑32%) on Day 29. Decrease in mean creatinine levels (up to ↓12%) for MDF, HDF, and d-MPHF on Day 29. No differences were seen after the recovery period.
Urinalysis	There was no test article- or d-MPH-related findings.
Gross Pathology	There was no test article- or d-MPH-related findings.

Organ Weights	Increases in absolute and relative liver (up to ↑23%) were observed for all female dose groups and d-MPH comparator on Day 29. Increases in absolute and relative kidney weights (up to ↑9%) were observed for HD and d-MPH females at Day 29. No differences were observed after the recovery period.
Histopathology Adequate battery: Yes	There was no test article- or d-MPH-related findings.

LD: low dose; MD: mid dose; HD: high dose.

A 28-Day Oral Toxicity Study with KP415 in Dogs with a 15-Day Recovery/Study No. 0436DK19.004:

- A dose-dependent increase in severity and/or incidence of clinical signs consistent with a stimulant, including increased activity, repetitive rapid movements from side to side, sudden intermittent movement, and increased respiration.
- Decreased body weight gain or body weight loss at the end of dosing consistent with a stimulant.
- Findings in SDX dose groups were similar to findings in the d-MPH comparator group.
- The NOAEL is <10 mg/kg based on the clinical signs and effects on body weight.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle control), 10 (LD), 20 (MD), 40/30 (HD)^ mg/kg/day SDX (KP515) Cl and 10 mg/kg/day d-MPH Cl Once daily for 28 days
Route of administration:	Oral gavage
Formulation/Vehicle:	Solution/deionized water
Species/Strain:	Dog/beagle
Number/Sex/Group:	5/sex/control, HD, and d-MPH groups (2/sex/group for recovery group); 3/sex/LD and MD groups
Age:	7 - 8 months
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

LD: low dose; MD: mid dose; HD: high dose
^Because of the severity and duration of adverse clinical signs, the doses were lowered for the SDX high dose group from 40 to 30 mg/kg on Day 10 for females and Day 11 for males.

Observations and Results: changes from control

Parameters	Major findings
Mortality	There was no test article- or d-MPH-related deaths.
Clinical Signs	Test article- and d-MPH-related clinical signs included increased activity, repetitive rapid movements from side to side, sudden intermittent movement, increased respiration, excessive licking, vocalization and small to medium amount of salivation. Frequency and severity of clinical signs increased with increasing dose.
Body Weights	Test article- and d-MPH-dosed dogs gained less weight compared to controls or lost weight over the dosing period [mean gain (kg) from Day 1 to Day 28: 0.29 control M, 0 LDM, 0.1 MDM, 0 HDM, -0.4 d-MPHM, 0.32 control F, -0.04 LDF, 0.06 MDF, -0.26 HDF, -0.58 d-MPHF]. HD and d-MPH males and females gained more weight compared to controls during the recovery period [mean gain (kg) 0.2 control M, 0.35 HDM, 0.3 d-MPHM, -0.1 control F, 0.55 HDF, 0.5 d-MPHF]. In general, decreased body weight gain correlated with decreased food consumption at timepoints throughout the dosing period and increased body weight gain correlated with increased food consumption at timepoints throughout the recovery period.
Ophthalmoscopy	There was no test article- or d-MPH-related findings.
ECG	There was no test article- or d-MPH-related findings.
Hematology	There was no test article- or d-MPH-related findings.
Clinical Chemistry	There was no test article- or d-MPH-related findings.
Urinalysis	There was no test article- or d-MPH-related findings.
Gross Pathology	There was no test article- or d-MPH-related findings.
Organ Weights	Increase in relative liver weight (↑24%) was observed for HD and d-MPH males on Day 29, but not after the recovery period.
Histopathology Adequate battery: Yes	There was no test article- or d-MPH-related findings.

LD: low dose; MD: mid dose; HD: high dose.

General toxicology; additional studies

Single-dose and 14-day oral gavage studies were conducted in rats [single doses ≤800 mg/kg (Study No. 0406RK19.004) and 14-day doses ≤ 48.8 mg/kg (Study No. 0437RK19.007)] and dogs [single doses ≤120 mg/kg (Study No. 0433DK19.004) and 14-day doses ≤9.8 mg/kg (Study No. 0437DK19.006)]. Findings were consistent with those observed with d-MPH (including hyperactivity, cage licking, excessive biting and self-mutilation).

Reviewer comment: Findings from general toxicology studies up to 28-days in duration in 2 species confirm that in rat and dog the dose-limiting toxicities for SDX administration are known stimulant effects attributed to d-MPH. No unique toxicities were observed that could be attributed to either SDX or a unique metabolite of SDX. However, even though SDX is a prodrug of an approved product (d-MPH), we determined that a chronic study adequately assessing SDX toxicity in an appropriate species was needed because SDX is an NME that has a longer half-life in humans (~5.7 hours) compared to other species (~0.5-2 hours). We determined that this study could be conducted in juvenile animals to cover the pediatric indication. Based on the Applicant's cross-species analysis, rabbit was determined to be the most appropriate species to characterize the effects of SDX (see Species Justification for Reproductive and Developmental Toxicology Studies, Section 1.5.4, for more details). Because no unique toxicities were identified in the chronic juvenile toxicology study in rabbits (study reviewed under Reproductive and Development Toxicology Section, Section 1.5.4, for more details), we conclude that a chronic toxicology study in a second species is not needed for SDX.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Bacterial Reverse Mutation Assay/Study No. AE52EC.502ICH (b) (4)

Key Study Findings:

- SDX was negative for mutagenicity in bacterial cells in a valid Ames assay.

GLP compliance: yes
Test system: *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2 *uvrA*; concentrations ≤ 5000 µg/plate in water ±S9
Study is valid: yes

In Vitro Assays in Mammalian Cells

In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)/Study No. AE52EC.348ICH (b) (4)

Key Study Findings:

- SDX was negative for clastogenicity in human lymphocytes in a valid in vitro micronucleus assay.

GLP compliance: yes
Test system: Human peripheral blood lymphocytes; concentrations ≤ 500 µg/mL in water ±S9
Study is valid: yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

In Vivo Mammalian Micronucleus Assay and Mammalian Alkaline Comet Assay in Rats with Flow Cytometry Analysis in Peripheral Blood Reticulocytes/ Study No. AE52EC.433MFLOWPBICH. (b) (4)

Key Study Findings:

- SDX was not clastogenic in a valid in vivo micronucleus assay and Comet assay up to a dose of 100 mg/kg.

GLP compliance: yes
Test system: rat, bone marrow micronuclei and Comet assay in liver, duodenum, and stomach cells; 4 daily doses of 25, 50, and 100 mg/kg in water by oral gavage; bone marrow was collected 3 to 4 hours after the last dose
Study is valid: yes

5.5.3. Carcinogenicity

Carcinogenicity studies were not conducted with SDX. The Applicant is relying upon the carcinogenicity data in the referenced product labeling.

Reviewer comment: Typically, an NME for a chronic indication would require carcinogenicity studies in two species. However, SDX is a prodrug for an approved product (d-MPH) that predominantly releases MPH and other products that are either found endogenously and/or obtained in diet at levels greater than what will be released at the MRHD. SDX has low oral bioavailability in humans (<3%), has no pharmacological activity at serotonin, dopamine, or norepinephrine transporters or 68 other molecular targets examined, and is not genotoxic in a battery of assays. The Applicant notes that >97% of SDX remains in the gastrointestinal (GI) tract in humans following oral administration. Therefore, potential for local GI effects should be addressed. However, because of the species differences in kinetics for SDX, rodents don't appear to be a relevant species to address local GI toxicity. Based on an approximate 20% decrease in body weight gain at 50 mg/kg in the 28-day rat toxicology study, the MTD for a carcinogenicity study would most likely be considered 25 mg/kg which is ~0.33-fold of human exposure (although we recognize that dosing is typically determined from 3- or 6- month rat studies where body weight effects could be different, the effect of d-MPH on body weight is very well recognized). In addition, the half-life of SDX is around 0.5 hours at 25 mg/kg in rats, suggesting that the amount of time of exposure in the GI tract in rats will be much shorter than in humans (half-life ~5.7 hours in humans). This indicates that rats are not a good model to observe for local GI toxicity. In addition, there were no toxicities identified in the GI tract in any toxicology study, including the chronic juvenile rabbit study (we recognize that the half-life in rabbits is still shorter than humans, but a half-life of ~2 hours at the high dose gives considerably more exposure time than in rats). Therefore, considering the weight-of-evidence, we agree that carcinogenicity studies are not needed for SDX.

5.5.4. Reproductive and Developmental Toxicology

Species Justification for Reproductive and Developmental Toxicology Studies: The Applicant determined that the rabbit was the most appropriate species for the pivotal embryo-fetal development and chronic juvenile animal study based on cross-species analysis using relative exposure ratios using dose normalized AUC values (see Appendix, page 129, for details). They concluded that rabbits may tolerate higher doses of SDX per body weight or per body surface

area than dogs if comparable d-MPH exposure produces comparable pharmacodynamic responses in dogs and rabbits because dogs have a higher d-MPH exposure at the same SDX dose.

*Reviewer comment: Although rabbit is not a conventional species for a juvenile animal study, we agree that it is the most appropriate species for the two pivotal studies (rabbit is typically used for embryo-fetal development). Because SDX is an NME that is not rapidly metabolized to d-MPH in humans ($T_{1/2}$ is ~5.7 hours) and will be used chronically, SDX needs to be adequately assessed for toxicity. In addition, because d-MPH-related clinical signs are dose-limiting in animals and already known (both for animals and humans), testing SDX in a species that minimizes d-MPH exposure is also needed in order to test adequate SDX doses that provide high margins to human doses. Based on the PK profiles comparisons across species [including concentration curves (*Figure 20*, page 124 and* Figure 21*, page 125)], rabbit appears to be the most appropriate species.*

Fertility and Early Embryonic Development

Fertility and early embryonic development studies were not conducted with SDX. The Applicant is relying upon the developmental toxicity data in the referenced product labeling.

Reviewer comment: Based on results from the embryo-fetal development and chronic juvenile animal studies, we agree that fertility and early embryonic development and prenatal and postnatal development studies do not need to be conducted with SDX. As previously stated, no unique toxicities were observed that could be attributed to either SDX or a unique metabolite of SDX in completed toxicology studies and the d-MPH-related effects are dose-limiting in rats at exposures ~0.33-fold the exposures of SDX at the MRHD.

Embryo-Fetal Development

Oral Gavage Embryo-Fetal Developmental Toxicity and Toxicokinetic Study with KP415 in Rabbits/Study No. 8381422

Key Study Findings

- There were no findings of maternal or fetal development toxicity.
- The NOAEL is 400 mg/kg SDX for maternal and fetal development toxicity which is 49-times, the human exposure at the MRHD ($AUC_{24h,ss}$ = 241 ng.h/mL).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 100 (LD), 200 (MD), 400 (HD) mg/kg SDX (KP415) Cl Once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Solution/deionized water

Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	22/group
Satellite groups:	None
Study design:	Dosing was from gestational day (GD) 7 through 19. A high dose of 400 mg/kg was chosen because 300 mg/kg was well tolerated in the dose range-findings study. In addition, 400 mg/kg KP415 is equimolar to 200 mg/kg d-MPH HCl which the Applicant says exceeded the highest does of d-MPH HCl used in a previous developmental toxicity study in rabbits.[1]
Deviation from study protocol affecting interpretation of results:	No

LD: low dose; MD: mid dose; HD: high dose

Observations and Results

Parameters	Major findings
Mortality	There were 2 unscheduled deaths that were not test article related. One LD dam (No. B0122) was euthanized on GD 19 because of an aborted fetus. This animal had lower body weight from predose (GD 4) through GD 17 with ears cold to touch from GD 14 through GD 17. One MD dam (No. B0209) was euthanized on GD 9 because of a fractured left hind limb and was replaced with another animal (No. B0223).
Clinical Signs	No remarkable findings.
Body Weights	HD group gained 15% more weight compared to controls from GD 7 to 20.
Necropsy findings Cesarean Section Data	No test article-related effects (see Table 47, page 130 in Appendix).
Necropsy findings Offspring	The number of litters and fetuses with malformations of any type were slightly higher at the HD compared to the controls; although, there is not a clear dose response (litters/fetuses with malformations: 4/7 control, 6/7 LD, 4/5 MD, and 10/10 HD). There was an increase in litters (but not fetuses) at the HD with fused sternebrae compared to controls (litters/fetuses with fused sternebrae: 3/6 control, 3/3 LD, 2/2 MD, and 6/7 HD).

[1] Beckman DA, M Schneider, M Youreneff and FL Tse (2008) Developmental toxicity assessment of d,l-methylphenidate and d-methylphenidate in rats and rabbits. Birth Defects Res B Dev Reprod Toxicol; 83(5):489-501.

	However, it is a common finding in rabbits and there is not a clear dose response. Therefore, these findings are unlikely test article related. See Table 48 and Table 49 for all offspring and malformation data, page 130 in Appendix.

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

A pre- and postnatal development study was not conducted with SDX. As noted above, further studies to characterize the effect of SDX and unique metabolites were not deemed warranted for the reasons stated. The Applicant is relying upon the reproductive and developmental toxicity data in the referenced product labeling.

Juvenile Animal Study

A dose range-finding study (Study No. 20144933) in New Zealand White rabbits was conducted from postnatal day (PND) 28 through PND 42 with oral gavage doses of 200, 400/300, and 800 mg/kg SDX. The 800 mg/kg dose group was euthanized prematurely on the second day of dosing (PND 29) because of adverse clinical signs (excessive licking, grooming, and scratching that resulted in self-mutilation), body weight loss from PND 28 to 29 for males (-16 g), and two females were found dead prior to dosing on PND 29. The mid dose was reduced from 400 mg/kg to 300 mg/kg on PND 31 because of mortality (1 MDM was found dead 8 mins after dosing on PND 33, 1 MDF was found dead 2 mins after dosing on PND 29, and 1 MDM was euthanized on PND 29 because of adverse clinical signs) and adverse clinical signs (excessive licking, scratching, grooming, and thin fur). The MTD for the definitive study was determined to be 300 mg/kg.

A 6-Month Study of KP415 Administered by Oral (Stomach Tube) Administration in Juvenile Rabbits with a 1-Month Recovery Period/Study No. 20144952

- Findings consistent with a stimulant include excessive licking, increased activity, and small decreases in mean body weight gain and mean body weight at the end of dosing (less than 10%); however, because these findings were mild, they were not considered adverse.
- SDX-related findings were limited to small increases in gamma-glutamyl transferase activity (GGT) for males dosed with 300 mg/kg and females dosed with 150 and 300 mg/kg (1.42, 1.41, and 1.72, respectively).
- Non-adverse, minimal-to-moderate hepatocellular pigmentation that may be lipofuscin was observed dose-dependently at the end of dosing and the end of the recovery period. Because there were similar findings in d-MPH females and lower to similar findings in d-MPH males the hepatocellular pigmentation is unlikely SDX related. Increases in GGT did not correlate with hepatocellular pigmentation findings.

- The NOAEL is 300 mg/kg, which is ~50-times the MRHD dose for juveniles based on body surface area (no human plasma levels at MRHD in juveniles were available).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (VC), 75 (LD), 150 (MD), 300 (HD) mg/kg SDX (KP415) Cl and 75 mg/kg d-MPH HCl^ Once daily for 6 months
Route of administration:	Oral gavage
Formulation/Vehicle:	Solution/reverse osmosis deionized water
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	10 sex/group main; 3/sex/group Recovery; 8 - 10/sex/group dose replacement
Age:	Postnatal day (PND) 28
Satellite groups/unique design:	No satellite groups.
	Dosing was from PND 28 to PND 196. Main group animals were euthanized on PND 197 and recovery group animals were euthanized on PND 224 (1-month recovery period). Four rabbits had a dosing holiday from PND 53 to 60.
	Because of the large mortality observed early in the study across all groups, replacement animals were used, and study endpoints were evaluated and included in the data. In addition, animals originally designated for TK (5/sex/group) were reassigned to the main or recovery groups to ensure enough animals were available. Bioanalytical sample collection was added at the end of dosing (PND 196) for main group animals and at the end of recover (PND 224) for recovery group animals.
Deviation from study protocol affecting interpretation of results:	No

VC: vehicle control; LD: low dose; MD: mid dose; HD: high dose.
^150 mg/kg SDX Cl is equimolar to 75 mg/kg d-MPH HCl

Observations and Results: Changes from Control

Parameters	Major findings
Mortality	There was no test article- or d-MPH-related deaths. There was a total of 63 premature mortalities across all dose groups (including controls) during the study and most of these deaths were determined to be gavage or probably gavage related (see Table 50, page 131 and Table 51, page 132 in Appendix). In support of this, 81% of the deaths occurred between PND 28 through 66, a period that the pharynx region of juvenile rabbits is undergoing continuous developmental changes.
Clinical Signs	Clinical signs observed include excessive licking (cage and self) in all male dose groups and MD and HD females and increased activity in HD male and female dose groups which is consistent with findings for the comparator d-MPH. In addition, clinical signs observed for the comparator d-MPH dose group include excessive grooming, dilated pupils, and/or twitches along the muzzle during the dosing period. No test article-related clinical signs were reported during the recovery period.
Body Weights	HD and d-MPH males gained less weight compared to controls over the dosing period (94%) and weighed 6% less than controls at the end of the dosing period. During the recovery period, mean body weight gains were variable across the dose groups and mean body weights remained lower compared to controls for HD and d-MPH males (88% HDM and 87% d-MPH). All dosed female groups gained less weight compared to controls over the dosing period (90% LDF, 94% MDF, 92% HDF, and 85% d-MPHF) and weighed less than controls at the end of dosing (-9% LDF, -6% MDF, -8% HDF, and -14% d-MPHF). During the recovery period, there was no difference in body weights compared to controls for SDX dosed females; however, mean body weight gain remained less than controls for d-MPH females (85%).
Ophthalmoscopy	There was no test article- or d-MPH-related findings.

Hematology	There were no test article-related effects on hematology or coagulation parameters. Decreases in red blood cell count (0.94X), hemoglobin (0.95X), hematocrit (0.96X), reticulocyte counts (0.82X), white blood cell counts (0.84X), and lymphocyte counts (0.78X) for d-MPH males compared to controls were noted. In addition, there was a small decrease in prothrombin time (PT) for MDM, HDM, and d-MPHM compared to controls (0.94x, 0.93X, and 0.93X, respectively). However, these are not test article-specific because similar findings were observed with the comparator d-MPH. No difference in PT was observed after the recovery period or in females.
Clinical Chemistry	Increases in gamma-glutamyl transferase activity (GGT) were noted for HDM (1.42X), MDF (1.41X), and HDF (1.72X) compared to controls. The only liver histopathologic findings noted were hepatocellular pigmentation. However, hepatocellular pigmentation was also noted in d-MPHF with no changes in GGT. Therefore, the increase in GGT did not correlate with microscopic liver findings and is most likely not adverse. Increases in total bilirubin (2.19X) and globulin (1.16X) and decreases in A/G ratio (0.85X) were noted for d-MPHF compared to controls. No differences in clinical chemistry parameters were observed after the recovery period.
Urinalysis	There was no test article- or d-MPH-related findings.
Gross Pathology	There was no test article- or d-MPH-related findings.
Organ Weights	There was no test article- or d-MPH-related findings.
Histopathology Adequate battery: Yes	Findings were limited to minimal-to-moderate hepatocellular pigmentation that may be lipofuscin observed at the end of dosing and the recovery period. Although pigmentation occurred in a dose-dependent manner in test article-dosed groups, the incidence and severity were similar for d-MPH males and females compared to the equimolar SDX groups (MD) at the end of dosing (females only) and the recovery period. Pigmentation was also observed in 1 or 2 male and female control animals and d-MPH males at the end of dosing. Therefore, the presence of hepatocellular pigmentation is unlikely test article related. See Appendix, page 133, for more details and Table 52, Table 53, Table 54, and Table 55.
Special Evaluation: Neurobehavioral Assessments	There were no abnormal findings noted on open field observations.

Special Evaluation: Sexual Maturity	There were no test article- or d-MPH-related effects on sexual maturation in males or females. The mean number of days to preputial separation and body weight at time of preputial separation for males were similar across groups (Day: 72.5 VC, 75.7 LD, 77.5 MD, 73.1 HD, 72.2 d-MPH; BW (g): 2139 VC, 2132 LD, 2212 MD, 2109 HD, 2070 d-MPH). The mean number of days to vaginal patency and body weight at time of vaginal patency for females were similar across groups (Day: 40.7 VC, 39.8 LD, 40.4 MD, 39.7 HD, 39.9 d-MPH; BW (g): 10090 VC, 923 LD, 933 MD, 896 HD, 925 d-MPH). According to the pathologist report, microscopic evaluation of reproductive tract structures was consistent with attainment of sexual maturity by most or all animals within all dose groups. There were no discernable test article-related effects on any of the reproductive organs evaluated in males and females.
Special Evaluation: Male Reproductive Assessment	There was no test article- or d-MPH-related effects on sperm motility or sperm concentrations in male rabbits at ~5.4 months (preconditioning phase, first ejaculate), at the end of dosing (~6.3 months, second ejaculate), or in the recovery period (~7.5 months). Based on the data, the male rabbits are considered to be sexually mature by the end of dosing.
Special Evaluation: Bone Density	There was no test article- or d-MPH-related effects on femur length or on bone density.

VC: vehicle control; LD: low dose; MD: mid dose; HD: high dose.

Reviewer comment: d-MPH exposures after a single-dose of 400 mg/kg SDX Cl in juvenile rabbits was 3-times the d-MPH exposures after a single-dose of 400 mg/kg SDX Cl in pregnant rabbits which might account for the observance of adverse clinical signs in juvenile rabbits but no clinical signs in pregnant rabbits.

5.5.5. Other Toxicology Studies

Local Tolerance

Evaluation of KP415 to Induce Hemolysis in Whole Human Blood (Study No. 0725XK19.001; GLP): SDX caused 55% hemolysis of human blood at 40 mg/mL; but, did not cause hemolysis at 8 and 16 µg/mL.

Evaluation of KP415 to Induce Flocculation in Human Plasma and Serum (Study No. 0726XK19.001; GLP): No precipitation or coagulation was observed macroscopically or microscopically in human plasma, serum, or phosphate buffered saline (PBS) samples containing SDX concentrations ≤20 mg/mL.

Intravenous Irritation Study in Rabbits (GLP) with KP415 (Study No. 0452LK19.001; GLP): A single bolus intravenous administration (~60 seconds) of 20 mg/mL SDX into the ear of rabbits resulted in findings (no to slight erythema and edema and histopathological vascular and perivascular findings) similar to vehicle (PBS). The histopathological vascular and perivascular findings are most likely related to the injection procedure rather than to vehicle or SDX.

Impurity Qualification

A (b) (4) process impurity, (b) (4) identified as a plausible mutagen by DEREK analysis (b) (4) was determined to be negative in a valid AMES assay (see below); therefore, (b) (4) is considered a Class 5 impurity.

Bacterial Reverse Mutation Assay (CI-KP415)/Study No. AF05WR.502ICH (b) (4)
Key Study Findings:

- (b) (4) was negative for mutagenicity in bacterial cells in a valid Ames assay.

GLP compliance: yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 *uvrA*; concentrations ≤ 5000 µg/plate in water ±S9

6 Clinical Pharmacology

6.1. Executive Summary

Commave Therapeutics SA has submitted a New Molecular Entity (NME) 505(b)(2) NDA for KP415 for the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients six years of age and older. The listed drug (LD), Focalin XR (NDA 21802), is an extended-release capsule formulation of dexmethylphenidate (d-MPH) hydrochloride, approved in 2005 for the indication of treating ADHD in patients aged six years and older.

KP415 is an oral, once-daily capsule that comprises immediate-release serdexmethylphenidate (SDX, a prodrug of d-MPH), and immediate-release d-MPH. It is formulated in a fixed molar dose ratio of 70% SDX chloride (Cl) to 30% d-MPH hydrochloride (HCl). Chemically, SDX consists of a single d-MPH molecule covalently attached via a carbamate bond to a methylene oxide linker, which in turn is connected to the nitrogen of the pyridine ring of a nicotinoyl-serine moiety. The final to-be-marketed formulation has been developed in three dosage strengths: 26.1/5.2 mg; 39.2/7.8 mg; 52.3/10.4 mg SDX/d-MPH (free-base weight), corresponding to total molar equivalent doses of 20, 30, and 40 mg Focalin XR, respectively.

The safety and efficacy of KP415 in treating patients with ADHD was established in a laboratory classroom study (KP415.E01) in children 6 to 12 years old. The study consisted of a screening period, a 3-week, open-label Dose-Optimization Phase, and a 1-week, double-blind Treatment Phase. The study met the prespecified primary endpoint of mean SKAMP score change from baseline (predose Visit 5) at Visit 6.

There is a total of ten clinical pharmacology studies conducted in the development program, assessing either SDX Cl alone or SDX Cl/d-MPH HCl combination (KP415). Pivotal PK studies include: a mass balance study with ^{14}C-labeled SDX Cl (KP415.111); a single-dose, relative bioavailability study comparing SDX/d-MPH to the LD, Focalin XR (KP415.107); a single-dose, dose-proportionality study, followed by a multiple-dose, steady-state phase with the highest dosage strength (KP415.110); a food effect study with highest dosage strength (KP415.104); and a PK study in pediatric and adolescent patients with ADHD (KP415.105). Additionally, PK information have also been obtained from three human abuse liability (HAP) studies where SDX was administered orally (KP415.A01), intranasally (KP415.A02), and intravenously (KP415.A03). QT-Concentration relationship was explored in the program. In vitro studies using human biomaterials were conducted to evaluate epithelial cell permeability, plasma protein binding, hepatic metabolism, and metabolism- and transporter-based drug-drug interaction potential of SDX.

OCP's major findings are summarized as follows:

1. Adequate linkage of KP415 to the LD Focalin XR has been established through a relative bioavailability study.
2. Similar PK profile shapes were demonstrated in children 6 to 12 years old, adolescents, and adults. The exposure of d-MPH in adolescents and adults are comparable, about 50% lower than that in children 6 to 12 years old, after the same dose administration of KP415.
3. KP415 can be administered with or without food. Capsules may be swallowed whole or opened and the entire contents sprinkled on applesauce or added to water.

In this review, SDX/d-MPH is used interchangeably with KP415.

6.1.1 Recommendations

Review Issue	Recommendations and Comments
General dosing instructions	The proposed starting dose of KP415 for patients 6 years and older is (b) (4) mg once daily in the morning. We recommend the dose should be started at 39.2/7.8 mg, which is same as the clinical trial dosing regimen. The dose may be titrated up or down weekly in increments of 13.1/2.6 mg based on response. Daily doses above 52.3/10.4 mg have not been studied and are not recommended.
Dosing in patient subgroups (intrinsic and extrinsic factors)	KP415 is given orally once daily in the morning with or without food. Capsules may be swallowed whole or opened and the entire contents sprinkled on applesauce or added to water. Dosage adjustment of KP415 is not considered necessary based on intrinsic or other extrinsic factors.
Labeling	Pending satisfactory agreement with the Applicant
Bridge between the to-be-marketed and clinical trial formulations	The formulation used in the clinical trials was same as the to-be-marketed formulation.

6.1.2 Post-Marketing Requirements and Commitments

None

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

KP415 is a combination product containing serdexmethylphenidate chloride (SDX Cl) and dexmethylphenidate hydrochloride (d-MPH HCl). SDX is a prodrug of d-MPH and is not deemed to have pharmacological activity. The conversion of SDX to d-MPH most likely takes place mainly in the lower gastrointestinal tract.

Steady state of d-MPH seems to be approached after the third once-daily dose of KP415. Mean steady state d-MPH exposures (C_{max} and $AUC_{0\text{-}24h}$) were approximately 37% higher compared to a single dose administration. No significant accumulation of SDX was observed after multiple once daily dosing. The mean relative exposure of SDX to d-MPH based on molar concentrations for C_{max}, C_{min}, and $AUC_{0\text{-}24hr}$ was about 101%, 8.5%, and 55.7%, respectively, following multiple once daily oral dosing in healthy adults under fasted conditions.

The following is a summary of the clinical pharmacokinetic features following KP415 administration:

Absorption: Mean maximal plasma concentrations of SDX and d-MPH were reached approximately 2 hours after oral dosing of KP415 under fasted conditions. Following administration of 52.3/10.4 mg KP415 and 40 mg Focalin XR in healthy volunteers under fasted conditions:

- The mean peak plasma concentration (Cmax) of d-MPH was 14.0 ng/mL and 28.2 ng/mL, respectively;
- The mean area under concentration curve (AUC) of d-MPH was 186 hour*ng/mL and 248 hour*ng/mL, respectively.

Distribution: Plasma protein binding of SDX and d-MPH was approximately 56% and 47%, respectively, at 5 uM in vitro. Mean volume of distribution of SDX was 29.3 L/kg after KP415 dosing, and d-MPH shows a mean volume of distribution of was 2.65 L/kg.

Elimination: The mean plasma terminal elimination half-life of SDX and d-MPH was about 5.7 hours and 11.7 hours, respectively, following a single dose of 52.3/10.4 mg KP415 administration in healthy adults. The mean oral clearance of SDX was 3.6 L/hr/kg after KP415 dosing. Dexmethylphenidate was eliminated with a mean clearance of 0.40 L/hr/kg after intravenous administration.

Metabolism: Conversion of SDX to d-MPH most likely takes place mainly in the lower gastrointestinal tract and enzymes involved in the process are yet to be identified.

Dexmethylphenidate is metabolized primarily via de-esterification to d-α-phenyl-piperidine acetic acid (also known as d-ritalinic acid). This metabolite has little or no pharmacological activity.

Excretion: After oral dosing of radiolabeled SDX (single moiety) in humans, approximately 0.4% and 11% of the dose was excreted unchanged in urine and feces, respectively. The main urinary and fecal metabolite of SDX was ritalinic acid (RA), accounting for approximately 63% of the total recovered dose.

After oral dosing of radiolabeled racemic methylphenidate, about 90% of the radioactivity was recovered in urine, with RA accounting for approximately 80% of the dose.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The recommended starting dose of KP415 for patients 6 years and older is 39.2/7.8 mg once daily in the morning. The dose may be titrated up or down weekly in increments of 13.1/2.6 mg. Daily doses above 52.3/10.4 mg have not been studied and are not recommended. The dose should be individualized according to the needs and response of the patient.

KP415 is given orally once daily in the morning with or without food. KP415 may be taken whole or the capsule may be opened, and the entire contents sprinkled on applesauce or added to water.

Therapeutic Individualization

Hepatic Impairment
KP415 has not been studied in patients with hepatic impairment. However, hepatic impairment is not expected to have significant effect on the pharmacokinetics following KP415 administration. Dosage adjustment is not expected to be necessary for patients with impaired hepatic function.

Renal Impairment
Because renal clearance is not an important route of SDX or d-MPH elimination, renal impairment is expected to have little effect on the pharmacokinetics following KP415 administration. Dosage adjustment is not considered necessary for patients with impaired renal function.

Race and Sex
Dose adjustment based on race and sex is not necessary. No significant differences in PK parameters of d-MPH were observed/expected by sex/race. Dose should be adjusted based on clinical response.

Food Effect
While the presence of food (sprinkled on applesauce or high-fat, high calorie food), decreased the absorption and exposure of SDX to varying degrees, the exposure to d-MPH, the active

moiety, was increased to a maximal of 33% for Cmax and 16% for AUC, compared to when KP415 capsule was administered intact under fasted conditions. The median time to peak plasma concentration (T_{max}) was lengthened from 2 to 4-4.5 hours in the presence of food. Minimal effect was observed on d-MPH exposure when KP415 capsule was opened and content was added to water. KP415 should be administered without regard to food.

Outstanding Issues

None

Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

- KP415 can be administered without regard to food. Adding the capsule contents to water or sprinkling on applesauce are acceptable alternative modes of drug administration.
- In general, dose adjustment is not necessary in patients based on race, gender, age, renal impairment, or hepatic impairment status.
- At a mean concentration 40 times the C_{max} for the highest dose of KP415 (52.3/10.4 mg base equivalent), SDX does not prolong the QT interval to any clinically relevant extent.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The mechanism of action of d-MPH in ADHD is unknown. However, d-MPH is a central nervous system stimulant that blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. SDX is a prodrug and is not deemed to have pharmacological activity until converted to d-MPH.
Active Moieties	d-MPH
QT Prolongation	The effect of SDX 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 Cmax of the highest dose of KP415 (52.3/10.4 mg base equivalent), SDX does not prolong the QT interval to any clinically relevant extent.
General Information	

<table>
<tr><td>Bioanalysis</td><td colspan="3">SDX and d-MPH concentrations were measured using LC-/MS/MS methods in clinical trials. A summary of the respective method deployed in each study was included in the individual study review.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td colspan="3">
<table>
<tr><td colspan="3">Plasma Exposure of SDX and d-MPH Following KP415 52.3/10.4 mg Once Daily Dosing on Day 4</td></tr>
<tr><td>PK Parameters</td><td>SDX</td><td>d-MPH</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>41.7 (38)</td><td>20.0 (4.73)</td></tr>
<tr><td>AUC_{24hr} (hr*ng/mL)</td><td>241 (160)</td><td>215 (49.4)</td></tr>
<tr><td colspan="3">Data presented as mean (SD);
-source: Tables 20 and 21 of study KP415.110 CSR</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Maximum tolerated dose or</td><td>Single Dose</td><td colspan="2">Not Available</td></tr>
<tr><td>Multiple Dose</td><td colspan="2">Not Available</td></tr>
<tr><td>Dose Proportionality</td><td colspan="3">Approximate linear PK seems to be demonstrated for d-MPH following single dose administration of SDX/d-MPH in the range of 26.1/5.2 mg to 52.3/10.4 mg</td></tr>
<tr><td>Accumulation</td><td colspan="3">Accumulation ratio: ~1.37 (d-MPH); ~1.0 (SDX)</td></tr>
<tr><td colspan="4">Absorption
- Absolutely bioavailability: less than 3% (SDX, cross-study calculation)
- T_{max} (median): 2 hours post dose under fasted conditions (SDX and d-MPH)
- Food effect: Ingestion of food (high-fat/high-calorie meal or apple sauce) resulted in about 24-34% and 14-16% increase in d-MPH C_{max} and $AUC_{inf,}$ respectively; a delay of approximately 2 hours in d-MPH T_{max} was observed.</td></tr>
<tr><td colspan="4">Distribution
- Volume of distribution: 29.3 L/kg (SDX, following KP415 administration), 2.65 L /kg (d-MPH, Focalin XR label)
- Plasma protein binding: 56% (SDX), 47% (d-MPH) in vitro at 5 uM (about 60-fold of therapeutic concentrations at the highest recommended dose)</td></tr>
<tr><td colspan="4">Elimination:
- Clearance: ~ 3.6 L/hour/kg (SDX, following KP415 administration) and 0.4 L/hour/kg (d-MPH, following IV administration of d-MPH Cl, from Focalin XR label)
- Mean terminal elimination $T_{1/2}$: ~5.7 hours (SDX) and 11.7 hours (d-MPH) following KP415 administration
- Metabolism: SDX is metabolized to d-MPH and enzymes involved in the process are not identified. Conversion from SDX to d-MPH most likely mainly takes place in the lower gastrointestinal tract. d-MPH is mainly metabolized to ritalinic acid.
- Relative exposure: Following multiple once daily oral dosing in healthy adults under fasted conditions, mean relative exposure of SDX to d-MPH based on molar concentrations for C_{max}, C_{min}, and $AUC_{0\text{-}24hr}$ was about 101%, 8.5%, and 55.7%, respectively.
- Renal excretion: After oral dosing of radiolabeled SDX in humans, about 0.4% of the dose was excreted as unchanged SDX in the urine. About 45% of the radioactivity was recovered as RA in the urine within 72 hours of dosing. Urinary excretion of unchanged methylphenidate accounted for 0.5% of an intravenous dose of d-MPH Cl.
- Transporters substrate: SDX does not appear to be a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE-1 or MATE2-K.</td></tr>
</table>

- Transporter inhibition: SDX does not appear to be an inhibitor of P-gp, BCRP, MRP1, MRP2, MRP3, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, ASBT, or NTCP transporters, or MATE-1 and MATE2-K. Significant drug interactions at clinically relevant concentrations are not expected.
- CYP enzymes: SDX are not metabolized by CYP enzymes to a clinically relevant extent. SDX does not appear to be an inducer or an inhibitor of 3A4, 2C9, 2D6, 1A2, 2C8, 2B6, 2E1 or 2C19. Significant drug interactions at clinically relevant concentrations are not expected.
- UGT enzymes: SDX was found not to be a substrate or inhibitor for UGT enzymes UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Is adequate linkage established between KP415 and the LD (Focalin XR)?

Yes, adequate linkage is established between KP415 and the LD (Focalin XR) through a relative bioavailability study in healthy subjects.

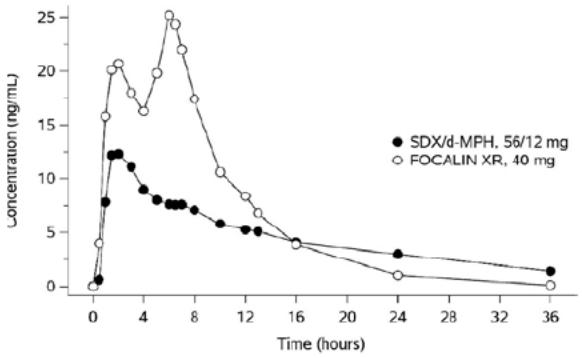
Compared to 40 mg Focalin XR, the mean C_{max} and AUC_{inf} of d-MPH following a single dose administration of 52.3/10.4 mg KP415 were approximately 39% and 25% lower, respectively, with the 90% CI of both ratios out of the 80-125% limits (Table 15). The shapes of d-MPH PK curves are also different, with two peaks observed following Focalin XR administration, while only one peak for KP415 (Figure 2). Even though not bioequivalent, an adequate linkage is considered established between KP415 and the LD (Focalin XR).

Table 15: PK Parameters of d-MPH Following Single Dose Administration of KP415 or Focalin XR under Fasted Conditions

Parameters	KP415 (T, n=29)	Focalin XR (R, n=29)	Geomean Ratio (T/R, 90% CI)
C_{max} (ng/mL)	14.0±4.4	28.2±8.3	61.1 (57.8, 64.6)
T_{max} (hr)	2.0±1.0	6.3±1.7	--
AUC_{last} (hr*ng/mL)	179±70.1	242±87.8	73.3 (70.1, 76.6)
AUC_{inf} (hr*ng/mL)	186±69.6	248±85.6	75.0 (71.7,78.4)
$T_{1/2}$ (hr)	10.1±2.7	3.9±0.5	--

Data are presented as arithmetic mean ±SD; Test (T): a single dose of 52.3/10.4 mg KP415; Reference (R): a single dose of 40 mg Focalin XR
-Source: Table 8 KP415.107 CSR

Figure 2: Mean Concentration Time Profiles of d-MPH Following Single Dose Administration of KP415 or Focalin XR under Fasted Conditions

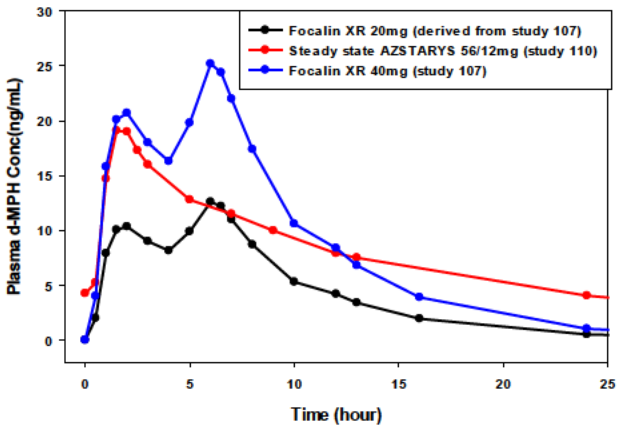


-Source: KP415.107 CSR

Upon multiple once daily dosing, about 37% increase in d-MPH exposure (AUC_{tau} and C_{max}) was observed for KP415, while about 2% increase in d-MPH exposure is expected for Focalin XR due to the shorter half life of Focalin XR (~ 4 hours). Therefore, d-MPH exposures between KP415 and Focalin XR become more comparable at steady state: mean C_{max} and $AUC_{0\text{-}24hr}$ of 52.3/10.4 mg KP415 were about 71% and 87% of 40 mg Focalin XR, respectively.

Of note, when compared to 20 mg Focalin XR, steady state concentrations of d-MPH at 52.3/10.4 mg KP415 are higher at most of the time points measured during the 24-hour dosing interval, except at the 2nd peak time of Focalin XR, where the levels appear similar (Figure 3). Per Focalin XR label, 20 mg was demonstrated to be an effective dose in adults, and there was no obvious increase in effectiveness with a dose higher than 20 mg (e.g., 30 mg or 40 mg). Therefore, the PK comparison of 52.3/10.4 mg KP415 and 20 mg Focalin XR in healthy subjects suggested that 52.3/10.4 mg KP415 may be effective in adults with ADHD.

Figure 3: Mean Plasma Concentration Time Profiles of d-MPH Following Multiple Dose Administration of KP415 or Focalin XR



-source: Reviewer's independent analysis

Note: Because minimal accumulation (~2%) of d-MPH is expected following multiple dosing of Focalin XR, data collected after single dose administration is employed in the figure. Additionally, data for 20 mg Focalin XR are derived from observed data following 40 mg Focalin XR administration, since Focalin XR label label states d-MPH demonstrated linear PK following Focalin XR administration.

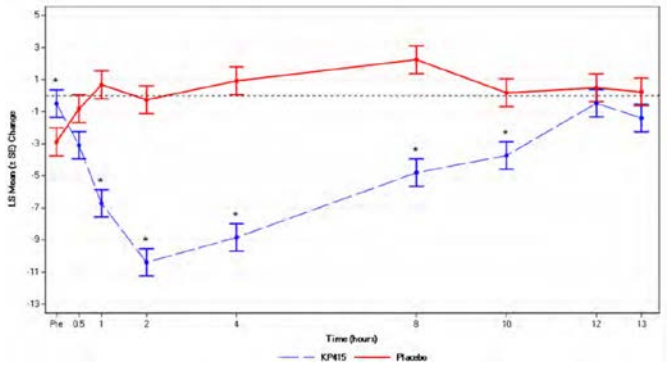
6.3.2.2 Can the indication for KP415 be approved in children aged 6-12 years, adolescents and adults?

Yes.

Children 6 to 12 Years Old

The safety and efficacy of KP415 in patients 6 to 12 years old with ADHD was established in a randomized, double-blind, placebo-controlled, parallel group, laboratory classroom study (KP415.E01, n=150). The study consisted of a screening period, a 3-week, open-label Dose-Optimization Phase, and a 1-week, double-blind Treatment Phase. In the open-label dose optimization phase (3 weeks), the initial dose for all subjects was 39.2/7.8 mg KP415 once daily in the morning. The dose could be titrated on a weekly basis to either 26.1/5.2 mg; 39.2/7.8 mg; 52.3/10.4 mg KP415 until an optimal dose or the maximum dose of 52.3/10.4 mg KP415 was reached. At the end of optimization period, subjects were randomly assigned into a 1-week parallel group treatment period to receive either the individually optimized dose of KP415 or placebo. The mean SKAMP change from baseline (predose Visit 5, primary endpoint) score for postdose time points (0.5. 1, 2, 4, 8, 10, 12, and 13 hours post-dose) at Visit 6 are shown in Figure 4. Refer to Section 8 for more discussion on study kp415.E01.

Figure 4: LS Mean (SE) SKAMP Combined Score from Baseline (Predose Visit 5) after Treatment with KP415 (KP415) or Placebo during Classroom Day

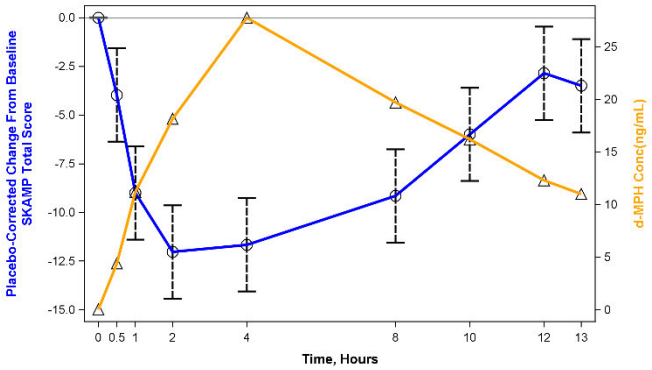


-source: Figure 3 KP415.E01 CSR

The pharmacokinetic/pharmacodynamic (PK/PD) relationship following KP415 administration in pediatric patients 6 to 12 years old was explored based on results from the pediatric PK study (KP415.105) and the safety and efficacy trial (KP415.E01). As demonstrated in Figure 5, the PD responses to MPH were closely mirrored by time-dependent plasma concentrations of MPH across the day, which is in alignment with literature-reported strong PK/PD correlation for MPH products. The discordance in Tmax for plasma concentration (~4 hours) and effect (~2 hours)

might be explained by the fact that PK study was conducted in fed condition (food delayed d-MPH Tmax from 2 hours postdose under fasted conditions to 4 hours postdose under fed conditions), while in efficacy trial whether the drug was taken with or without food was not well documented.

Figure 5: PK/PD Analysis after Treatment with KP415 in Children 6 to 12 Years old



-source: reviewer analysis

Adolescents and Adults

The efficacy and safety of KP415 in adolescent and adult patients have not been evaluated in clinical trials. However, KP415 is expected to be safe and effective in adolescents and adults from a clin pharm perspective, based on the following findings:

- Upon multiple dosing, KP415 52.3/10.4 mg has a comparable AUC and a lower Cmax of d-MPH as compared to Focalin XR 40 mg, the highest recommended dose of Focalin XR. Based on linear PK, KP415 26.1/5.2 mg and 39.2/7.8 mg are expected to have comparable AUCs of d-MPH as Focalin XR 20 mg and 30 mg, respectively.
- Steady state concentrations of d-MPH over 24 hours following adminstration of 52.3/10.4 mg KP415 is higher than that following adminstration of 20 mg Focalin XR. Per Focalin XR label, 20 mg Focalin XR was demonstrated to be effective in adults, and there was no obvious increase in effectiveness with a dose higher than 20 mg (e.g., 30 mg or 40 mg).
- Shapes of d-MPH PK profiles were shown to be similar in children, adolescents and adults following KP415 administration. The exposure were comparable in adolescents and adults after the same dose administration of KP415.
- Adequate bridge has been established between KP415 and Focalin XR (which is indicated in children, adolescents and adults), and KP415 (26.1/5.2 mg, 39.2/7.8 mg and 52.3/10.4 mg) was demonstrated to be safe and effective in children aged 6 to 12 years with ADHD.
- The clear PK/PD relationship across various methylphenidate formulations.
- The clinical practice of MPH pharmacotherapy is to individually titrate patients to find the optimal dose for ADHD.

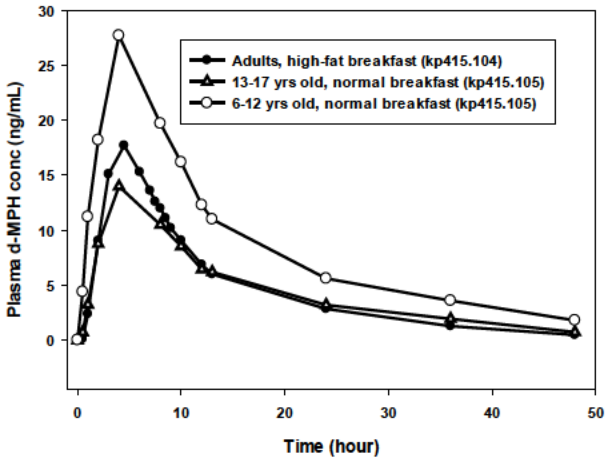
6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimen is required based on age, hepatic impairment, renal impairment, race or gender.

Age

The shapes of d-MPH concentration time profiles appear similar across age groups (Figure 6). The d-MPH exposure was comparable in adolescents and adults, about 50% lower than that in children 6-12 years old, after same dose administration of KP415 (Table 16). This may be because CL/F increases with age due to intrinsic body weight differences between younger children and adolescents/adults. After body-weight normalization, CL/F values of d-MPH were comparable across age groups. Exposure levels appear to be comparable between 6-8 years old and 9-12 years old (Table 16).

Figure 6: Plasma d-MPH Concentration Time Profiles Across Age Groups Following Single Dose Administration of 52.3/10.4 mg KP415



-Source: reviewer analysis

Note: Data in 6-12 age group contain dose-normalized concentration from 26.1/5.2 mg dose in children 6-8 years old and 52.3/10.4 mg dose in children 9-12 years old.

Table 16: PK Parameters (Mean (SD)) of d-MPH After Single Dose Administration of KP415 Across Age Groups

PK Parameters	Children (6-8 yrs)	Children (9-12 yrs)	Adolescents (13-17 yrs)	Adolescents (13-17 yrs)	Adults
Dose	26.1/5.2 mg (n=10)	52.3/10.4 mg (n=10)	26.1/5.2 mg (n=5)	52.3/10.4 mg (n=5)	52.3/10.4 mg (n=28)
C_{max} (ng/mL)	17.2 (5.02)	25.9(9.69)	8.88(3.18)	14.0(1.72)	18.5(4.91)
AUC_{last} (hr*ng/mL)	219.8(72.3)	391.6 (129.9)	116.5 (39.2)	217.0 (24.4)	225.1 (84.0)

AUC_{inf} (hr*ng/mL)	228.2 (79.4)	459.7(145.4)	125.3(40.97)	234.6 (25.6)	229.8 (84.3)
T_{max} (hr)#	4.0 (1.0-4.0)	4.0 (1.0-10.0)	4.0 (2.0-4.0)	4.0 (4.0-4.0)	4.50 (3.0-7.0)
$T_{1/2}$ (hr)	12.57 (2.79)	19.36 (8.98)	10.28 (2.75)	11.08 (4.01)	8.20 (1.27)
Cl/F/weight (L/hr/kg)	3.36 (1.36)	2.45 (0.74)	2.56 (0.25)	2.66 (0.27)	2.53 (0.82)
# data presented as median (range) -Source: data for 6-17 yrs CSR KP415.105 breakfast was given 20 minutes prior to drug administration; data for adults CSR KP415.104 a high-fat meal was given 30 minutes prior to drug administration					

The exposures of SDX after single dose administration of AZSTARY across age groups were summarized in Table 17. Following 52.3/10.4 mg administration under fed conditions, SDX C_{max} and AUC_{inf} in adults was about 17% and 45% lower, respectively, compared to children 9-12 years old. And adolescent exposures were about 20-25% lower compared to children. The higher SDX exposure may partly explain the higher d-MPH exposure observed in children (Table 2). SDX exposure levels appear to be comparable between 6-8 years old and 9-12 years old after dose normalization.

Table 17: PK Parameters (Mean (SD)) of SDX After Single Dose Administration of KP415 Across Age Groups

PK Parameters	Children (6-8 yrs)	Children (9-12 yrs)	Adolescents (13-17 yrs)	Adolescents (13-17 yrs)	Adults
Dose	26.1/5.2 mg (n=10)	52.3/10.4 mg (n=10)	26.1/5.2 mg (n=5)	52.3/10.4 mg (n=5)	52.3/10.4 mg (n=28)
C_{max} (ng/mL)	9.66 (3.92)	14.9 (5.4)	6.88 (3.3)	10.5 (1.1)	12.4(9.7)
AUC_{inf} (hr*ng/mL)	78.9 (21.7)	167 (47.8)	60.1 (24.0)	124 (17.3)	91.6(31.5)
Cl/F(L/hr)	377 (95.5)	363(115)	534 (223)	458 (75.2)	675 (207)
Vz/F(L)	4017 (1112)	5030(1604)	5131 (1174)	4175 (921)	6185 (2873
T_{max} (hr)#	4.0 (2.0-8.0)	4.0 (1.0-8.0)	4.0 (2.0-4.0)	4.0 (4.0-4.0)	4.5 (0.5-4.5)
$T_{1/2}$ (hr)	7.4 (0.97)	9.98 (3.2)	7.6 (3.6)	6.4 (1.3)	6.3 (1.6)
# data presented as median (range) -Source: data for 6-17 yrs CSR KP415.105 breakfast was given 20 minutes prior to drug administration; data for adults CSR KP415.104 a high-fat meal was given 30 minutes prior to drug administration					

Though d-MPH exposure in adolesents and adults is about half of that in children 6-12 years old after same dose administration of KP415, the exposure in healthy subjects were found to be higher following adminstration of KP415 52.3/10.4 mg than that following adminstration of Focalin XR 20 mg (Figure 3). Given that 1) Focalin XR 20 mg was demonstrated to be effective in the treatment of ADHD in adults (Focalin XR label) and there was no obvious increase in effectiveness with a dose higher than 20 mg (e.g., 30 mg or 40 mg); 2) The exposure were comparable in adolescents and adults after the same dose administration of KP415; and 3) the clinical practice of MPH pharmacotherapy is to individually titrate patients to find the optimal dose for ADHD, dosage adjustment of KP415 based on age is not considered necessary.

Hepatic Impairment

KP415 has not been studied in subjects with hepatic impairment, however, hepatic impairment is not expected to have significant effect on the pharmacokinetics following KP415 administration.

Available data suggest that SDX does not appear to be metabolized in the liver. In vitro studies showed that SDX was stable when incubated with human liver S9 fractions or hepatocytes, which is consistent with the finding that there was little conversion to d-MPH systemically after IV administration of SDX Cl single moiety. SDX does not appear to be a substrate or perpetrator for major transporters, Phase I or Phase II enzymes, therefore any changes that may be caused by impaired hepatic function in the activities of the major hepatic transporters and enzymes are not anticipated to affect the pharmacokinetics of SDX.

Literature data showed that d-MPH was metabolized to d-ritalinic acid (RA) primarily by carboxylesterase 1A1 (CES1A1) in the liver, therefore there is a theoretical risk that hepatic impairment may increase d-MPH plasma concentrations because of decreased CES1A1 activities. However, no reports on effects of hepatic impairment are known from either a pharmacokinetic or safety point of view, despite the long-history usage of MPH products in ADHD therapy. In addition, studies with drugs that are also highly metabolized by CES1A1 have demonstrated that CES1A1 has a high catalytic capacity. For example, oseltamivir (Tamiflu) undergoes extensive presystemic conversion to active oseltamivir carboxylate by CES1A1, but clinical studies found no significant change in the exposure to oseltamivir or oseltamivir carboxylate in patients with mild or moderate hepatic impairment (oseltamivir label).

Collectively speaking, hepatic impairment is not expected to have significant effect on the PK of SDX/d-MPH based on the available data. Therefore, dosage adjustment is not considered necessary for patients with impaired hepatic function.

Renal Impairment

KP415 has not been studied in subjects with renal impairment. Because renal clearance is not an important route of serdexmethylphenidate or methylphenidate elimination, renal impairment is expected to have little effect on the pharmacokinetics following KP415 administration. Dosage adjustment is not considered necessary for patients with impaired renal function.

Gender

The effect of gender on the PK following KP415 administration has not been evaluated in a specific study. Pooled analysis showed that clearance (CL/F/W) and volume of distribution (Vz/F/W) of SDX and d-MPH after single oral administration of SDX/d-MPH and at steady state after multiple (daily) oral doses of SDX/d-MPH were similar between males and females (Table 18).

Table 18: Clearance and Volume of Distribution of SDX and d-MPH by Gender after Single and Multiple Oral Doses of SDX/d-MPH

	SDX		d-MPH	
	Males	Females	Males	Females
Single Dose [a]				
N	126	64	126	65
CL/F/W (L/h/kg)	4.88 (60.7)	5.11 (66.4)	2.59 (36.5)	3.16 (33.7)
V_z/F/W (L/kg)	41.4 (90.7)	43.6 (85.5)	41.6 (47.5)	53.3 (46.0)
Steady State [b]				
N	42	17	42	17 [16 for V_z/F/W]
CL_{ss}/F/W (L/h/kg)	4.60 (37.5)	5.04 (44.0)	2.55 (27.1)	2.85 (27.9)
V_z/F/W (L/kg)	34.6 (48.63)	40.2 (49.0)	33.3 (36.3)	37.5 (45.3)

Values are Mean (CV%). [a] Data pooled from studies KP415.105, KP415.110, KP415.109, KP415.104, and KP415.107.
[b] Data pooled from studies KP415.109 and KP415.110.
-Source: Table 40 of Module 2.7.2

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No clinically relevant interactions with food or comedications have been reported or expected.

Food Effect

Though the presence of food (high-fat, high-calorie food or sprinkled on applesauce), decreased the absorption and exposure of SDX to varying degrees, the exposure to d-MPH, the active moiety, was increased to a maximal of 33% for Cmax and 16% for AUC, compared to when KP415 capsule was administered intact under fasted condition (Table 19). The median time to peak plasma concentration (T_{max}) was lengthened from 2 to 4-4.5 hours in the presence of food. Minimal effect was observed on d-MPH exposure when KP415 capsule was opened and content was added to water. KP415 can be administered without regard to food. Adding the capsule contents to water or sprinkling on applesauce are acceptable alternative means of oral drug administration.

Table 19: Summary Statistics of the Plasma PK Parameters of SDX and d-MPH Compared to Fasted State (%Geomean Ratio, [90%CI])

PK Parameters	Added to water/fasted	Sprinkled on Apple sauce/fasted	High-fat, High calorie/fasted
SDX			
C_{max} (ng/mL)	76.9 (66.0, 89.6)	54.3 (46.6,63.3)	29.2 (25.1,34.0)
AUC_{inf} (hr*ng/mL)	91.2 (81.6, 101.9)	49.5 (44.3,55.3)	38.0(34.0, 42.4)
d-MPH			
C_{max} (ng/mL)	102.9(95.9,110.4)	133.6(124.6,143.3)	123.6(115.2,132.5)
AUC_{inf} (hr*ng/mL)	104.1(99.96,108.3)	116.2(111.7,121.0)	114.2(109.7,118.9)

-Source: Tables 10-15 of CSR KP415.104

Acid Reducing Agents (ARAs)

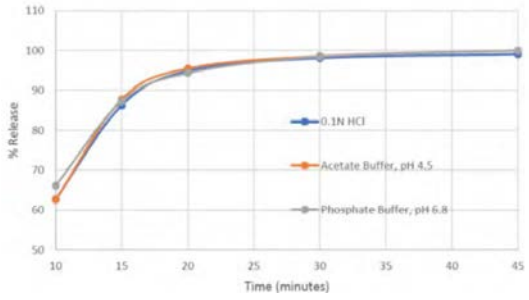
There is no evidence to suggest a strong drug interaction potential between KP415 and an acid reducing agent.

The dissolution profiles and solubility table for individual moiety (both are immediate release) of KP415 are summarized in Figure 7 below. For SDX, the dissolution profiles in 0.1N HCl, pH 4.5, or pH 6.8 media were essentially superimposable, and solubility in various media with a pH ranging from 1 to 8 was greater than 1.6 g/mL. Therefore, it is considered there is no pH-dependent dissolution or solubility for the SDX moiety in KP415. For the d-MPH component, the dissolution profiles in 0.1N HCl and pH 4.5 media were also superimposable, but complete dissolution in pH 6.8 media was not reached. However, the solubility at pH 6.8 for d-MPH was about 136.6 mg/mL (pH 7.0 media with 0% salinity), which is much greater than the luminal concentration of d-MPH (the d-MPH dose in KP415 capsule divided by 250 mL (10.2 mg/120 mL=0.085 mg/mL). Per our draft Guidance - Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents, it is unlikely for d-MPH to have in vivo drug interactions with ARAs.

Though the effects of gastrointestinal pH alterations on the absorption of KP415 have not been studied, the immediate release properties and in vitro dissolution and solubility findings for SDX and d-MPH do not suggest that coadministration of acid reducing agents could impact the absorption of KP415.

Figure 7: Dissolution Profiles and Solubility in Media with Different pH

SDX: Dissolution profile



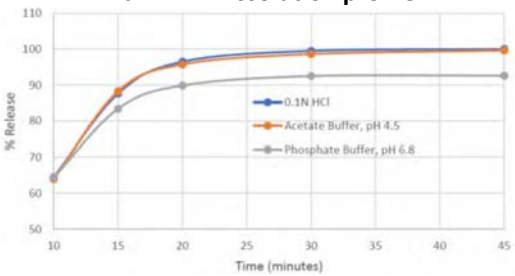
-source: Figure 2 Module 3.2.p.2

SDX: Solubility

Initial pH	0% Salinity		0.9% Salinity		1.2% Salinity	
	pH at 24 h	Solubility (mg/mL)	pH at 24 h	Solubility (mg/mL)	pH at 24 h	Solubility (mg/mL)
1	1.2	209.0	1.2	154.6	1.1	209.7
3	2.8	>8 g in 5 mL	3.0	>8 g in 5 mL	2.9	>8 g in 5 mL
5	5.0		4.9		5.1	
7	6.7		6.7		7.1	
8	7.2		7.3		8.0	

-source: Table 21 Module 3.2.p.2

d-MPH: Dissolution profile



-source: Figure 3 Module 3.2.p.2

d-MPH: Solubility

Initial pH	0% Salinity		0.9% Salinity		1.2% Salinity	
	pH at 24 h	Solubility (mg/mL)	pH at 24 h	Solubility (mg/mL)	pH at 24 h	Solubility (mg/mL)
1	0.9	122.1	1.1	98.5	1.0	94.7
3	2.8	137.7	2.9	107.6	2.8	103.7
5	4.2	138.5	4.3	105.9	4.3	106.3
7	4.8	136.6	4.8	107.4	5.0	107.0
8	5.9	128.7	6.0	101.6	6.1	99.2

-source: Table 20 Module 3.2.p.2

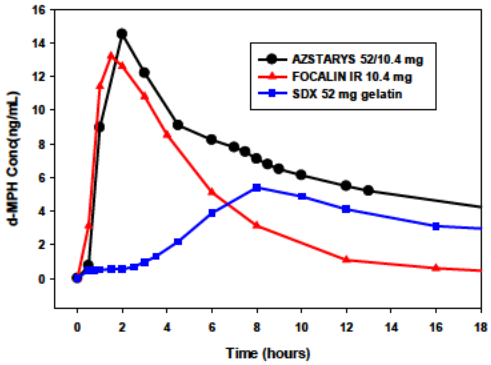
6.3.2.5 What is the contribution of SDX to the observed overall clinical effects following KP415 administration?

After oral dosing of AZSTAYS, the systemic d-MPH comes from the two individual drug substance components in the combination product: d-MPH contained in the immediate release d-MPH HCl component and d-MPH derived from SDX. SDX itself is a prodrug to d-MPH and has negligible pharmacological activity. Because it is widely accepted that that pharmacodynamic responses to MPH are closely mirrored by plasma concentration time profiles of MPH, contribution of SDX to the observed overall clinical effects can be estimated from SDX-derived d-MPH concentration time profiles after KP415 administration.

The compiled PK profiles (Figure 8) showed that there was minimal d-MPH generated for the first 3-4 hours after oral administration of 52 mg SDX single moiety. It also clearly showed that mean d-MPH plasma concentrations estimated for a 10.4 mg d-MPH IR closely traced the mean profile following an oral dose of 52.3/10.4 mg KP415, especially for the first 4 hours postdose. From approximately 6 hours postdose onwards, the rising SDX-derived d-MPH concentration began to exceed the decreasing concentration from d-MPH IR. At approximately 10 hours following administration of KP415, d-MPH plasma concentrations were mostly from SDX-derived d-MPH.

Overall, the PK profile of d-MPH after an oral dose of KP415 seems to be a composite of the underlying d-MPH exposure derived from the d-MPH HCl and SDX Cl components. Early exposure to d-MPH seems to primarily come from d-MPH HCl immediately release component, and thus the early pharmacodynamic effect observed after AZSTRARYS administration. SDX component gradually converts to d-MPH and mainly contributes to the late exposure of d-MPH, and the late-day pharmacological effect.

Figure 8: Mean Concentration Time Profile of d-MPH Following Administration of KP415, Focalin IR, or SDX Single Moiety



– Focalin IR 10.4 mg: approximated using dose-adjusted data for 2×10 mg d-MPH HCl administered orally under fasted conditions, Figure 5.2 2001 OCP review Focalin NDA21278;
– SDX 52.3 mg gelatin: dose-adjusted from 60 mg SDX Cl, fasted condition, study KP415.108; KP415 52.3/10.4 mg: fasted condition, study KP415.104.

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

The KP415 development program consists of 15 clinical trials (see the table below). These include two phase 3 trials, ten phase 1 trials, and three studies of abuse liability.

Table 20 Table of Clinical Studies

Trial Identifier	NCT no.	Trial Description
		Controlled Studies to Support Efficacy and Safety
KP415.E01	NCT03292952	Open-label dose optimization x3 weeks followed by randomization to double-blind KP415 or placebo x7 days, with a classroom laboratory evaluation on the last day. Patients were children ages 6 to 12 years with ADHD (DSM-5); OL N=155, DB N=74 on drug, 76 on placebo. KP415 doses (total d-MPH) were 26.1 mg SDX/5.2 mg d-MPH, 39.2 mg SDX/7.8 mg d-MPH, and 52.3 mg SDX/10.4 mg d-MPH each morning. The primary efficacy endpoint was the change from baseline in the SKAMP-C scores averaged over the classroom day.
		Studies to Support Safety
KP415.S01	NCT03460652	Dose-optimized, open-label, 12-month study in 238 children ages 6 to 12 years with ADHD (DSM-5) to assess long-term safety and tolerability. Patients were from Study KP415.E01 or *de novo*. KP415 doses were the same as in Study KP415.E01.
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)
KP415.101	N/A	Exploratory PK comparison between SDX and Concerta in 24 healthy adults.
KP451.102	N/A	Exploratory PK and dose proportionality study with SDX in 24 healthy adults.
KP415.104	N/A	Food effect study of KP415 capsules in 28 healthy adults.
KP415.105	N/A	PK study with the final KP415 capsules in 31 children and adolescents with ADHD.
KP415.106	N/A	Exploratory urinary excretion study with SDX in 12 healthy adults.
KP415.107	N/A	PK bridging study of KP415 capsules to Focalin XR in 30 healthy adults.
KP415.108	N/A	Exploratory food effect study with SDX in 14 healthy adults.
KP415.109	N/A	Exploratory PK study of different SDX/d-MPH ratios in 48 healthy adults.
KP415.110	N/A	Dose proportionality and steady state PK study of KP415 capsules in 23 healthy adults.
KP415.111	N/A	Mass balance, metabolism, and excretion study of radiolabeled SDX in 8 healthy male adults.
		Human Abuse Liability Studies
KP415.A01	N/A	Oral human abuse potential study of SDX, Focalin XR, and phentermine in 45 adult recreational stimulant users.
KP415.A02	N/A	Intranasal human abuse potential study of SDX and d-MPH in 45 adult recreational stimulant users.
KP415.A03	N/A	Intravenous human abuse potential study of SDX and d-MPH in 30 adult recreational stimulant users.

Source: Module 5.2, eCTD Sequence #0001.

Review Strategy

In the clinical review which follows, KP415 refers to the combination product consisting of serdexmethylphenidate (SDX) and immediate-release dexmethylphenidate (d-MPH).

The clinical and statistical reviews of efficacy were based on the results from a single key efficacy trial (Study KP415.E01) in children ages 6 to 12 with ADHD. Extrapolation across age ranges relied on comparative PK data, which were derived from Studies KP415.105, KP415.107 and KP415.110.

The overall strategy for the clinical review of safety was to 1) examine AEs at the more serious end of spectrum from all 15 clinical trials, 2) evaluate common AEs and other standard safety analyses from Studies KP415.E01 and Study KP415.S01, and 3) examine height and weight data from the 12-month safety trial (Study KP415.S01).

The Controlled Substance Staff (CSS) reviewer examined data regarding the abuse potential of SDX from the three human abuse liability studies (KP415.A01, KP415.A02, and KP415.A03).

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

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

Trial Design

This study consisted of the following phases:

1. A **screening period** of up to 49 days to evaluate study eligibility.

2. An **open-label dose optimization phase** of 21 ±3 days. Patients began treatment with a KP415 dose of 39.2 mg SDX/7.8 mg d-MPH, taken once each morning. The dose could be decreased to 26.1 mg SDX/5.2 mg d-MPH to improve tolerability or increased to 52.3 mg SDX/10.4 mg d-MPH to improve effectiveness. Patients were not to take KP415 2 days before the last day of dose optimization so that baseline efficacy assessments could be obtained on the last day after a washout of KP415. After the baseline assessment was complete, patients received their KP415 dose. Investigators evaluated eligibility criteria for entering the next phase prior to this washout (by phone and prior to the Day 21 visit) which were as follows: 1) a reduction of ≥30% from baseline in the ADHD-RS-5 score, 2) a CGI-I score of 1 or 2 points (very much improved or much improved), and 3)

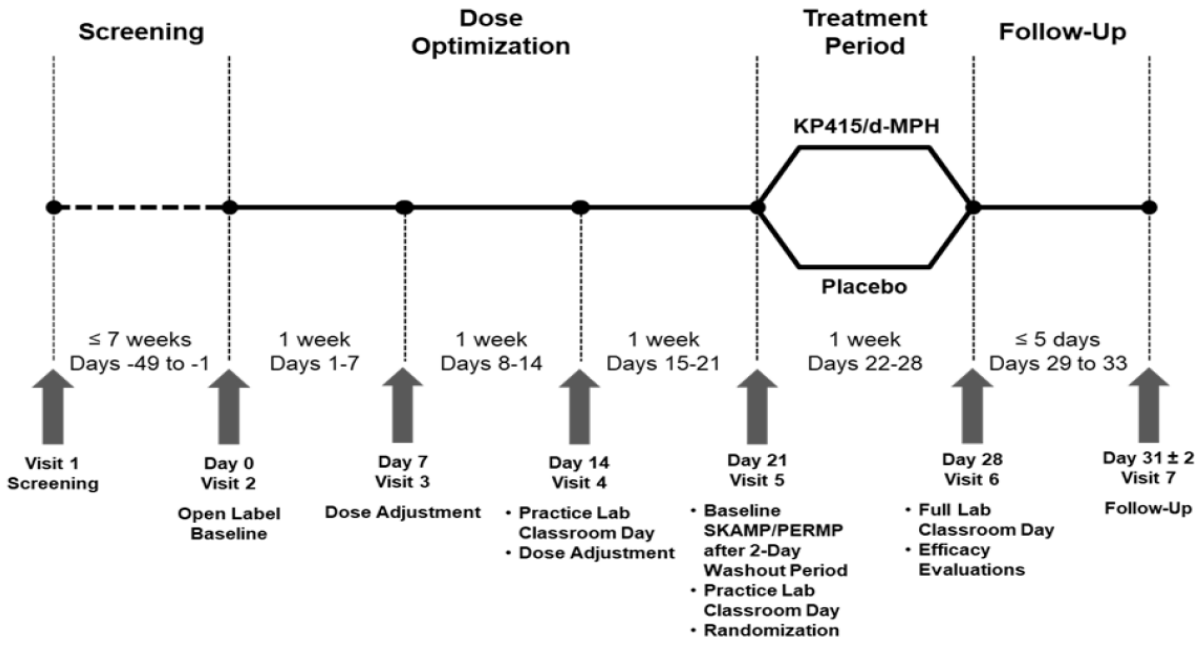
acceptable tolerability of KP415.

3. **Double-blind treatment phase**. Patients were randomized (stratified by site) in a 1:1 ratio to receive their optimized dose of KP415 or placebo on Day 21 for 7 days. Investigators assessed efficacy and safety after the last dose of study drug, during a laboratory classroom day on Day 28. On this day, the dose of study drug was administered immediately after breakfast.[2]

4. A **follow-up visit** occurred 3 ±2 days after the last dose to evaluate safety.

The study design is shown schematically in the following figure.

Figure 4: Study KP415.E01 Study Design



Source: Figure 1 in the Clinical Study Report for Study KP415.E01.

Study Endpoints

According to the Amendment #2 of the protocol for Study KP415.E01, the primary efficacy endpoint was the difference between KP415 and placebo in the average of the mean changes from baseline in the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale combined score (SKAMP-C) across all postdose time points on the classroom day (Day 28). The protocol defined baseline as the predose score on Day 21 and the intent-to-treat population as all randomized patients who received at least one dose of double-blind study medication and have at least one

[2] The Applicant confirmed the administration of study drug immediately after breakfast in a February 4, 2021, email response to an Information Request.

post-dose SKAMP-C assessment on Day 28.

The SKAMP is a validated rating of impairment of classroom behaviors in children with ADHD. The scale is comprised of 13 items grouped under the categories of attention, deportment, quality of work, and compliance, each rated on a 7-point scale (0=normal to 6=maximal impairment). Higher scores indicate greater impairment. Summing the rating values for the 13 items provides the SKAMP combined score.

The SAP states that demonstration of statistical significance on the primary efficacy endpoint would permit analysis of the mean changes from baseline in the SKAMP-C at each time point during the classroom day as secondary efficacy endpoints, and use of these data to estimate onset and duration of clinical efficacy.

After the Applicant unblinded and analyzed the efficacy data, they requested that the Agency consider a revision of the baseline definition as a post-hoc analysis. They proposed that the baseline be defined as the SKAMP-C assessment at the predose timepoint on the classroom day (Day 28) for purposes of analyzing the primary endpoint and estimating the onset of action and duration of effect. The reason for this proposal was the Applicant's opinion that the protocol-specified analysis did not reflect the true magnitude of the time-dependent differences over the course of the classroom day. They felt that, in retrospect, the SAP was flawed in that the Day 28 predose assessment should have served as the baseline for computing changes to estimate onset and duration of effect. In a Written Response dated October 10, 2018, the Agency agreed to consider this proposal during the review of the marketing application.

Clinical Reviewer's Comments: The Applicant provided a number of explanations for accepting the post-hoc analysis of efficacy, including reliance on a post-hoc analysis in the Agency review of Adhansia XR, the desirability of facilitating the ability of the prescriber to compare similar measures across products, supportive results from a secondary endpoint in Study KP415.E01, and a close relationship between pharmacodynamic effects and the PK profile of drugs to treat ADHD. The acceptance of a post-hoc analysis in the case of Adhansia XR was based on an outcome that could not have been foreseen during protocol development. The other reasons are too weak to overturn adherence to good scientific practices. I consider the use of the post-hoc analysis that was proposed after study completion and data unblinding to be inconsistent with good scientific principles and unacceptable despite the Applicant's explanations.

Statistical Analysis Plan

The estimate of the difference between KP415 and placebo on the primary endpoint was based on a repeated measures analysis using a mixed-effect model repeated measure (MMRM) model where:

- Time, treatment, the interaction of time and treatment, and site were fixed effects;
- Baseline SKAMP-C score (predose Visit 5 (Day 21)) was included as covariate;

- Subject was the random effect.

The Toeplitz covariance structure was specified. To check if the assumptions of the MMRM model are met, residuals were examined through histograms, normal plots, Shapiro-Wilk's test, and plots of the residuals versus fitted values.

Statistical reviewer's note: *In eCTD 11 the Agency asked the Applicant to use the unstructured covariance matrix. In eCTD 37 the Applicant pre-specified un. However, the Applicant changed from un to Toeplitz in eCTD 49. The Agency was not aware that it was changed to Toeplitz in this last SAP amendment embedded in a meeting package. The objective of the meeting was not to review the SAP, but to discuss the acceptability of the proposed post-hoc analysis (i.e., change of baseline from Day 21 to Day 28 in primary efficacy endpoint model). This reviewer conducted the analysis (primary efficacy and comparison at time points) using the un structure. The results mirror the results using the Toeplitz with only minor deviations (plus/minus 0.1 in the LS means) and no change in conclusions.*

If the primary endpoint was statistically significant, then general secondary endpoint analyses were performed. The same MMRM model used for the primary endpoint was used to estimate the least square means and corresponding 95% confidence intervals at each time point and treatment on Day 28. Differences in least square means between the treatment groups and unadjusted p-values were reported for each time point. The onset of effect was defined as the earliest post-dose time point at which a statistically significant difference (p-value <0.05) between KP415 and placebo in the mean change in the SKAMP-C scores was shown. The duration of effect was defined in the study protocol as the length of the time interval such that statistically significant differences between KP415 and placebo were reached at each time point during the interval. Onset and duration of effect were not prespecified as key secondary endpoints in either the study protocol or the statistical analysis plan.

A sample size of 126 subjects was calculated based on an assumed minimum clinically important difference between KP415 and placebo of 0.5 on the SKAMP-C and a standard deviation of 1 to achieve 80% power at a two-sided significance level of 0.05. Then, assuming a 20% dropout rate during open-label dose optimization and a 10% dropout rate during double-blind treatment, a target sample size of 176 subjects was planned.

Protocol Amendments

The Applicant submitted the original protocol for Study KP415.E01 in a meeting package on May 12, 2017 (IND 130463 eCTD Sequence# 0012). Clinical and statistical comments were discussed with the Applicant in a face-to-face meeting on June 14, 2017, and meeting minutes were conveyed to the Applicant on July 14, 2017. The Applicant subsequently amended the protocol for this trial on three occasions, as shown in the table below.

Table 21 Study KP415.E01 Protocol Amendments

Amendment Date	Submission Date	eCTD Sequence Number	Statistical Review Date	Comments to Applicant Date
August 4, 2017	August 25, 2017	0018	Nov 22, 2017	Nov 22, 2017
Nov 13, 2017	Dec 15, 2017	0024	March 26, 2018	March 26, 2018
April 6, 2018	April 11, 2018	0037	June 13, 2018	June 13, 2018

Source: FDA Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).

The clinical and statistical review of Study KP415.E01 was based on the latest amended version of the study protocol (dated April 6, 2018) and statistical analysis plan (Version 2, dated June 18, 2018). The study completion date was May 16, 2018. The Applicant states in the study report that the SAP was finalized and approved before the database was locked and unblinded.

8.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant has confirmed that this trial was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice guidelines.

Financial Disclosure

No investigator in Study KP415.E01 had disclosable financial interests. Please see Section 18.2 for further details.

Patient Disposition

A total of 178 patients were screened at five trial sites. Of these, 155 patients were enrolled in the open-label dose optimization phase. Five patients dropped out of the trial during dose optimization (four due to an AE and one because of failure to meet randomization criteria). The remaining 150 patients were randomized to 1 week of double-blind treatment (74 to KP415 and 76 to placebo) and comprised the intent-to-treat (ITT) population, defined as all randomized patients who received at least one dose of double-blind study drug and completed at least one SKAMP assessment on the classroom day. One patient who was randomized to placebo was lost to follow-up.

Protocol Violations/Deviations

During the 3-week dose optimization phase, there were 20 protocol deviations in 18 patients, most commonly an improper dose, dosing time, or washout/missed a dose of study drug. One patient took a prohibited concomitant medication during this phase: Patient (b) (6) took a single dose of melatonin on Day 3 to treat insomnia.

During the double-blind treatment phase, there were two protocol deviations: one patient

taking KP415 missed a visit or had a visit outside of the permissible window and one patient taking placebo had an improper dose, dosing time or washout/missed a dose of study drug. No patient was reported as having taken a prohibited concomitant medication during this study phase.

Table of Demographic Characteristics

The demographic characteristics of patients who entered Study KP415.E01 and who were randomized to double-blind treatment are displayed in the following table. The two double-blind treatment arms were roughly comparable in terms of age, sex, race, and ethnicity.

Table 22 Demographic Characteristics (Study KP415.E01)

Demographic Parameters	Open-Label Dose Optimization (N=155) n (%)	Double-Blind Treatment (N=150)	
		KP415 (N=74) n (%)	Placebo (N=76) n (%)
Sex			
Male	93 (60%)	44 (59%)	48 (63%)
Female	62 (40%)	30 (41%)	28 (37%)
Age			
Mean years (SD)	10.0 (1.6)	10.1 (1.7)	10.1 (1.6)
Median (years)	10.1	10.4	9.9
Min, max (years)	6.3, 12.9	6.3, 12.9	6.4, 12.9
Age Group			
6 to 9 years	76 (49%)	33 (45%)	38 (50%)
10 to 12 years	79 (51%)	41 (55%)	38 (50%)
Race			
White	80 (52%)	38 (51%)	38 (50%)
Black/African American	57 (37%)	25 (34%)	31 (41%)
Asian	7 (5%)	5 (7%)	2 (3%)
Multiple	10 (6%)	6 (8%)	4 (5%)
Other	1 (<1%)	0 (0%)	1 (1%)
Ethnicity			
Hispanic or Latino	41 (26%)	20 (27%)	20 (26%)
Not Hispanic or Latino	114 (74%)	54 (73%)	56 (74%)

Source: Created by the Clinical Reviewer from the dataset adsl.xpt using JMP 15.0.0.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The KP415 and placebo double-blind treatment groups were similar in terms of ADHD subtype and severity of illness (see the table below). Most patients had the combined ADHD subtype

and, on average, were markedly ill, as measured by their CGI-Severity rating.

Table 23 Study KP415.E01 Baseline Illness Characteristics

	KP415 N=74	Placebo N=76
ADHD Subtype		
Inattentive	9 (12%)	9 (12%)
Hyperactive/Impulsive	0 (0%)	0 (0%)
Combined	65 (88%)	67 (88%)
Mean (SD) CGI-Severity Score	5.0 (0.8)	4.9 (0.8)

Source: Table 9 in the Clinical Study Report for Study KP415.E01.

Approximately 40% of patients had prior use of a medication for ADHD, the most common medication being a methylphenidate product (22% of KP415-treated patients and 26% of placebo-treated patients). Amphetamine products had been taken by 15% of patients in each treatment arm.

Treatment Compliance and Concomitant Medications

Compliance rates were based on the reported number of missed doses and the number of treatment days between that visit and the previous visit. Compliance rates were generally high. During dose optimization, the mean compliance rate was 97%. During the treatment phase, the mean compliance rate among KP415-treated patients was 98% and among placebo-treated patients 96%.

A total of six subjects started other medication for ADHD prior to entering the trial and continued that medication throughout the study. The medications were Adderall, Aptensio, methylphenidate products, and Vyvanse. Three of these subjects were randomized to KP415 and three to placebo during the double-blind phase of the study.

Reviewer's Comments: Because a relatively small number of patients received concomitant medication for ADHD throughout Study KP415.E01 and the numbers of patients were balanced between KP415 and placebo during double-blind treatment, I do not expect this medication use to have appreciably biased the efficacy findings of this trial.

Efficacy Results – Primary Endpoint

Results on the primary efficacy endpoint (i.e., the average change from baseline in the SKAMP-C score across all post-dose time points on Day 28) for both the protocol-specified analysis (using the Day 21 baseline) and the post-hoc analysis (using the Day 28 baseline) are shown in the table below.

Table 24: Study KP415.E01 Primary Efficacy Endpoint Results

	Mean SKAMP-C Score			
	Protocol-Specified Analysis		Post-Hoc Analysis	
	KP415 N=74	Placebo N=76	KP415 N=74	Placebo N=76
Baseline Score	17.9	17.9	17.0	14.8
Average Change from Baseline (Day 28)	-4.87	0.54	-3.13	4.13
Treatment Difference (95% CI)	-5.4 (-7.1, -3.7)		-7.3 (-9.0, -5.5)	
p-value	<0.001		<0.001	

Source: Tables 14 and 26 in the CSR for Study KP415.E01. Results confirmed by statistical reviewer.

Using either the protocol-specified analysis (Day 21 baseline) or post-hoc analysis (Day 28 baseline), the average decrease in the SKAMP-C score across all post-baseline time points on Day 28 was greater among KP415-treated patients than placebo-treated patients to a statistically significant degree.

Patients were randomized on Day 21. The mean pre-dose SKAMP-C scores on this day were equivalent between treatment groups. It is notable that patients randomized to placebo on average had much greater improvement on the Day 28 pre-dose assessment than patients randomized to KP415. Mean changes in the SKAMP-C were -3.1 and -0.9, respectively, at the Day 28 predose assessment (Table 25) compared with the Day 21 pre-dose assessment. Thus, if the Day 28 predose assessment were used as baseline for evaluating the treatment effect during the classroom day, the relatively worse mean baseline score for the KP415-treated patients would lead to an exaggeration of the therapeutic effect compared to that observed with the protocol-specified analysis. This difference is an additional reason to use the protocol-specified analysis as primary for the evaluation of efficacy in this trial.

Table 25: Pre-dose SKAMP-C Scores on Day 21 and Day 28

	KP415 N=74	Placebo N=76
Pre-dose on Day 21 (SE)	17.9 (1.1)	17.9 (1.2)
Pre-dose on Day 28 (SE)	17.0 (1.0)	14.8 (1.0)
Difference (pre-dose Day 28- pre-dose day 21)	-0.9	-3.1

Source: CSR for Study KP415.E01

Data Quality and Integrity

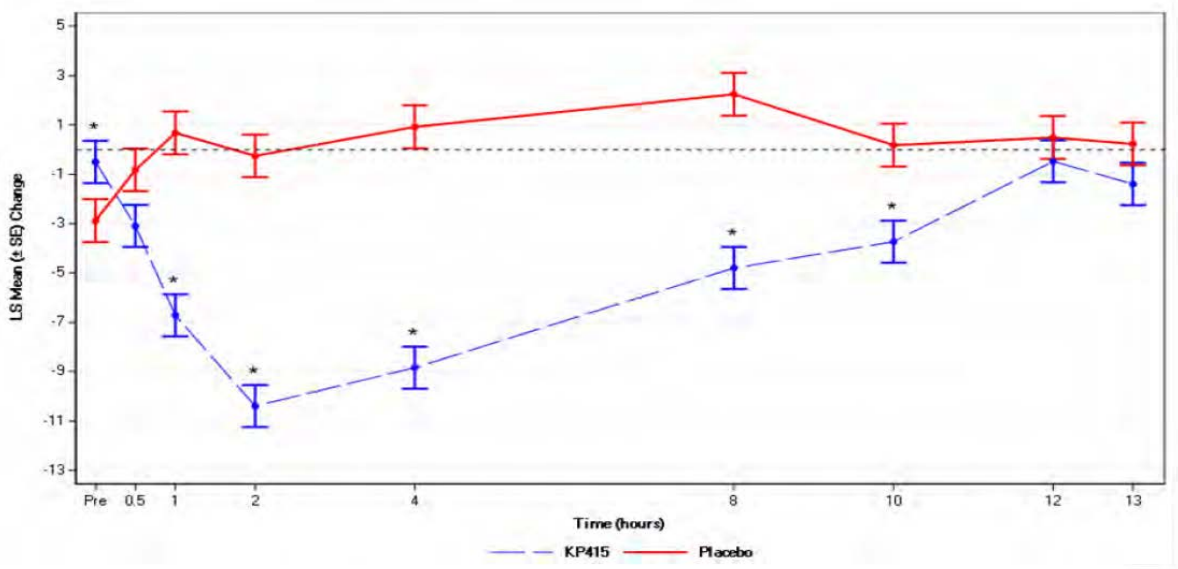
The Office of Computational Science on March 5, 2020 completed a Core Data Fitness (CoreDF) assessment and identified no substantial problems with the submitted datasets for this trial.

Efficacy Results – Secondary and other relevant endpoints

Treatment effects on the SKAMP-C during the classroom day (Day 28) are displayed in the two figures below, the first based on the protocol-specified analysis and the second based on the post-hoc analysis. The changes at each time point are secondary endpoints that reflect the onset and duration of action of KP415, as defined above.

Based on the protocol-specified analysis, the onset of action occurred at 1 hour post-dose with action demonstrated to 10 hours post-dose, yielding a duration of action of 9 hours.

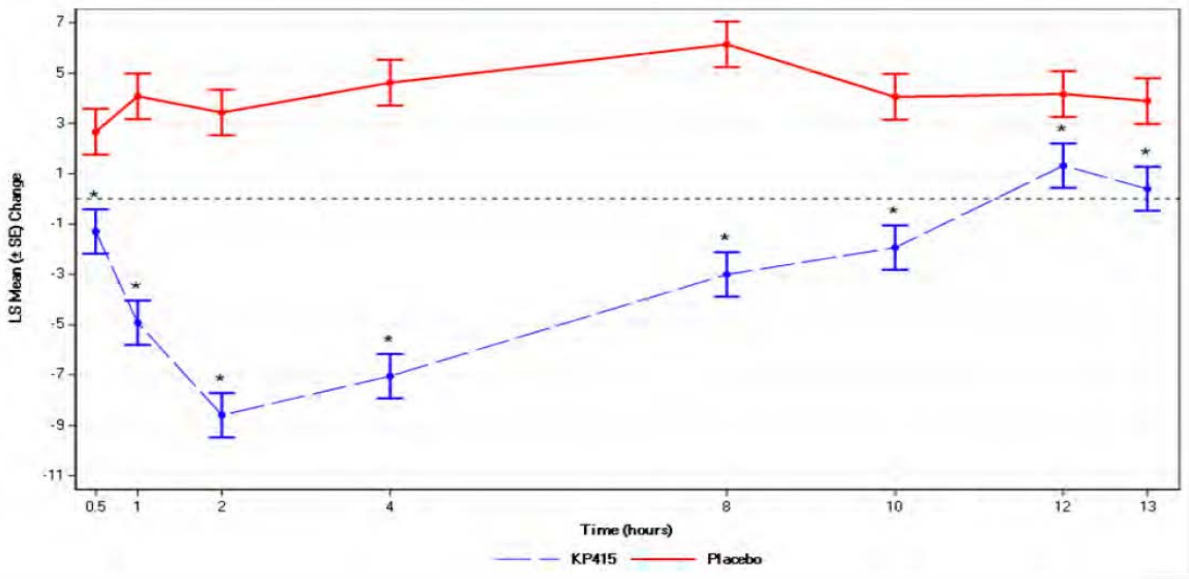
Figure 5: SKAMP-C Changes from Baseline on Day 28 (Protocol-Specified Analysis)



Abbreviations: ITT=Intent-to-Treat; LS=least squares; SE=standard error; SKAMP-C=Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale – Combined score.
*Denotes p<0.05 KP415/d-MPH compared with placebo.
Note: "Pre" refers to the predose measurement at Visit 6. Time points 0.5 through 13 are postdose measurements at Visit 6.

Source: Figure 3 in the CSR for Study KP415.E01.

Figure 6: SKAMP-C Changes from Baseline on Day 28 (Post-Hoc Analysis)



Abbreviations: ITT=Intent-to-Treat; LS=least squares; SE=standard error; SKAMP-C=Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale – Combined score.
*Denotes p<0.05 KP415 compared with placebo.
Note: Time points 0.5 through 13 are postdose measurements at Visit 6.
Source: Figure 12 in the CSR for Study KP415.E01.

Clinical Reviewer's Comments: *I consider the use of the protocol-specified analysis to evaluate primary efficacy to be scientifically sound, as opposed to the post-hoc analysis proposed by the Applicant. The prespecified analysis does support the efficacy of KP415 in children, with an onset at 1 hour post-dose and a duration of 9 hours (i.e., to the 10-hour time point).*

Because administration of KP415 with food appears to delay the time to maximum blood concentration (T_{max}) of d-MPH, it is possible that taking KP415 without food may decrease the time to onset of therapeutic effect and the time to maximum effect. This issue was discussed with the OCP review team, who felt that existing data are insufficient to include a statement in labeling regarding the effect of food on the timing of the therapeutic effect. Given that the T_{max} after KP415 administration with food (4 hours from Study KP415.105) and the time to maximum effect after administration with food (2 hours from Study KP415.E01) do not match, it is difficult to definitively determine the effect of food on the timing of the clinical effect of KP415, and I agree that such information should not be labeled.

Statistical Reviewer's Comments: **Protocol-specified versus Post-Hoc Primary Analysis**

As described in the section above the applicant was making the case for using the pre-dose baseline SKAMP-C score at Day 28 (Visit 6, laboratory classroom day) in the primary efficacy analysis model and not the protocol and SAP pre-specified pre-dose score at Day 21 (Visit 5, randomization visit, practice laboratory classroom day). The Applicant contacted the Agency

prior NDA submission, but after unblinding and analysis of the data, regarding this proposal. Further supporting documents were submitted with the NDA and at various instances during the NDA review.

Such change in the analysis would not affect the overall positive efficacy conclusion for KP415 versus placebo (Table 26), but would increase the point estimate of the difference in the change from baseline in SKAMP-C score (primary efficacy endpoint) by two units and would also result in additional nominally statistically significant differences at individual time points on the laboratory classroom day (i.e., onset at 0.5 hours and duration until hour 13 versus onset at 1 hour and duration until hour 10; Table 27).

Table 26. Primary Efficacy Analysis of SKAMP-C (with Pre-specified and Post-hoc Baseline as Covariate)

	Baseline = Predose Visit 5 Mean			**Baseline = Predose Visit 6 Mean**		
	SDX/d-MPH	**Placebo**	**Trt Diff (95% CI)**	**SDX/d-MPH**	**Placebo**	**Trt Diff**
LS Mean of Average Change from BL	-4.87	0.54	**-5.4** (-7.1, -3.7) p < 0.001	-3.13	4.13	**-7.3** (-9.0, -5.5) p < 0.001

(Source: Statistical Reviewer)

Table 27. Change from Baseline by Time Point for SKAMP-C (Pre-specified Versus Post-hoc Baseline and Covariate)

Time point (hours post dose)	**Baseline = Predose Visit 5 Mean**			**Baseline = Predose Visit 6 Mean**		
	SDX/d-MPH	**Placebo**	**Trt Diff**	**SDX/d-MPH**	**Placebo**	**Trt Diff**
0.5	-3.1	-0.8	-2.3	-1.3	2.7	**-4.0**
1	-6.7	0.7	**-7.4**	-4.9	4.1	**-9.0**
2	-10.4	-0.3	**-10.1**	-8.6	3.4	**-12.0**
4	-8.8	0.9	**-9.7**	-7.0	4.6	**-11.6**
8	-4.8	2.3	**-7.1**	-3.0	6.1	**-9.1**
10	-3.7	0.2	**-3.9**	-1.9	4.1	**-6.0**
12	-0.5	0.5	-1.0	1.3	4.2	**-2.9**
13	-1.4	0.2	-1.6	0.4	3.9	**-3.5**

(Source: Statistical Reviewer; bold font indicates nominally statistically significant difference)

Exploratory Analyses

Modeling the SKAMP-C total score with or without Day 21 (Visit 5) pre-dose as covariate results in consistent conclusions (Table 28). Also the results are in line with the pre-specified model regarding onset and duration (Table 29).

Table 28. Exploratory Analyses using SKAMP-C Total Score (Day 21 Baseline as Covariate Versus no Baseline Covariate)

	Predose Day 21 Score as Covariate			No Baseline Score as Covariate		
	SDX/d-MPH [SE]	**Placebo [SE]**	**Trt Diff (95% CI)**	**SDX/d-MPH [SE]**	**Placebo [SE]**	**Trt Diff**
LS Mean of total score average	13.03 [0.62]	18.43 [0.70]	**-5.4** (-7.1, -3.7) p < 0.001	14.06 [0.78]	19.56 [0.99]	**-5.5** (-7.8, -3.2) p < 0.001

(Source: Statistical Reviewer)

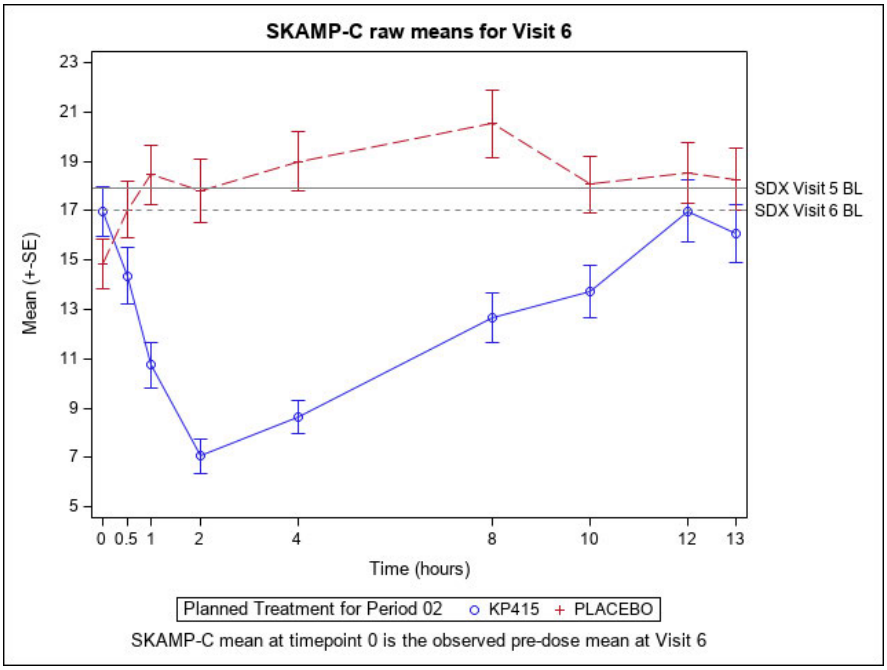
Table 29. Exploratory Analysis - LS Means SKAMP-C Total Score by Time Point (Day 21 Baseline as Covariate)

Time point (hours post dose)	Baseline Day 21 Score as Covariate			No Baseline Score as Covariate		
	SDX/d-MPH	**Placebo**	**Trt Diff**	**SDX/d-MPH**	**Placebo**	**Trt Diff**
0.5	14.9	17.2	-2.3 (p=0.058)	15.9	18.3	-2.4 (p=0.01)
1	11.2	18.7	**-7.4**	12.3	19.8	**-7.5**
2	7.6	17.7	**-10.2**	8.6	18.8	**-10.3**
4	9.1	18.9	**-9.8**	10.1	20.0	**-9.9**
8	13.2	20.2	**-7.1**	14.2	21.3	**-7.2**
10	14.2	18.2	**-3.9**	15.3	19.3	**-4.0**
12	17.5	18.5	-1.0 (p=0.42)	18.5	19.6	-1.1 (p=0.46)
13	16.6	18.2	-1.6 (p=0.17)	17.6	19.3	-1.7 (p=0.23)

(Source: Statistical Reviewer; bold font indicates nominally statistically significant difference)

It is instructive to consider the following figures. Figure 11 displays the raw means of the SKAMP-C total score over the laboratory classroom day (Day 28, Visit 6). Without any adjustment by the choice of model and model specifications the raw mean differences indicate separation between KP415 (SDX) and placebo starting at hour 1 and sustained through hour 10.

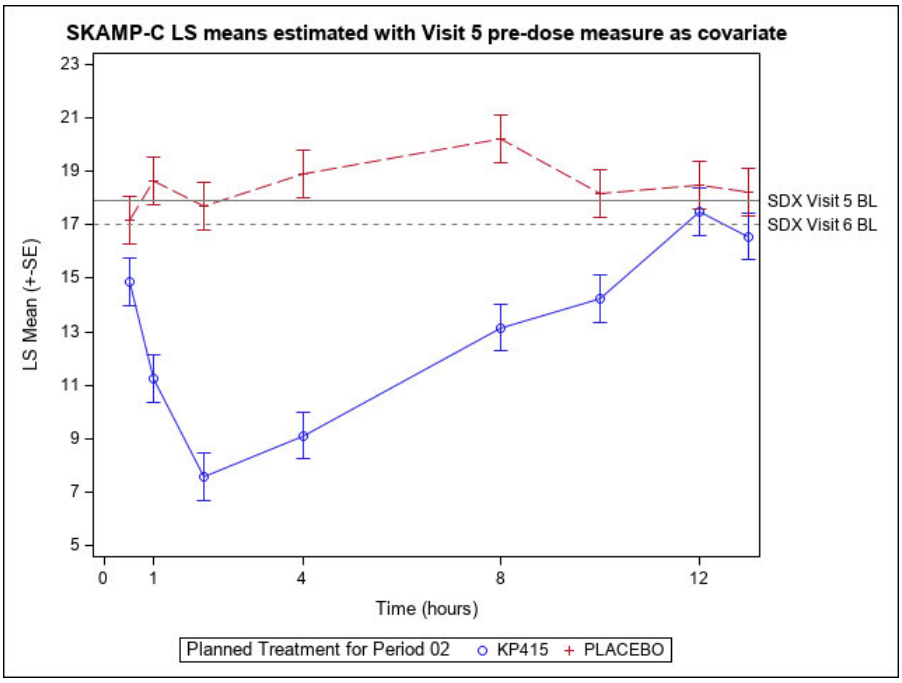
Figure 7. SKAMP-C Total Score Raw Means for Day 28



(Source: Statistical Reviewer)

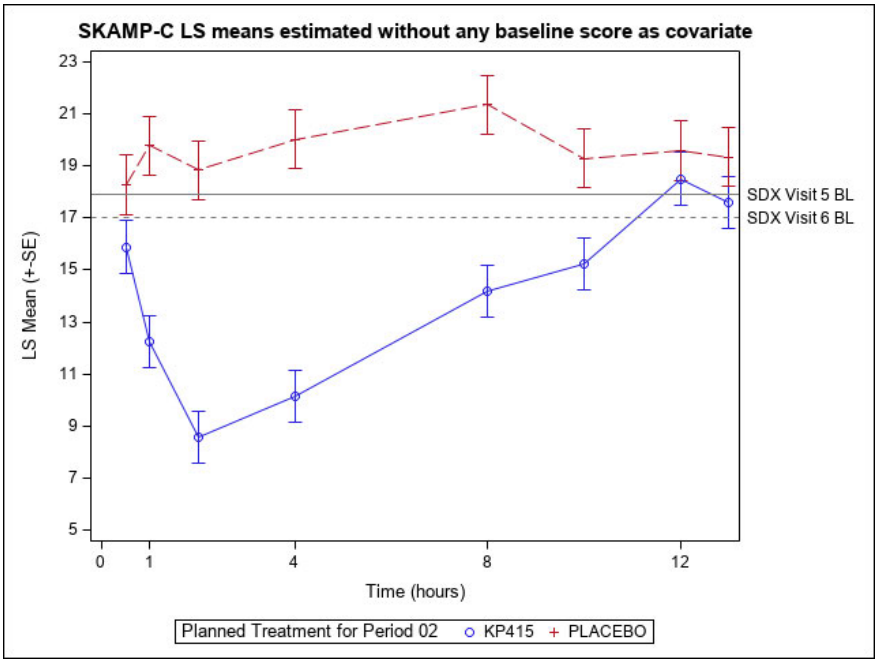
The following three figures provide the efficacy trajectories from the exploratory analyses modeling the SKAMP-C total score using the Day 21 (Visit 5) pre-dose as baseline covariate (Figure 12), no baseline covariate (Figure 13), and the Day 28 (Visit 6) pre-dose score as covariate (Figure 14). As mentioned previously the first two model configurations provide identical conclusion (i.e., onset at 1 hour, duration through hour 10). In contrast, Figure 14 illustrates the impact of including the Day 28 (Visit 6) pre-dose score as baseline covariate. Here, the separation between KP415 and placebo appears to begin at hour 0.5 and lasts through hour 13. Note, when the baseline score is included as a covariate, the result from modeling the SKAMP-C total score would be equivalent to that from modeling change from baseline without the covariate in the model.

Figure 8. Exploratory Analysis – SKAMP-C Total Score LS Means for Day 28 (with Day 21 Baseline as Covariate)



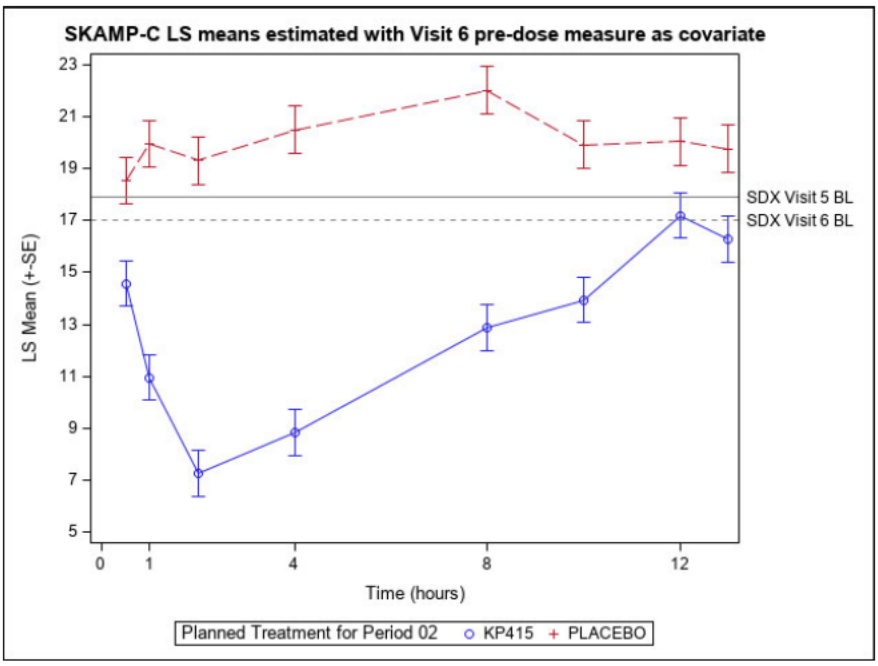
(Source: Statistical Reviewer)

Figure 9. Exploratory Analysis – SKAMP-C Total Score LS Means for Day 28 (no Baseline Covariate)



(Source: Statistical Reviewer)

Figure 10. Exploratory Analysis – SKAMP-C Total Score LS Means for Day 28 (with Day 28 Baseline as Covariate)



(Source: Statistical Reviewer)

The late cycle minutes issued on 12/23/2020 summarize the position of the Division regarding the proposed use of the post-hoc analysis approach for the primary endpoint (minor review issue #5):

> *You have assessed efficacy during the laboratory classroom day in Study KP415.E01 using the pre-dose assessment on Day 21 as baseline (per the protocol-specified analysis) and the predose assessment on Day 28 as baseline (per your proposed post hoc analysis). We do not agree* [redacted] *reiterated the following points:*

- *The Agency had asked the Applicant about their selection of Day 21 as baseline before the study started (June 2017 End-of-Phase 1 meeting preliminary comments) and the Applicant did not respond.*

- *The Applicant's use of a 2-day washout toward the end of the dose optimization phase indicates that the Applicant clearly wanted to use the Day 21 baseline for the primary analysis. This selection was not a typographical error or an oversight.*

- *Finally, the Applicant could have made an amendment to the SAP to make Day 28 the baseline anytime during the study. Only after the study was completed and unblinded, and the Applicant saw the results, did they change to a Day 28 baseline. Using a post-hoc analysis for the primary analysis under these circumstances is unacceptable.*

(b) (4)

Post-meeting Comment from Division of Biometrics I

Although we do not know whether either choice of baseline day provides an unbiased estimate of the true baseline value, it appears that choosing Day 21 (the pre-specified day and also day of randomization) where the baseline means are almost identical between the KP415 and placebo groups, introduces less confounding compared to choosing the baseline values at Day 28 where a markedly lower baseline value for the placebo group compared to the KP415 group may inflate the effect size.

Dose/Dose Response

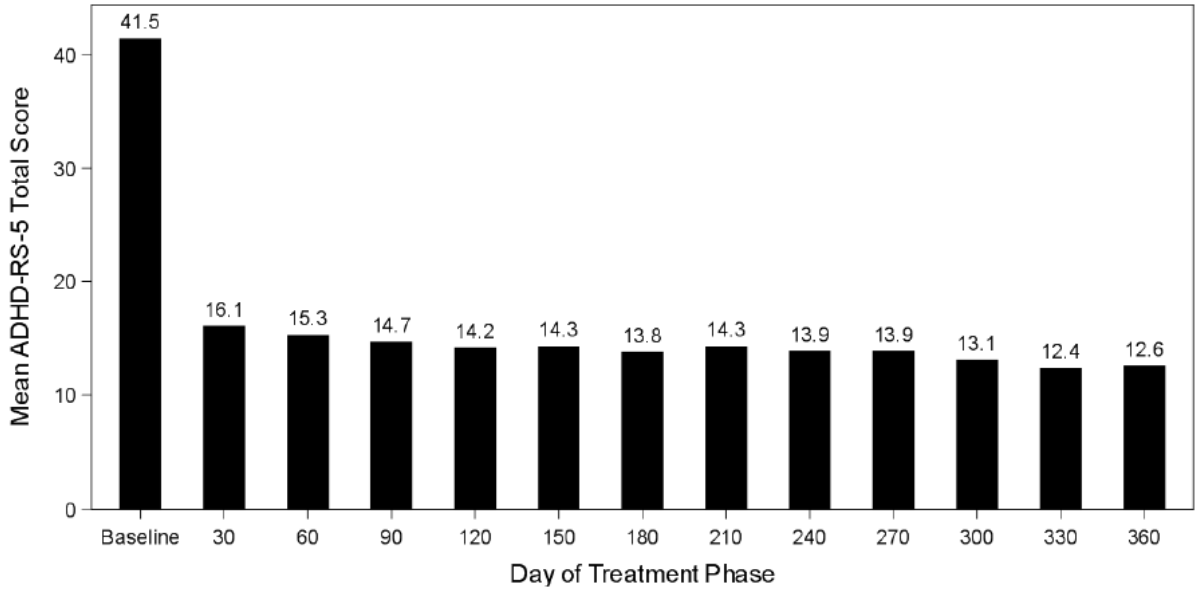
Dose-response was not formally evaluated because this study did not use a fixed-dose design. All patients began dose optimization at a daily dose of 39.2 mg SDX/7.8 mg d-MPH. The daily dose could be adjusted downward to 26.1 mg SDX/5.2 mg d-MPH to improve tolerability or upward to 52.3 mg SDX/10.4 mg d-MPH to improve efficacy. At the end of dose optimization, 3%, 46%, and 51% of the 150 patients remaining in the study were receiving daily doses of 26.1 mg SDX/5.2 mg d-MPH, 39.2 mg SDX/7.8 mg d-MPH, and 52.3 mg SDX/10.4 mg d-MPH,

respectively. The mean dose at the end of the optimization phase was 33.8 mg/day. This suggests that few patients experienced tolerability problems with KP415, but about half of the patients required a higher dose to achieve improved efficacy.

Persistence of Effect

Persistence of effect could not be assessed in Study KP415.E01 because of the brief study duration. Study KP415.S01 followed patients treated with open-label KP415 for up to 12 months. The mean ADHD-RS-5 scores for patients in this study at each visit are shown in the figure below. There was marked improvement from baseline within the first 30 days and apparent persistence of effect during the remainder of the study for subjects who remained on the drug.

Figure 11 Study KP415.S01 Mean ADHD-RS-5 Scores by Visit (Observed Cases)



Source: Figure 11-1 in the Clinical Study Report for Study KP415.S01

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

There were no patient reported outcomes in this trial.

Additional Analyses Conducted on the Individual Trial

The Applicant analyzed the average change from the Day 21 baseline across all post-dose SKAMP-C scores on Day 28 by sex, age, and site. The results are summarized in the table below:

Table 30: Subgroup Analysis of the Primary Efficacy Endpoint

Average Post-Dose Change from Day 21 Baseline in SKAMP-C Scores on Day 28				
	LS Mean Change		Difference in LS Mean Changes	
	KP415	Placebo	KP415 minus Placebo	95% Confidence
Sex				
Male (N=92)	-4.82	1.70	-6.52	-8.72, -4.31
Female (N=58)	-5.15	-0.77	-4.38	-6.75, -2.01
Age (years)				
6 to 9 (N=71)	-4.07	1.90	-5.98	-8.72, -3.23
10 to 12 (N=79)	-5.31	-0.76	-4.55	-6.80, -2.29
Site				
Site 1 (N=12)	-3.58	-0.44	-3.14	-11.05, 4.78
Site 2 (N=36)	-4.57	1.91	-6.48	-9.75, -3.21
Site 3 (N=28)	-8.39	-2.49	-5.91	-9.86, -1.96
Site 4 (N=21)	-7.20	-2.45	-4.75	-11.49, 1.99
Site 5 (N=53)	-4.22	0.80	-5.02	-7.45, -2.58

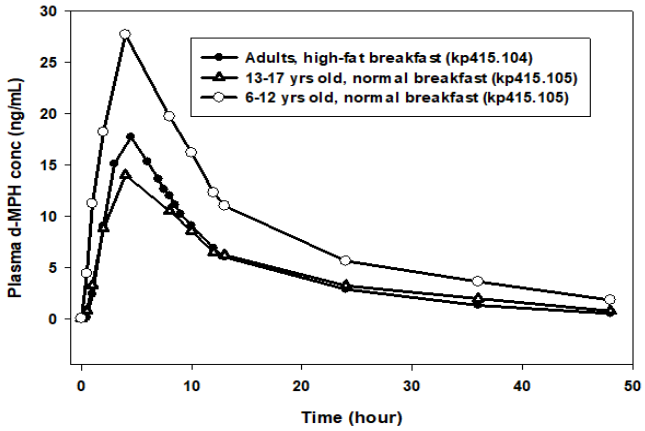
Source: Table 16.1.9.1 in the CSR for Study KP415.E01.

Efficacy results were similar between sex and age subgroups. At each site, KP415 was numerically superior to placebo. Although the 95% confidence intervals included the null at Sites 1 and 4, suggesting a non-significant difference, the study was not powered to show statistical significance at each site, and thus, the results at these two sites do not impact the overall efficacy conclusions.

Extrapolation of Efficacy to Older Age Groups

The Applicant proposes to bridge efficacy from the children in Study KP415.E01 to adolescents and adults (b) (4). Although the Agency views ADHD as essentially the same condition across all ages, there are differences in d-MPH exposure across these age ranges, with exposure (C_{max} and AUC) in adolescents and adults approximately 50% of that in children (see the graph below). These differences raised the question of whether efficacy can be bridged aacross the three age ranges (b) (4) (b) (4).

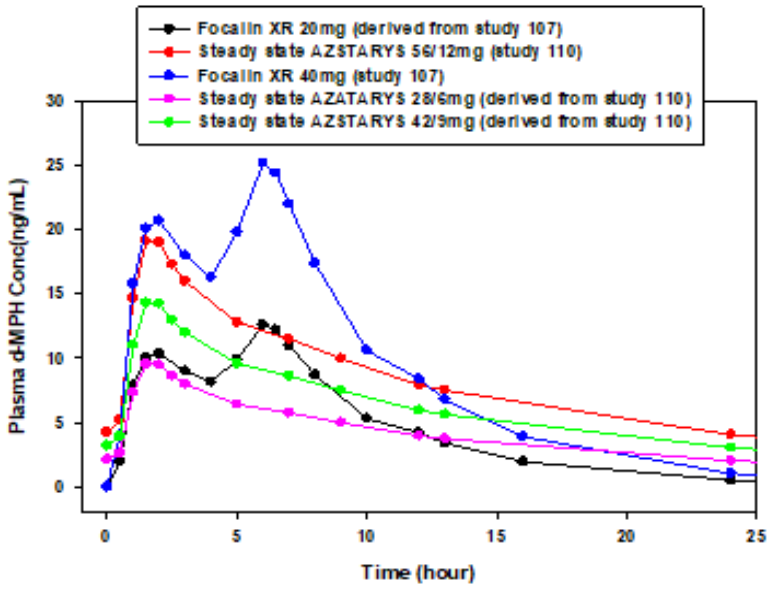
Figure 12: Comparative PK Across Age Ranges Following Single Dose KP415 52.3 mg SDX/10.4 mg d-MPH



Source: Courtesy of the Clinical Pharmacology reviewer, Dr. Zhang.

The following considerations address this concern. A comparison of 1) d-MPH plasma levels in adults at steady state following administration of KP415 52.3 mg SDX/10.4 mg d-MPH/day with 2) the levels following a single dose of Focalin XR 20 mg/day shows that the concentrations produced by KP415 equal or exceed those produced by Focalin XR at all postdose time points (the red line and the black lines, respectively, in the figure below). However, this is not true for the d-MPH concentrations produced by the KP415 39.2 mg SDX/7.8 mg d-MPH/day and 26.1 mg SDX/5.2 mg d-MPH/day dosages at steady state (the green and purple lines, respectively, in the graph below).

Figure 13: Comparative d-MPH Exposure in Adults After KP415 vs. Focalin XR Administration



Source: Courtesy of the Clinical Pharmacology reviewer, Dr. Zhang.

Because Focalin XR is effective for the treatment of adults with ADHD at the 20 mg/day dosage, I conclude that KP415 52.3 mg SDX/10.4 mg d-MPH/day is effective in the adult age range.

However, the above data do not clearly support the efficacy of the 26.1 mg SDX/5.2 mg d-MPH/day and 39.2 mg SDX/7.8 mg d-MPH/day dosages in adults and those dosages may not provide therapeutic d-MPH levels in many adult patients.

Regarding the adolescent age range, I believe that the time-concentration curves of d-MPH in adolescents and adults are sufficiently similar that efficacy in adults can be extrapolated downward to adolescents (see the graph above comparing PK across age ranges).

As discussed in the Clinical Pharmacology review above, steady state levels of d-MPH with KP415 treatment are achieved by Day 3 of treatment. Thus, it is possible that subtherapeutic levels might be produced on the first two days of KP415 treatment, given that single doses of KP415 produce d-MPH levels less than those produced by an equivalent dose of Focalin XR. I do not consider this two-day delay in achieving efficacy to be clinically significant in the context of the long-term treatment for this chronic condition.

Reviewer Comment: In summary, the above data support the efficacy of KP415 in adolescents and adults at a dose of 52.3 mg SDX/10.4 mg d-MPH.

8.1.3 Assessment of Efficacy Across Trials

The Applicant conducted no other efficacy trials with KP415.

8.1.4 Integrated Assessment of Effectiveness

Studies KP415.E01, KP415.105, KP415.107, KP415.110, as well as data from the approval of Focalin XR provide substantial evidence of the effectiveness of KP415 in the treatment of patients 6 years of age and older with ADHD.

In Study KP415.E01, the average change from baseline in the SKAMP-C score on the laboratory classroom day in the KP415-treated patients was statistically significantly greater than that in the placebo-treated patients, using either the prespecified or post-hoc analysis. The Agency required only one efficacy trial because the effectiveness of d-MPH has already been established for the LD, Focalin XR.

8.2 Review of Safety

8.2.1 Safety Review Approach

The approach to the clinical review of safety was as follows:

1. I reviewed deaths, other serious AEs, and dropouts due to AEs from all 15 clinical studies to detect clinically important events associated with KP415.

2. I examined the incidence of common AEs and systematically collected data regarding suicidal ideation and behavior (SI/B), laboratory tests, vital sign measurements, and electrocardiogram (ECG) tracings from Studies KP415.E01 and KP415.S01 to ascertain the general safety profile of KP415.

3. I reviewed the long-term safety trial (Study KP415.S01) to detect any AEs not reported with the LD (Focalin XR), evaluate systematically collected data regarding sleep, and examine age- and sex-adjusted longitudinal data on height and weight.

8.2.2 Review of the Safety Database

Overall Exposure

A total of 374 children and adolescents with ADHD and 120 healthy adult volunteers were exposed to KP415 in phase 1 and phase 3 studies. Study KP415.E01 enrolled 155 patients and, of these, 94 patients entered Study KP415.S01. Of those 94 patients, 70 patients enrolled as roll-over patients, and 24 patients were “new” patients because their last dose of KP415 in Study KP415.E01 was more than 45 days prior to their first dose in Study KP415.S01. These 24 patients underwent dose optimization in Study KP415.S01. Another 188 patients enrolled as *de novo* patients in Study KP415.S01; these patients did not participate in Study KP415.E01 and also underwent dose optimization in Study KP415.S01. In the two phase 3 studies combined, 343 children received at least one dose of KP415, and 76 received at least one dose of placebo.

The Applicant defined the safety population for each study as all patients who received at least

one dose of study drug and had at least one post-dose safety assessment. An enumeration of all patients in the safety population by study, study phase, and treatment is shown below.

Table 31 Phase 3 Safety Database

Study	Study Phase	KP415	Placebo
KP415.E01	Dose Optimization Phase	155	0
	Randomized Phase	74	76
KP415.S01	Dose Optimization Phase	208	0
	Treatment Phase	238	0

Source: Clinical Study Reports for Studies KP415.E01 (Figure 2) and KP415.S01 (Table 10.1).

Of the 343 children treated with KP415 in phase 3 trials, 196 were treated for at least 6 months and 155 were treated for at least 12 months.

Adequacy of the safety database:

Neither phase 3 trial in the development program is adequately designed to permit a thorough evaluation of safety. Study KP415.E01 exposes all patients to open label KP415 for 3 weeks prior to randomization to drug or placebo for one week. This design does not allow for a pure comparison of safety findings between KP415 and placebo as found in a parallel group study with randomization on the first day of study drug treatment. Study KP415.S01 has no placebo control arm to allow an adequate interpretation of observed safety findings. Of course, given the 12-month duration of this trial, a placebo arm would be neither practical nor ethical. Furthermore, in terms of exposure, this database does not comply with the recommendations set forth in ICH E1.

Nevertheless, given that SDX is not thought to be pharmacologically active, and d-MPH is present at comparable levels in several approved stimulant products with which we have considerable safety experience for many years, I consider the database to be adequate.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

I audited the consistency of AE information across the Case Report Form (CRF), narrative summary, and AE dataset (adae.xpt) for approximately 10% of the patients who experienced either a serious AE or an AE that led to dropout in the two phase 3 studies. I randomly selected the following five patients for auditing:

- Study KP415.E01: Patient (b) (6).
- Study KP415.S01: Patients (b) (6)

I found the information to be consistent across all data sources for all five patients.

The Division of Psychiatry requested that the Office of Scientific Investigations (OSI) perform on-site clinical inspections for Sites 3 and 4 in Study KP415.E01. OSI was not able to inspect these two sites due to the ongoing Covid-19 pandemic. OSI had previously inspected these sites (Site 3 in January 2018 and Site 4 in January 2010). Both inspections had been classified No Action Indicated (NAI), because there were no Good Clinical Practice (GCP) concerns at either site. In addition, there are no compelling reasons to require current inspections at either site. Therefore, I do not feel that the lack of clinical inspections should preclude regulatory action on this application.

Categorization of Adverse Events

For Studies KP415.E01 and KP415.S01, the Applicant coded reported AE terms (under the variable AETERM) to MedDRA Preferred Terms or PTs (under the variable AEDECOD) using MedDRA version 22.0. I reviewed the accuracy of the coding for all AEs in the AE datasets (adae.xpt) for both studies and found the coding to be acceptable.

I further examined the PTs in the adae.xpt datasets to ascertain whether the Applicant categorized closely related AEs under different PTs as a result of the granularity of MedDRA AE categorization. For PTs that appeared to represent related clinical events, I combined related terms into common AE terms for purposes of calculating reporting rates, as shown in the table below.

Table 32 Re-Categorization of MedDRA Preferred Terms

Common Term	Subsumed MedDRA PTs
Abdominal Pain	Abdominal pain, abdominal pain upper, abdominal discomfort.
Anxiety	Anxiety, feeling jittery, nervousness.
Behavioral Changes	Aggression, agitation, defiant behavior, energy increased, head banging, logorrhea, psychomotor hyperactivity.
Ear Infection	Ear infection, otitis media.
Gastroenteritis	Gastroenteritis, gastroenteritis viral.
Headache	Headache, exertional headache, sinus headache, tension headache.
Insomnia	Insomnia, initial insomnia, middle insomnia, terminal insomnia.
Lower Respiratory Tract Infection	Bronchitis, pneumonia, croup infectious.
Mood Changes	Affect lability, anger, apathy, depression, depressed mood, emotional disorder, emotional distress, flat affect, suicidal ideation, tearfulness, irritability, mood altered.

Common Term	Subsumed MedDRA PTs
Movement Disorder Symptoms	Tremor, resting tremor, tardive dyskinesia, tongue movement disorder, tic, excessive eye blinking, periodic limb movement disorder.
Psychosis	Hallucinations visual, psychotic disorder.
Upper Respiratory Tract Infection	Upper respiratory tract infection, nasopharyngitis, pharyngitis, pharyngitis streptococcal, influenza, oropharyngeal pain, rhinorrhea, rhinovirus infection, sinusitis, acute sinusitis, tonsillitis, viral pharyngitis.

Source: Created by the Clinical Reviewer based on the dataset adae.xpt for Studies KP415.E01 and KP415.S01.

Routine Clinical Tests

In Study KP415.E01, investigators assessed vital signs at baseline and weekly. They measured blood pressure, pulse rate, respiratory rate, and oral temperature in the sitting position. Laboratory tests, 12 -lead ECGs, weight, and height were obtained at screening and at the end of the study (1 to 5 days after the last dose of study drug). Laboratory tests included hematology (RBC, WBC with differential, and platelet counts), chemistry (including liver transaminases, total bilirubin, BUN/creatinine, and electrolytes), and urinalysis. Investigators administered the Columbia-Suicide Severity Rating Scale (C-SSRS) Pediatric Version at baseline and at weekly visits thereafter.

In Study KP415.S01, investigators measured vital signs and administered the C-SSRS at baseline and weekly during dose optimization for new patients. For this study, protocol defined the baseline assessment as the beginning of dose optimization for new patients and as the beginning of the 12-month treatment phase for rollover patients from Study KP415.E01. Patients who had not participated in Study KP415.E01 or whose last dose in Study KP415.E01 was more than 45 days before entering this study received KP415 during the dose optimization phase. Other patients skipped the dose optimization phase and rolled over directly into the treatment phase. Laboratory tests, 12-lead ECGs, height (measured with a stadiometer), and weight were obtained at screening and investigators assessed the Children's Sleep Habits Questionnaire (CSHQ) at baseline during the dose optimization phase. During the treatment phase, investigators assessed vital signs, weight, height, the CSHQ, and the Pediatric Version of the C-SSRS at baseline and every 30 days thereafter. Laboratory tests and 12-lead ECGs were conducted on Days 180 and 360 during the treatment phase.

Reviewer's Comments: AE and vital sign assessments were conducted at appropriate times during Studies KP415.E01 and KP415.S01 to assess the safety of KP415 in children, ages 6 to 12 years of age, with ADHD. However, because post-baseline laboratory tests and 12-lead ECGs in Study KP415.E01 were obtained from 1 to 5 days (3 ±2 days) after the last dose of study drug, the timing of these measurements may allow any adverse effects to dissipate by the time of assessment and, thus, results on those safety measures may not be completely reliable. Nonetheless, based on cumulative safety data with other MPH products, I do not expect any

substantial effects on laboratory or ECG parameters. Therefore, I do not consider this issue to be a major deficiency.

8.2.4 Safety Results

Deaths

There were no fatal AEs in any of the 15 clinical trials in the KP415 development program.

Other Serious Adverse Events

There were four patients who experienced serious AEs (SAEs) in this development program. Three events occurred in the long-term safety trial (Study KP415.S01) and one occurred in the intravenous abuse potential study (Study KP415.A03). These cases are summarized below.

Study KP415.S01
Patient (b) (6) was a 7-year-old male who exhibited aggressive behavior 24 days after starting KP415. He impulsively hit his mother after she took a toy from him during a visit to his psychiatrist. He was hospitalized to prevent further aggression, and study medication was discontinued. The event resolved, and he was discharged 6 days later.

Patient (b) (6) was a 6-year-old female who experienced a seizure on Study Day 233. She also had an elevated temperature and postictal confusion. An EEG showed diffuse slowing and rare focal spikes over the right frontal region. A diagnosis of epilepsy was made, and the seizure was considered a symptom of the epileptic condition. Investigators discontinued her from the study, because treatment with a contraindicated medication was started.

Patient (b) (6) was a 9-year-old female with a past medical history that included diabetes mellitus and asthma. During her 10-month participation in the study, she was hospitalized on five occasions for complications of asthma (status asthmaticus, bronchospasm, and acute respiratory failure) as well as hyperglycemia on one of those occasions. These events were not reported to the study site in a timely manner, and KP415 was continued throughout this period. Also, it is notable that this patient had been hospitalized for an exacerbation of asthma for 3 days immediately before beginning KP415 treatment. Investigators termined the patient prematurely from the study after about 10 months of treatment due to use of prohibited medication.

Study KP415.A03
Patient (b) (6) was a 34-year-old male who was in a motor vehicle accident 3.5 days after receiving intravenous SDX 30 mg. He sustained multiple injuries in the accident. It was determined that he was driving while intoxicated with alcohol at the time of the event.

Reviewer's Comments: With the exception of aggression, which I consider possibly drug-related, none of these SAEs appears to be reasonably attributable to KP415 treatment.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study KP415.E01, four patients dropped out due to adverse reactions during the 3-week dose optimization phase:

- Patient (b) (6) was a 7-year-old female who discontinued treatment with KP415 39.2 mg SDX/7.8 mg d-MPH after 3 days because of severe insomnia as well as bronchospasm, constricted affect, tearfulness, dizziness, dry mouth, and upper abdominal pain. This event resolved 2 days after stopping KP415.

- Patient (b) (6) was a 6-year-old female who stopped treatment with KP415 39.2 mg SDX/7.8 mg d-MPH after 12 days because of severe insomnia as well as aggression and irritability. These events resolved within 2 days of stopping drug.

- Patient (b) (6) was an 8-year-old female who stopped treatment with KP415 39.2 mg SDX/7.8 mg d-MPH after 7 days due to head banging and affect lability, which resolved 10 days after stopping KP415.

- Patient (b) (6) was an 8-year-female who dropped out of treatment with KP415 39.2 mg SDX/7.8 mg d-MPH after 13 days due to moderate dizziness. This event resolved within a day of discontinuing KP415.

No patient dropped out during the randomized, double-blind phase of this trial.

During Study KP415.S01, 11 patients discontinued treatment due to the following AEs, each in one patient (except where noted otherwise): irritability (3 patients), insomnia (2 patients), decreased appetite, aggression, depression, leukopenia and neutropenia, nausea, psychotic disorder, suicidal ideation, and tardive dyskinesia. The following AEs that led to dropout merit further discussion:

Patient (b) (6) was a 12-year-old Black/African-American male who experienced leukopenia and neutropenia on Study Day 180 and was discontinued from treatment on Day 211 due to leukopenia. Screening and on-treatment WBC and neutrophil counts are shown below:

Study Day	WBCs per µL	Neutrophils per µL
Screening	3,120	1,350
180	2,050	530
211	4,620	2,680

The lower limit of the reference range was 5,240/µL (WBC count) and 2,730/µL (neutrophil count). He experienced no other AEs.

- Patient (b) (6) was a 7-year-old male who experienced a psychotic disorder on Study Day 4. The dose of KP415 was increased from 39.2 mg SDX/7.8 mg d-MPH/day to

52.3 mg SDX/10.4 mg d-MPH/day on Day 4. The investigator described this event as a toxic psychosis. Past medical history was unremarkable for any psychiatric disorder other than ADHD. Study drug was withdrawn on Day 6, and the event resolved the following day without therapeutic intervention.

- Patient (b) (6) was an 8-year-old male who experienced moderate tardive dyskinesia after the first dose of KP415 39.2 mg SDX/7.8 mg d-MPH on Study Day 1. Concomitant medications were cetirizine (an antihistamine) and melatonin. The investigator described the event as the lower jaw moving backward and forward, which the investigator considered to be consistent with bruxism. There were no other abnormal movements. Study drug was stopped, and the event resolved that evening without therapeutic intervention.

- Patient (b) (6) was a 12-year-old male who experienced severe depression and suicidal ideation on Study Day 183 at an KP415 dose of 52.3 mg SDX/10.4 mg d-MPH/day. Fluoxetine 10 mg/day was started on Day 195. Study drug was continued at that time but withdrawn on Day 210 because of these events.

Among the other 13 studies in the KP415 development program, two patients dropped out due to AEs after receiving SDX or KP415:

- In Study KP415.110, Patient (b) (6) was a 27-year-old male who experienced ventricular extrasystoles 2 hours after receiving oral KP415 (42 mg/9 mg). There were no cardiac symptoms and no history of cardiac problems. This finding resolved within 2 hours of onset.

- In Study KP415.A02, Patient (b) (6) was a 32-year-old male who experienced claustrophobia 2 days after receiving SDX 80 mg intranasally. This event resolved after 6.5 hours.

Reviewer's Comments: Both insomnia and decreased appetite are expected adverse reactions to d-MPH, and the above reports of those events were likely caused by KP415. The report of psychosis is possibly drug-related, given that Focalin XR labeling contains a statement under Warnings and Precautions regarding new onset psychosis in some patients treated with stimulants. Other events that I consider possibly related to KP415 are depression, suicidal ideation, aggression, head-banging, affect lability, nausea, dyskinesia, dizziness, and ventricular extrasystoles. The case of leukopenia and neutropenia seems unlikely to be drug-related because these findings improved considerably with continued treatment and may represent underlying benign ethnic neutropenia. The case of claustrophobia shows no clear relationship to the drug, in part given its onset 2 days after receiving SDX.

Treatment Emergent Adverse Events and Adverse Reactions

Study KP415.E01
Study KP415.E01 consisted of a 3-week, open-label, dose optimization phase in which all patients received KP415 (N=155), followed by a 1-week, double-blind phase in which patients were randomized to treatment with KP415 (N=74) or placebo (N=76). During the open-label treatment phase, AEs reported in at least 5% of patients included: decreased appetite (25%), mood changes (24%), insomnia (17%), abdominal pain (10%), headache (8%), and behavioral changes (5%).[3] Because of the trial design, the AE rates described in the double-blind phase are lower than expected in clinical practice. During the 1-week, double-blind, placebo-controlled treatment phase, the only AE that was reported in at least 5% of KP415-treated patients and at a rate higher than the placebo rate was headache, which was reported in 5% of KP415-treated patients and 1% of placebo-treated patients.

Study KP415.S01
Study KP415.S01 was comprised of a 3-week, open-label, dose optimization phase for new patients and a 12-month open-label treatment phase for all patients. Because the safety profile of KP415 was expected to differ substantially between these two phases, I analyzed them separately. A total of 208 patients were in the safety population of the dose optimization phase and 238 patients were in the safety population of the treatment phase. In Studies KP415.E01 and KP415.S01 together, a total of 343 unique patients received at least one dose of KP415.

During the dose optimization phase of this study, AEs reported in at least 5% of patients were: decreased appetite (19%), insomnia (13%), and mood changes (13%). These events are similar to those reported during the dose optimization phase of Study KP415.E01. During the 12-month treatment phase, the following AEs were reported in at least 5% of patients: upper respiratory tract infection (22%), decreased appetite (19%), mood changes (11%), insomnia (9%), weight decreased (8%), headache (5%), and weight increased (5%).[4]

Three AEs were not reported in Focalin XR labeling but were reported by multiple patients who received KP415 in the two phase 3 studies:

1. **Compulsive behaviors** consisted of dermatillomania, dermatophagia, trichotillomania, compulsive lip biting, and onychophagia. In the two phase 3 trials combined, 2% of patients experienced one of these events.

2. **Bleeding events** consisted of epistaxis, tendency to bruise, contusion, and menorrhagia. These events were experienced by a total of 2% of patients in the two phase 3 studies.

3. Two patients from the same site in Study KP415.S01 were reported to have an

[3] Mood changes, insomnia, abdominal pain, and behavioral changes are combined AE terms that include the MedDRA PTs, as indicated above.
[4] For Study KP415.S01, the following are combined AE terms that subsume multiple MedDRA PTs, as described above: mood changes, insomnia, upper respiratory tract infection, and headache.

intraventricular conduction defect, an event not reported with Focalin XR. The QRS interval increased from 87 msec at baseline to 93 msec in Patient (b) (6) and from 83 msec at baseline to 90 msec in Patient (b) (6). Neither value was considered clinically significant by the investigator, and both were rated as mild in severity. Neither patient experienced any cardiovascular symptoms. With continued KP415 treatment, the QRS intervals decreased to 89 msec and 87 msec, respectively.

Reviewer's Comments: The most commonly reported AEs in the phase 3 studies have been reported with Focalin XR and are typical for those observed with other stimulant medication. Upper respiratory tract infections are common in this age range and unlikely to be caused by KP415. Compulsive behaviors are not specifically mentioned in Focalin XR labeling and should be added to the Adverse Reactions section of labeling for KP415. The two reports of intraventricular conduction defect were not considered clinically significant by the investigator, and a causal link to KP415 is doubtful given that both findings improved with continued drug treatment. Thus, I do not feel that this event must be added to labeling.

Laboratory Findings

Criteria used to identify markedly abnormal laboratory results are shown in the table below:

Table 33 Criteria for Markedly Abnormal Laboratory Values

Clinical Chemistry	
AST	>120 U/L
ALT	>120 U/L
Bilirubin	>30 µmol/L
Sodium	<125 mmol/L >150 mmol/L
Potassium	<3 mmol/L >6 mmol/L
Calcium	<2 mmol/L >3 mmol/L
BUN	>8 mmol/L
Creatinine	>100 µmol/L
Glucose	<3 mmol/L >7 mmol/L
Alkaline phosphatase	>450 U/L
Creatine kinase	>450 U/L
Hematology	
Erythrocytes	$<3.5 \times 10^{12}$/L $>5.5 \times 10^{12}$/L
Hematocrit (ratio)	<0.30 >0.45

Hemoglobin	<10 g/L >15 g/L
Leukocytes	<2.0 x10^9/L >12 x10^9/L
Neutrophils	<1.0 x10^9/L >8.0 x10^9/L
Eosinophils	>10%
Platelets	<150 x10^9/L >450 x10^9/L
Coagulation	
Activated partial thromboplastin time (aPTT)	<26 sec (ages 6 to 10 years) <28 sec (ages 11 to 12 years) >50 sec (ages 6 to 10 years) >52 sec (ages 11 to 12 years)
Prothrombin time (PT)	<9 sec (ages 6 to 10 years) <10 sec (ages 11 to 12 years) >18 sec (ages 6 to 10 years) >19 sec (ages 11 to 12 years)
Urinalysis	
Glucose	Greater than trace
Protein	Greater than trace
Ketones	Greater than trace
Hemoglobin	Moderate or large
Leukocyte Esterase	Moderate or large

Source: Criteria were selected by the Clinical Reviewer to identify patients with markedly abnormal values. For coagulation indices (aPTT and PT), the criteria were based on the normal ranges by age group that were recommended by the pediatric hematology consultant, Dr. Fadi Nossair.

The proportions of patients who had a normal or missing baseline value and met a criterion for a markedly abnormal laboratory value at any time during KP415 treatment in the two phase 3 studies are shown in the following table. Note that laboratory tests were done under fasted conditions in Study KP415.S01 but were performed under either fasted or non-fasted conditions in Study KP415.E01. (Parameters for which no patient in either study met the criterion are not shown.)

Table 34 Proportions of Patients with Markedly Abnormal Laboratory Values

Laboratory Parameter	Study KP415.E01	Study KP415.S01
Increased ALT	0%	<1%
Increased bilirubin	0%	1%
Increased potassium	0%	1%
Increased BUN	0%	2%
Decreased glucose	0%	1%

Laboratory Parameter	Study KP415.E01	Study KP415.S01
Increased glucose	1%	3%
Increased alkaline phosphatase	0%	1%
Increased creatine kinase	0%	1%
Increased RBCs	0%	1%
Increased hematocrit	0%	2%
Increased hemoglobin	0%	1%
Increased WBC count	0%	3%
Decreased neutrophil count	0%	2%
Increased neutrophil count	0%	2%
Increased % eosinophils	3%	3%
Decreased aPTT	0%	1%
Increased aPTT	0%	8%
Increased PT	2%	4%
Urine glucose	0%	2%
Urine protein	4%	12%
Urine ketones	0%	5%
Urine hemoglobin	1%	3%
Urine leukocyte esterase	0%	2%

Source: Computed by the Clinical Reviewer from the adlb.xpt dataset for each study using JMP 15.0.0.

Increased Coagulation Parameters

The proportions of patients in Study KP415.S01 who had a markedly increased aPTT or PT are noteworthy. Regarding patients with increased bleeding times, none used a concomitant anticoagulant drug during the study and none had a history of a bleeding disorder, such as von Willebrand's disease. Only one of these patients (Patient (b) (6) from Study KP415.S01), experienced a bleeding-related AE (easy bruising). Mean changes from baseline in coagulation parameters were unremarkable in both phase 3 studies.

DP informally consulted Fadi Nossair, MD, a pediatric hematologist in the Division of Nonmalignant Hematology, for assistance in evaluating the increased incidence of elevated aPTT and PT values in these trials.[5] At the request of Dr. Nossair, DP requested additional information relevant to these findings from the Applicant on September 4, 2020. The Applicant responded to this Information Request on September 18, 2020 (eCTD Sequence #0015) and September 28, 2020 (eCTD Sequence #0016). DP provided this information to Dr. Nossair, who provided his review via email on October 6, 2020. He stated that the data analyses did not support an effect of KP415 on coagulation, but the lack of a control arm and a significant amount of missing data at baseline do not permit a definitive conclusion. He further indicated

[5] The Applicant also provided data on the prothrombin time international normalized ratio (PT INR) to assess coagulation in these trials. Dr. Nossair stated that the PT INR is less useful in the clinical trial setting than the PT. Thus, this review focused on the PT instead of the PT INR.

that bleeding-related AEs in these studies were infrequent, mild, did not require intervention, and were consistent with rates in the general population. Therefore, he concluded that the clinical significance of any drug effect on coagulation was minimal, if present.

Proteinuria

The large proportion of patients with proteinuria, especially in Study KP415.S01, is also remarkable. Of the 23 patients who met the outlier criterion on-treatment in that study, 19 had 1+ (30 mg/dL) proteinuria and 4 had 2+ (100 mg/dL) proteinuria. None of the 23 patients experienced urinary AEs.

On September 18, 2020, the Applicant responded to the Mid-Cycle Communication Meeting with supplementary information pertaining to proteinuria (eCTD Sequence #0014). They confirmed that no patients in either phase 3 trial experienced an AE related to urinary protein. They explained that proteinuria is commonly observed in children, with up to 10% of children experiencing protein on routine urinalysis testing.[6] This finding is often explained by orthostatic proteinuria or pronounced diurnal variability in urinary protein excretion, with increased urinary protein in the upright position or at the end of the day, respectively. Thus, they consider the incidence of proteinuria in these studies to be consistent with background rates in this population. They further stated that among the 139 patients with urinalysis data at both Day 180 and Day 360 in Study KP415.S01, only 2 (1.4%) patients had abnormal urine protein at both visits. Finally, the Applicant points out that among patients with abnormal urine protein (defined as 1+, 2+, or 3+) at baseline in that study, 54.5% had normal urine protein at each post-baseline visit. For these reasons, the Applicant asserts that the proteinuria detected in these trials was random, not clinically significant, and unrelated to KP415 treatment.

DP consulted with Shamir Tuchman, MD, a pediatric nephrologist in the Division of Pediatrics and Maternal Health, for advice on the clinical evaluation of proteinuria in Study KP415.S01. Dr. Tuchman completed a consultative review dated December 18, 2020. He explained that false positive tests for protein on urinalysis can occur with concentrated urine specimens (a specific gravity >1.015), an alkaline urine (pH ≥7), or contamination with antiseptic agents or iodinated radiocontrast agents. He stated that proteinuria may be transient, orthostatic, or persistent. Transient proteinuria can be caused by factors such as fever, exercise, seizure, contamination with mucus, or a urinary tract infection. Dr. Tuchman also stated that children can manifest orthostatic proteinuria, which is characterized by protein in the urine when the patient is upright that is not present when the patient is recumbent. Both transient and orthostatic proteinuria are not associated with an increased risk of chronic kidney disease compared to the general population. Confirmation of whether an increased protein concentration on urinalysis constitutes true abnormal excretion of protein is evaluated by quantification of the ratio of protein to creatinine content in a urine collection. A ratio <0.2 is considered normal in children older than 24 months with mature kidney function.

[6] For example, see: Leung A and A. Wong, 2010, Proteinuria in Children, *American Family Physician*, 82(6):645-651.

Dr. Tuchman's review of urinalysis data from Study KP415.S01 indicated that most patients with proteinuria on study drug had 1+ proteinuria and concentrated urine specimens. Four patients had >1+ proteinuria while taking study drug. In two of these patients, there was persistent proteinuria of 2+ to 3+ and, in one of these patients, there were signs of infection (white blood cells and bacteria). In the other two patients, proteinuria was observed at the 12-month visit with no subsequent testing to confirm persistence of the finding. It is unclear whether any of the observed proteinuria was due to orthostatic proteinuria or transient causes. Dr. Tuchman stated that it did not appear that the majority of proteinuria cases were clinically significant, but it was not possible to definitively exclude persistent proteinuria in patients who received KP415. If proteinuria continues to be a concern for this product, he did recommend that protocols for future studies specify that first morning urine specimens should be collected and, if greater than trace proteinuria is observed, that the protein to creatinine ratio be quantified.

Neutropenia

With respect to patients with decreased neutrophil counts, two white male patients in Study KP415.S01 experienced very low counts. (These patients are in addition to the Patient (b) (6) (b) (6), who dropped out because of leukopenia and neutropenia and was discussed above.) Neither had a medical history suggesting pre-existing neutropenia, and neither took a concomitant medication known to cause neutropenia. The time course of the neutrophil counts (per µL) are shown below:

Study Day	**Patient** (b) (6)	**Patient** (b) (6)
Screening	2,750	4,150
180	620	850
210	3,070	1,740
360	2,350	910

As with Patient (b) (6), both patients demonstrated increased neutrophil counts 30 days after a low count on Day 180 despite continuing KP415 treatment. The count had decreased again in Patient (b) (6) by the end of the study on Day 360. Patient (b) (6) had no AEs. Patient (b) (6) had brief episodes of infection during KP415 treatment (bronchitis, viral gastroenteritis, and sinusitis) that were not temporally related to the low neutrophil counts.

Hyperbilirubinemia

Two patients (b) (6)) in Study KP415.S01 had serum bilirubin levels slightly above the markedly abnormal limit. Neither patient had elevated liver transaminase levels (SGPT or SGOT) and neither had a relevant AE.

Reviewer's Comments: Regarding the coagulation abnormalities (increased aPTT and PT), although the results from Study KP415.E01 are unremarkable, I have doubts about the reliability of lab data from this trial because, as I discussed in Section 8.2.3 above, about one-half of patients had post-baseline blood samples for laboratory testing were collected 3 days or longer

after the last dose of study drug. The data from Study KP415.S01, which I consider more reliable, show that, among patients with normal values at baseline, 8% and 4% of patients had on-treatment aPPT and PT values, respectively, that were considerably higher than the upper limit of the age-adjusted normal range. Although I agree with Dr. Nossair that the analyses submitted by the Applicant do not clearly indicate a drug effect on coagulation, no analysis conducted by the Applicant directly refutes the above findings and, in any event, no analysis can be considered definitive absent a placebo control arm. Likewise, without a placebo arm and coagulation testing performed at the time of most of the bleeding events, I cannot definitively conclude that the reported bleeding events were not causally related to abnormal coagulation parameters. Although I agree that the significance of any clinical effect on coagulation appears to have been limited, I believe that the incidence of elevated aPTT results should be included in labeling.

With respect to proteinuria, it does seem that this finding on urinalysis is common among children in the age range studied in the phase 3 trials (6 to 12 years) for a variety of possible reasons. It is not possible to objectively evaluate the role of these factors in these studies without more information that cannot be produced at this point, such as the protein to creatinine ratios in several cases of 1+ proteinuria with concentrated urine specimens, as discussed by Dr. Tuchman. In addition, without a concurrent, randomized placebo control, it is not feasible to definitively ascertain the extent to which this finding is attributable to KP415. That said, there are no known AEs related to proteinuria in these studies and prominent labeling of this laboratory finding is not warranted. Nevertheless, given the 12% incidence of proteinuria in Study KP415.S01, I believe that this finding should be mentioned in labeling.

The time courses of the neutrophil counts in the three cases of marked neutropenia, i.e., improvement with continued drug exposure, are not consistent with a drug effect. In addition, the proportions of patients with markedly low neutrophil counts and markedly high neutrophil counts were the same in Study KP415.S01, suggesting that these were random findings. Therefore, I do not feel that these cases of neutropenia were likely to be caused by KP415.

Vital Signs

The following table displays the criteria that were used to identify markedly abnormal vital sign readings in Studies KP415.E01 and KP415.S01.

Table 35 Criteria for Markedly Abnormal Vital Sign Values

Parameter	Criteria
↓ Systolic Blood Pressure (mmHg)	≤70 and ≥20 decrease from baseline (6 to 12 years)
↑ Systolic Blood Pressure (mmHg)	≥120 and ≥20 increase from baseline (6 to 12 years)
↓ Diastolic Blood Pressure (mmHg)	≤40 and ≥15 decrease from baseline (6 to 12 years)
↑ Diastolic Blood Pressure (mmHg)	≥80 and ≥15 increase from baseline (6 to 12 years)
↓ Pulse Rate (bpm)	≤60 and ≥15 decrease from baseline (6 to 10 years) ≤50 and ≥15 decrease from baseline (11 to 12 years)

Parameter	Criteria
↑ Pulse Rate (bpm)	≥135 and ≥15 increase from baseline (6 to 10 years) ≥120 and ≥15 increase from baseline (11 to 12 years)
↓ Respiratory Rate (breaths/min)	<10 breaths/min
↑ Respiratory Rate (breaths/min)	>28 breaths/min
↑ Temperature (°C)	≥38.3 and ≥0.8 increase from baseline

Source: Extracted from Table 7.1 from the Outlier Analysis Tables document, eCTD Sequence #0009.

During the dose optimization phase of Study KP415.E01, markedly abnormal values for increased systolic blood pressure (SBP) and increased diastolic blood pressure (DBP) were observed in 8% and 14% of patients, respectively. A markedly decreased pulse rate was reported in 5% of patients. No patient met these criteria for abnormal respiratory rate or temperature.

In Study KP415.S01, markedly abnormal values for increased SBP and increased DBP were observed in 16% and 19% of patients, respectively. A markedly low pulse rate was reported in 3% of patients. One patient had a markedly increased pulse rate and one patient had a marked increase in body temperature.

The mean changes from baseline to each week in vital sign measures among 74 KP415-treated patients in Study KP415.E01 are displayed in the table below.

Table 36 Mean Changes in Blood Pressure and Pulse (Study KP415.E01)

Study Week	SBP (mmHg)	DBP (mmHg)	Pulse (bpm)
1	1.9	2.6	2.1
2	0.5	6.1	-0.8
3	-0.4	5.5	-1.1
4	-0.2	5.9	-2.3

Source: Tables 14.3.1.5.1 to 14.3.1.5.5 in the Clinical Study Report for Study KP415.E01.

The observed cases and completers analyses of mean changes from baseline in blood pressure and pulse rate during the treatment phase of Study KP415.S01 are shown in the next two tables.

Table 37 Mean Changes in Blood Pressure and Pulse (Study KP415.S01 Observed Cases)

Study Month	SBP (mmHg)	DBP (mmHg)	Pulse (bpm)
3	2.7	1.8	5.0
6	2.7	3.7	2.5
9	4.4	2.8	5.2

Study Month	SBP (mmHg)	DBP (mmHg)	Pulse (bpm)
12	4.3	2.6	2.4

Source: Table 14.3.6.1 in the Clinical Study Report for Study KP415.S01.

Table 38 Mean Changes in Blood Pressure and Pulse (Study KP415.S01 Completers)

Study Month	SBP (mmHg)	DBP (mmHg)	Pulse (bpm)
3	3.1	1.8	4.6
6	2.8	3.6	2.8
9	4.7	2.6	4.9
12	4.3	2.7	2.4

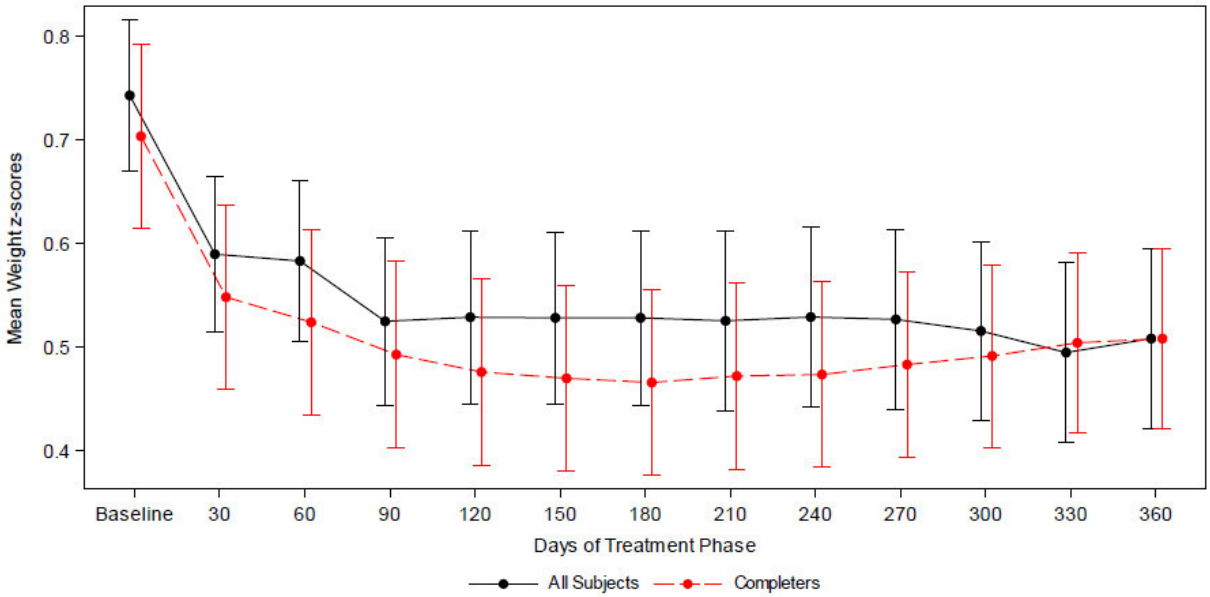
Source: Computed by the Clinical Reviewer using the dataset advs.xpt and JMP 15.0.0.

In both studies, mean changes in respiratory rate and body temperature were consistently small (≤0.5 breaths/min and ≤0.3 ^{o}C).

The effect of KP415 on body weight was evaluated in Study KP415.S01 using z-score analyses. The mean weight at baseline among all patients was 38.6 kg. Mean weights decreased slightly in the first 3 months of treatment (-0.18 kg at 90 days) but then increased during the remained of the 12-month trial. At the end of the study, the mean weight increase was 3.43 kg among study completers. Because an increase in weight is expected among children in this age range, a z-score analysis was used to determine whether the patients maintained a trajectory of weight gain expected for their age and sex, according to 2000 CDC growth curves. The following figure displays the change in mean weight z-scores over time for all patients as well as the 155 completers in Study KP415.S01.

The study sample was, on average, heavier at baseline than expected after adjustment for sex and age (mean z-score = 0.74). There was an appreciable decrease in mean z-scores in the first 120 days of treatment, with a subsequent leveling off. Mean z-score changes from baseline were -0.23, -0.24, -0.22, and -0.20 at 4, 6, 9, and 12 months, respectively. This trend suggests a lower than expected increase in weight compared to children of the same sex and age. This pattern was roughly similar between sexes, across age groups, and among BMI quartiles. The mean percentile for weight was at the 68th percentile at baseline and steadily decreased during the study, ending at the 63rd percentile by 12 months.

Figure 14 Mean Weight Z-Scores Over Time (Study KP415.S01)



Source: Figure 4 in the Weight and Height Analysis report in the Clinical Study Report for Study KP415.S01.

Reviewer's Comments: An appreciable number of patients experienced markedly abnormal blood pressure increases and pulse rate decreases from baseline. Increased blood pressure is expected with drugs in the stimulant class. The decreases in pulse rate may represent a baroreceptor response to the increased blood pressure. However, in the long-term study, mean increases in both blood pressure and pulse rate were observed. These were moderate in magnitude but similar to observations with other stimulant drugs. The z-score analysis of body weight suggests that patients gained weight less rapidly than their peers in the first 4 months of treatment but then gained weight at approximately the expected rate for the rest of the trial. However, in the absence of a randomized placebo-control group, and given the frequency of dropouts during long-term studies, this interpretation must be made with caution.

Electrocardiograms (ECGs)

The following table displays the results of outlier analyses of electrocardiographic data from patients treated with KP415 in Studies KP415.E01 and KP415.S01. I selected QTc data using the Fridericia correction of the QT interval for presentation here over the Bazett's corrected data because the former has been shown to be more useful in predicting mortality.[7]

[7] Vandenberk B, et al, 2016, Which QT Correction Formulae to Use for QT Monitoring, *J Am Heart Assoc*, doi: 10.1161/JAHA.116.003264.

Table 39: Proportion of Patients Meeting ECG Outlier Criteria

Parameter/Outlier Criteria	Study KP415.E01	Study KP415.S01
Heart rate ≥20 bpm ↑ from baseline	6%	21%
Heart rate ≥20 bpm ↓ from baseline	13%	8%
PR interval ≥220 msec and ≥20% ↑ from baseline	0%	0%
QRS interval ≥120 msec and ≥20% ↑ from baseline	0%	0%
QTc Analyses		
↑ QTcF >30 msec	0%	8%
↑ QTcF >60 msec	0%	<1%
QTcF >480 msec	0%	0%
QTcF ≥500 msec	0%	0%
QTcF >480 msec and ↑ >30 msec	0%	0%
QTcF ≥500 msec and ↑ >30 msec	0%	0%

Source: Tables 4.11.1 and 4.12.1 from the Outlier Analysis Tables document, eCTD Sequence #0009.

The mean changes from baseline in ECG parameters in KP415-treated patients in Studies KP415.E01 and KP415.S01 are shown in the next table:

Table 40 Mean Changes from Baseline in ECG Parameters

Parameter	Study KP415.E01	Study KP415.S01	
		Study Day 180	Study Day 360
Heart rate (bpm)	-1.8	3.4	3.6
PR interval (msec)	-0.7	-1.8	-1.7
QRS interval (msec)	0.0	0.9	1.6
QT interval (msec)	-1.1	-3.7	-1.7
QTcF interval (msec)	-3.1	1.3	3.3

Source: Tables 14.3.1.6.2 through 14.3.1.6.7 in the Clinical Study Report for Study KP415.E01 and Table 14.3.6.2.1 in the Clinical Study Report for Study KP415.S01.

Reviewer's Comments: There was a tendency for a decrease in heart rate in Study KP415.E01 and an increase in heart rate in Study KP415.S01. This tendency may represent short-term versus chronic effects on heart rate in response to increases in blood pressure. A placebo-control group may have been useful in interpreting these findings. Other ECG findings were unremarkable.

QT IRT Consultative Review

The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies was consulted to evaluate the Applicant's justification to waive the requirement for a thorough QT (TQT) study with KP415. The IRT completed a consultative review on May 21, 2020, which is summarized below.

The effect of SDX on the QT interval was evaluated in Study KP415.A02, which was a human abuse potential study that compared intranasal SDX 80 mg, d-MPH 40 mg, and placebo in 46 healthy subjects. This dose provided a greater than 40-fold exposure margin for the therapeutic dose of KP415 and, thus, supported waiving the requirement for a positive control. An exposure-response analysis of these data did not suggest that SDX is associated with significant QTc prolongation. At one hour post-dose, the ΔΔQTcF was +0.9 msec (90% CI -2.5, +4.3 msec) at a concentration of 1745 ng/ml. Data at 24 hours post-dose did not suggest a delayed effect on the QTcF interval. The IRT review did not evaluate the effect of MPH on the QTc interval. Nonetheless, systemic exposure to MPH after repeated dosing with KP415 was reported to be 20.0 ng/ml at the highest recommended dose. This exposure was not higher than that observed with Focalin XR, which was examined in a previous TQT study that did not reveal a clinically relevant QT prolonging effect.

The IRT recommended the following language for labeling under Section 12.2 Pharmacodynamics:

Cardiac Electrophysiology
The effect of serdexmethylphenidate on the 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) *(52.3/10.4 mg base equivalent), serdexmethylphenidate does not prolong the QT interval to any clinically relevant extent.*

Immunogenicity

I searched the AE databases (adae.xpt) for Studies KP415.E01 and KP415.S01 for events suggestive of hypersensitivity reactions.

In Study KP415.E01, one patient (b) (6) experienced bronchospasm on Day 2 of KP415 treatment. Treatment was stopped and the event, which was considered non-serious, resolved. Two other patients experienced possible hypersensitivity events (right forearm rash on Day 6 of KP415 optimization and wheezing on Day 29 of the 28-day study). Neither of the latter two events were serious.

In Study KP415.S01, a total of 16 events were experienced by a total of eight patients. These events were acute respiratory failure, asthma, status asthmaticus, bronchospasm, eyelid rash, pruritus, and rash. A 9-year-old female (Patient (b) (6)) had a history of asthma was hospitalized five times during 10 months of KP415 treatment for complications of this condition, the first after 32 days of KP415 treatment. She experienced acute respiratory failure, asthma, status asthmaticus, and bronchospasm at various times. This patient was discussed above under serious AEs. Among the remaining seven patients, none were serious or led to dropout and four of these patients had events with onset after Day 50 of KP415 treatment. The other three patients experienced arm pruritus, generalized rash, and pruritus on Days 3, 15, and 17 of KP415 treatment, respectively.

Reviewer's Comments: The events experienced by Patient (b) (6) unlikely represented hypersensitivity reactions to KP415 given her history of asthma, onset of the first event after 32 days of treatment, and event-free periods up to 3 months in duration while receiving KP415. I consider many of the other events as unlikely to be related to KP415 because of the long times to onset. However, I do believe that the cases of bronchospasm, rash, and pruritus are possible hypersensitivity reactions to KP415 and have incorporated the relevant information into Section 4 of labeling.

8.2.5 Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Assessment of Sleep

Investigators systematically assessed sleep during Study KP415.S01 using the modified, abbreviated version of the Children's Sleep Habits Questionnaire (CSHQ) at each monthly visit. This scale consists of a 33-item, parent-rated questionnaire that rates sleep behavior over the prior week or in the most recent typical week if sleep during the prior week was affected by unusual factors, such as physical illness. The sleep endpoint was the Total Sleep Disturbance Score (TSDS) which sums the responses from the 33 items. A decrease in the TSDS represents improvement in sleep behavior.

Mean changes from baseline over time in the TSDS for all patients and for the 155 completers in this study are presented in the following table.

Table 41 Mean Change from Baseline in CSHQ Total Sleep Disturbance Score

Study Month	All Patients			Completers	
	N	Score	Change	Score	Change
3	208	44.8	-6.6	45.1	-6.0
6	189	44.7	-6.7	44.9	-6.2
9	168	44.3	-7.1	44.5	-6.6
12	155	43.9	-7.2	43.9	-7.2

Source: Computed by the Clinical Reviewer from the dataset adqs.xpt using JMP 15.0.0.

Reviewer's Comments: Mean TSDS values decreased slightly over time although it appears that improvement from baseline was largest within the first three months after baseline. Given that TSDS scores of 41 or higher are generally considered an indication of a sleep problem, patients

continued to experience some sleep disturbance throughout the study, on average.[8] It is unknown how these data would compare to those with other longer-acting d-MPH or MPH products because of the lack of an active control group in Study KP415.S01.

Suicidal Ideation and Behavior

Investigators monitored suicidal ideation and behavior (SI/B) using the C-SSRS at each visit during Studies KP415.E01 and KP415.S01.

During the dose optimization phase of Study KP415.E01, 1/155 patients (1%) reported a wish to be dead on item 1 of the C-SSRS at Week 1 of dose optimization. No patient reported SI/B on the C-SSRS during the randomized treatment phase. There were no reports of suicidal behavior during this trial.

During dose optimization in Study KP415.S01, no patient reported SI/B on the C-SSRS. During the treatment phase, a total of 3/277 patients (1%) reported suicidal ideation. Two reported a wish to be dead (item 1), three reported non-specific active suicidal thoughts (item 2), and one reported active suicidal thoughts without intent to act or a specific plan (item 3).[9] A total of 8 patients (3%) engaged in suicidal behavior and another 2 patients (1%) engaged in self-injurious behavior with unknown intent. None of the patients who attempted suicide reported suicidal ideation on the C-SSRS, and none had any suicidal behavior reported as an AE.

Reviewer's Comments: The occurrence of suicidal behavior in 3% of patients during the treatment phase of Study KP415.S01 is notable. However, the degree to which these cases can be attributed to KP415 is unknown, given the absence of a placebo-control group.

8.2.7 Safety Analyses by Demographic Subgroups

I analyzed the reporting rates of AEs that were reported in at least 5% of patients during the dose optimization phase of Study KP415.E01 by two demographic variables: sex (male versus female) and race (white versus Black/African American(AA)). The following table displays the results of my demographic analysis:

[8] Owens JA, et al, 2000, The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children, *Sleep*, 23(8):1043-51.
[9] One patient had all three types of suicidal ideation and another had two types of suicidal ideation. Thus, the total number of patients with suicidal ideation is only three.

Table 42 Adverse Event Incidence by Demographic Subgroup

Adverse Event[10]	Sex		Race	
	Male	Female	White	Black/AA
Decreased Appetite	24% (22/93)	26% (16/62)	24% (19/80)	25% (14/57)
Mood Changes	24% (22/93)	24% (15/62)	33% (26/80)	9% (5/57)
Insomnia	16% (15/93)	18% (11/62)	19% (15/80)	9% (5/57)
Abdominal Pain	10% (9/93)	11% (7/62)	8% (6/80)	14% (8/57)
Headache	9% (8/93)	6% (4/62)	8% (6/80)	9% (5/57)
Behavioral Changes	4% (4/93)	6% (4/62)	6% (5/80)	4% (2/57)

Source: Computed by the Clinical Reviewer from the dataset adae.xpt using JMP 15.0.0.

There were no major differences in AE reporting rates between sexes. However, between race subgroups, white patients reported more mood changes and insomnia and Black/AA patients experienced more abdominal pain.

Reviewer's Comments: I do not consider the observed differences between the two race subgroups definitive in the absence of a placebo control group during the dose-optimization phase. Without an estimate of the reporting rates in the background population, these findings cannot be reliably interpreted. Note that no analysis by age was performed because of the relatively narrow age range of patients in this trial (6 to 12 years) and the fact that most patients were age 8 years or older. Also, no analysis by other race groups was performed, because of the small numbers of patients in those groups.

Because d-MPH plasma levels in adolescents and adults are, on average, considerably less than those seen in children, I expect that the safety in adolescents and adults can be assessed from the above safety findings in children and known safety profile of the LD. Thus, I believe that no further evaluation of safety in adolescents or adults is required for approval of this application.

8.2.8 Specific Safety Studies/Clinical Trials

No specific safety studies with KP415 were conducted.

8.2.9 Additional Safety Explorations

Human Reproduction and Pregnancy

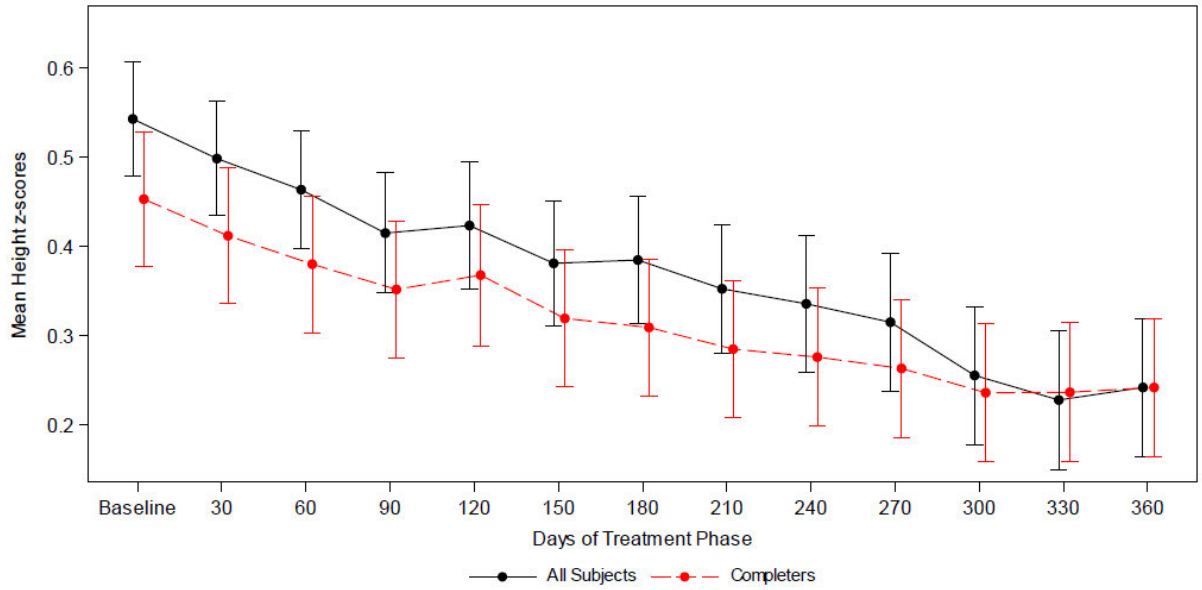
[10] The AE terms mood changes, insomnia, abdominal pain, and behavioral changes are combined terms that subsume specific MedDRA Preferred Terms, as described above.

No pregnancies were reported in the phase 3 studies. Published studies and postmarketing reports regarding methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. CNS stimulants can cause vasoconstriction and decrease placental perfusion. No fetal or neonatal adverse reactions have been reported by clinicians with the use of therapeutic doses of methylphenidate during pregnancy.[11]

Pediatrics and Assessment of Effects on Growth

The Applicant evaluated the effect of KP415 on growth in Study KP415.S01 using z-score analyses. The mean height at baseline among all patients was 139.6 cm. Mean height increased steadily throughout the 12-month trial and, at the end of the study, the mean height increase was 4.90 cm among study completers. Because an increase in height is expected among children in this age range, a z-score analysis was used to determine whether the patients maintained a trajectory of growth expected for their age and sex, according to 2000 CDC growth curves. The following figure displays the change in mean height z-scores over time for all patients as well as the 155 completers in Study KP415.S01. The study sample was, on average, taller at baseline than expected after adjustment for sex and age. There was a steady, modest negative effect on height, with a z-score change from baseline of -0.14 at 6 months and -0.21 at 12 months, indicating a lower than expected increase in height compared to children of the same sex and age. This pattern was similar between sexes, across age groups, and among BMI quartiles. The mean percentile for height was at the 65th percentile at baseline and steadily decreased during the study, ending at the 57th percentile by Day 360.

Figure 15 Mean Height Z-Scores Over Time (Study KP415.S01)



[11] Source: Section 8.1 of Focalin XR labeling.

Source: Figure 14 in the Weight and Height Analysis report in the Clinical Study Report for Study KP415.S01.

Reviewer's Comments: These data suggest a suppressive effect of KP415 on linear growth. However, as with the z-score analysis of weight gain, this analysis must be interpreted with caution because there was no randomized, placebo control group for comparison, and there are dropouts affecting overall results in long-term studies. The LD label includes language in Warnings and Precautions related to long term suppression of growth; this language will be retained in labeling for this product.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdosages were reported in one patient from Study KP415.E01 and eight patients from Study KP415.S01. These cases involved accidental administration of double-doses or, in one case, an increase in dose to achieve an enhanced therapeutic effect. None of the overdosages appear to represent intentional acts of self-harm.

Three cases of possible diversion of KP415 doses were reported in Study KP415.S01.

No reports of euphoria were reported in either phase 3 trial. Nevertheless, misuse or abuse of KP415 may occur to experience the following effects:

- Stimulation effects (insomnia, energy increased, psychomotor hyperactivity) were experienced by 18% of patients in Study KP415.E01 and 17% of patients in Study KP415.S01.

- Decreased appetite or weight loss were reported by 25% of patients in Study KP415.E01 and 31% of patients in Study KP415.S01.

- Visual hallucinations were reported in 1% of patients in Study KP415.S01.

Withdrawal and rebound effects were not systematically evaluated in the KP415 development program.

CNS stimulants, including d-MPH, have a high potential for abuse and are associated with tolerance and dependence. Because KP415 contains immediate-release d-MPH and SDX, which is a prodrug of d-MPH, KP415 should be classified as a Schedule II drug under the Controlled Substances Act.

The Applicant conducted three human abuse potential studies: KP415.A01, KP415.A02, and KP415.A03 in SDX only. These studies examined the abuse liability of SDX compared to d-MPH and placebo. Because none evaluated the KP415 combination product (SDX/d-MPH), these trials cannot yield useful information on the abuse potential of KP415 and will not be included in labeling per CSS.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

KP415 has not been approved in any country. Therefore, there are no postmarketing safety data with this product.

Important adverse reactions from postmarketing experience with methylphenidate products or other CNS stimulants that are described under Section 4 (Contraindications) or Section 5 (Warnings and Precautions) of Focalin XR labeling are the following:

- Hypersensitivity reactions, such as angioedema and anaphylaxis.
- Abuse and dependence.
- Sudden death, stroke, and myocardial infarction.
- Exacerbation of preexisting psychotic illness and new psychotic symptoms.
- Induction of mania.
- Priapism.
- Peripheral vasculopathy, including Raynaud's phenomenon.

Other adverse reactions that have been reported from postmarketing experience with methylphenidate products include the following: rhabdomyolysis, leukopenia, thrombocytopenia, anemia, pancytopenia, depressed mood, affect lability, dyskinesia, convulsions, serotonin syndrome in combination with serotonergic drugs, blurred vision, cardiac arrhythmias (including ventricular extrasystole), transaminase elevation, severe liver injury, erythema multiforme, thrombocytopenic purpura, and hyperpyrexia.[12]

Expectations on Safety in the Postmarket Setting

In general, I expect that the safety profile of KP415 in the postmarket setting will be similar to that for other methylphenidate products. The clinical consequences of the increased bleeding times and proteinuria observed in the phase 3 studies remain uncertain at this time.

8.2.11 Integrated Assessment of Safety

KP415 was commonly associated with a number of AEs in the phase 3 trials:

- Decreased appetite and abdominal pain.
- Insomnia.
- Mood changes including depression, irritability, and affect lability.
- Behavioral changes including aggression and compulsive behaviors.
- Increases in systolic and diastolic blood pressure.

[12] Source: Section 6.2 of Focalin XR labeling.

- Decreased weight gain and growth rate compared to peers.
- Headache.

To various degrees, these findings have been observed with other methylphenidate products. In addition, the following events were less commonly observed but have been reported with this drug class:

- Suicide attempts
- Dyskinesia
- Psychotic symptoms
- Possible hypersensitivity events including bronchospasm, rash, and pruritus.

Furthermore, the following laboratory findings are not known to be associated with methylphenidate but were observed in the phase 3 studies in multiple patients:

- Bleeding events and increased bleeding times per aPTT and PT elevations
- Proteinuria.

These findings were evaluated by appropriate Agency consultants and, based on the totality of information, I do not consider these to be major safety concerns attributable to KP415.

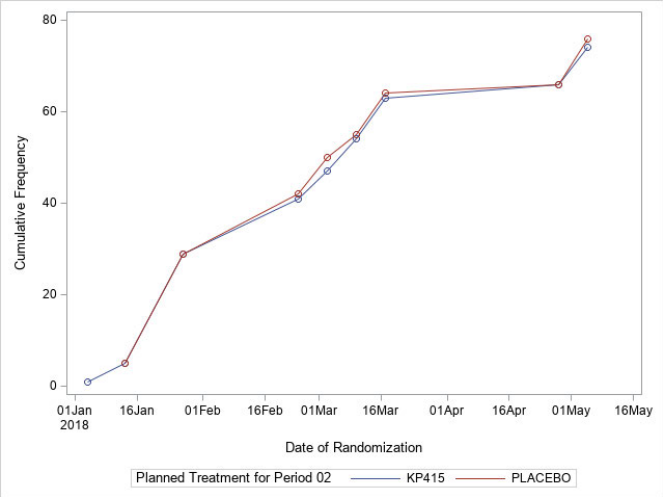
The possibility of hepatic injury was considered at the outset of this review. However, the data, including laboratory findings, do not indicate the occurrence of any cases of substantial hepatic AEs in these trials.

Because of the study designs, a definitive assessment of the causal link between the above AEs and KP415 treatment is not possible. Thus, the adverse reaction tables in labeling should rely on data with the Listed Drug (Focalin XR). Overall, I do not think that these safety findings should preclude approval of this application. However, these events, particularly those not commonly observed with other CNS stimulants, should be adequately labeled.

8.3 Statistical Issues

Randomization
All randomizations occured between January and May 2018. Randomization was not continuous, but occured in batches (likely due to grouping of subjects for laboratory classroom days). There are no appararent issues with the randomization - treatment assignments appear balanced between the two groups at the multiple randomization instances (Figure 18).

Figure 16. Assignment to Treatments Groups over Time

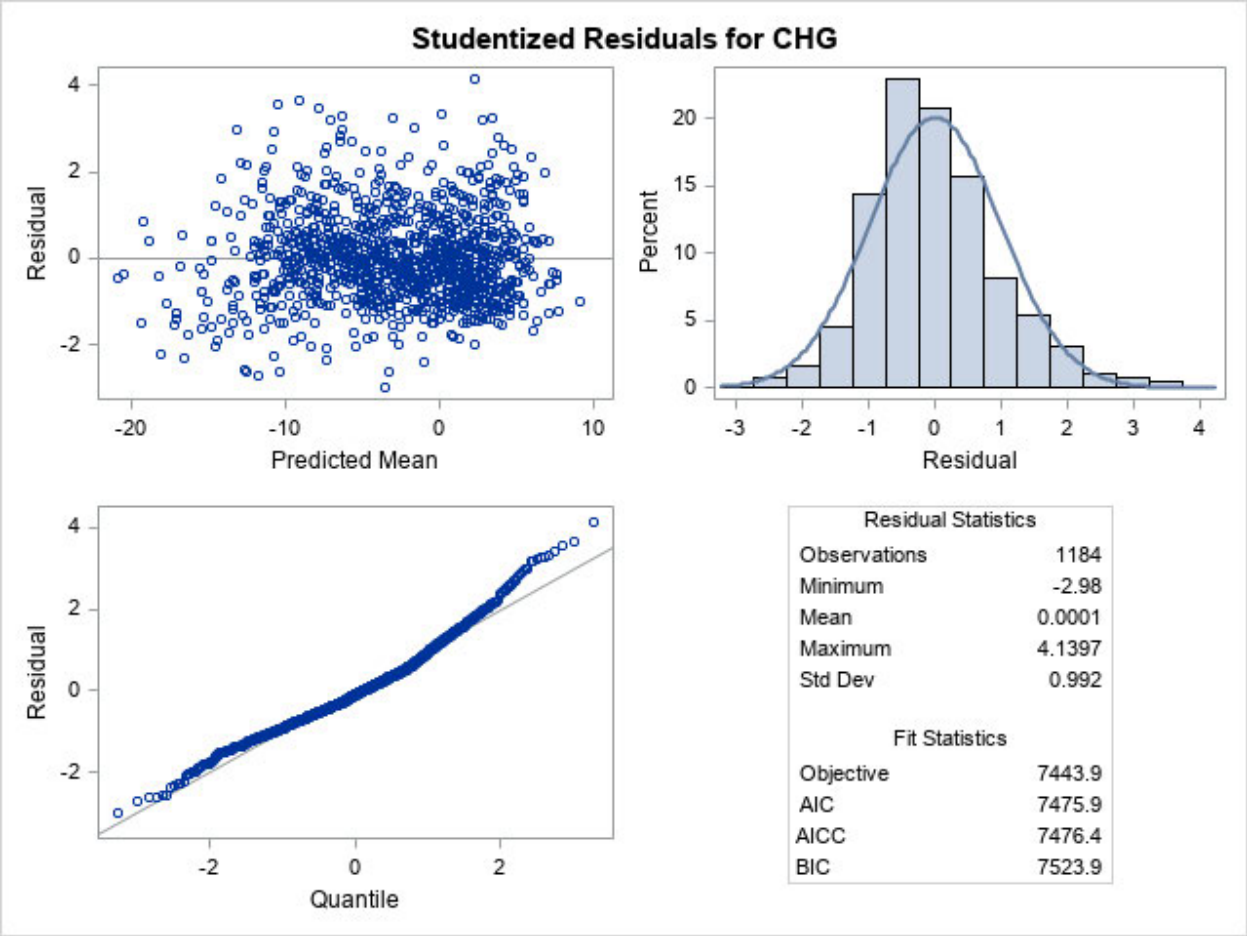


(Source: Statistical Reviewer)

Model Assumptions Check for Primary Efficacy Analysis Model

The normality assumption appears to hold (Shapiro-Wilk's W = 0.98 for studentized residuals over all post-dose time points for change from baseline in SKAMP-C score). The MMRM model appears suitable for analysis of the primary efficacy endpoint.

Figure 17. Plots for Studentized Residuals from Primary Efficacy Model



(Source: Statistical Reviewer)

8.4 Conclusions and Recommendations

From a clinical and statistical perspective, the safety and efficacy of KP415 in the treatment of patients age 6 years and older with ADHD have been adequately demonstrated.

We recommend approval of this application under the conditions of use described in labeling. We further recommend that PK, safety, and efficacy be assessed in children 4 to less than 6 years of age and that placebo-controlled safety data be obtained in patients 6 to 12 years of age (see Section 13 below).

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultations were deemed to be necessary for this application.

10 Pediatrics

The Agreed Initial Pediatric Study Plan (iPSP), dated August 1, 2018, addresses the KP415 pediatric clinical studies by the following age ranges:

0 to <4 years	A waiver will be requested because studies in this age range are highly impractical.
	(b) (4)

The Pediatric Team in the Division of Pediatric and Maternal Health (DPMH) was consulted for assistance with the pediatric assessment of safety in this application, specifically regarding laboratory abnormalities observed in Studies KP415.E01 and KP415.S01.

The Pediatric Review Committee (PeRC) discussed this application with DP on February 2, 2021. This discussion was focused on the Divisions's proposed PMRs at that time. The PeRC agreed with PMRs for 1) a randomized, placebo-controlled, parallel group, safety and efficacy trial in patients ages 4 through 12 years; 2) a 12-month, open-label safety study in patients ages 4 to

less than 6 years; and 3) a randomized, placebo-controlled, parallel group, safety and efficacy study in adolescent patients ages 13 through 17 years. Subsequent to that meeting, DP concluded that adequate safety and efficacy data existed to support approval in adolescent patients and, therefore, the last PMR was dropped from further consideration.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Prescribing information

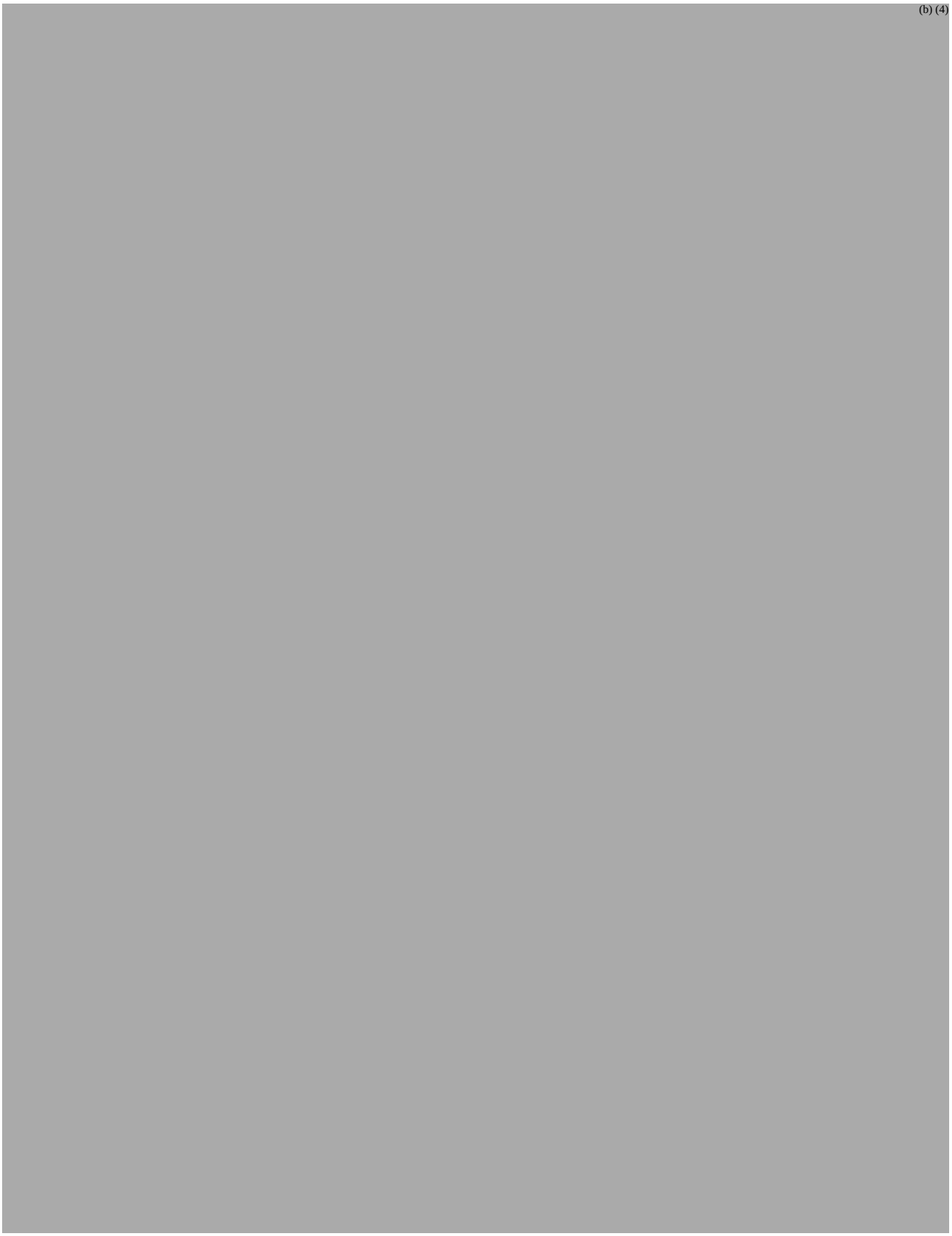
As discussed in Section 8.1.2, after completion of the study and unblinding of the efficacy data from Study KP415.E01, the Applicant requested that we consider, (b) (4) (b) (4)

After consideration of this request, the NDA review team decided that use of the requested (b) (4) was not acceptable, (b) (4) (b) (4) (b) (4) s. Therefore, the review team proposes that labeling describe only results from the original prespecified analysis.

The Applicant disagreed with the review team on this issue and has posed a number of assertions intended to support their request. Their assertions and the review team's response to each assertion are as follows:

(b) (4)

(b) (4)



12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS were deemed to be necessary to ensure the benefits for this product outweigh its risks.

13 Postmarketing Requirements and Commitments

Postmarketing Requirements (PMRs)

PREA PMR 3980-1
Conduct a randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study of Azstarys in male and female children 4 to 12 years of age diagnosed with ADHD. Randomization should be stratified by two age groups, i.e., 4 to less than 6 years and 6 to 12 years of age. Also, this study must include sparse pharmacokinetic (PK) sampling in children ages 4 to less than 6 years to characterize the shape of the PK curve in this population.

PREA PMR 3980-2
Conduct a 12-month, open-label study to obtain information on safety and tolerability of Azstarys in male and female children 4 to less than 6 years of age diagnosed with ADHD.

14 Appendices

14.1 Financial Disclosure

Covered Clinical Study (Name and/or Number): KP415.E01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0		

Sponsor of covered study: KemPharm		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

14.2 Nonclinical Pharmacology/Toxicology

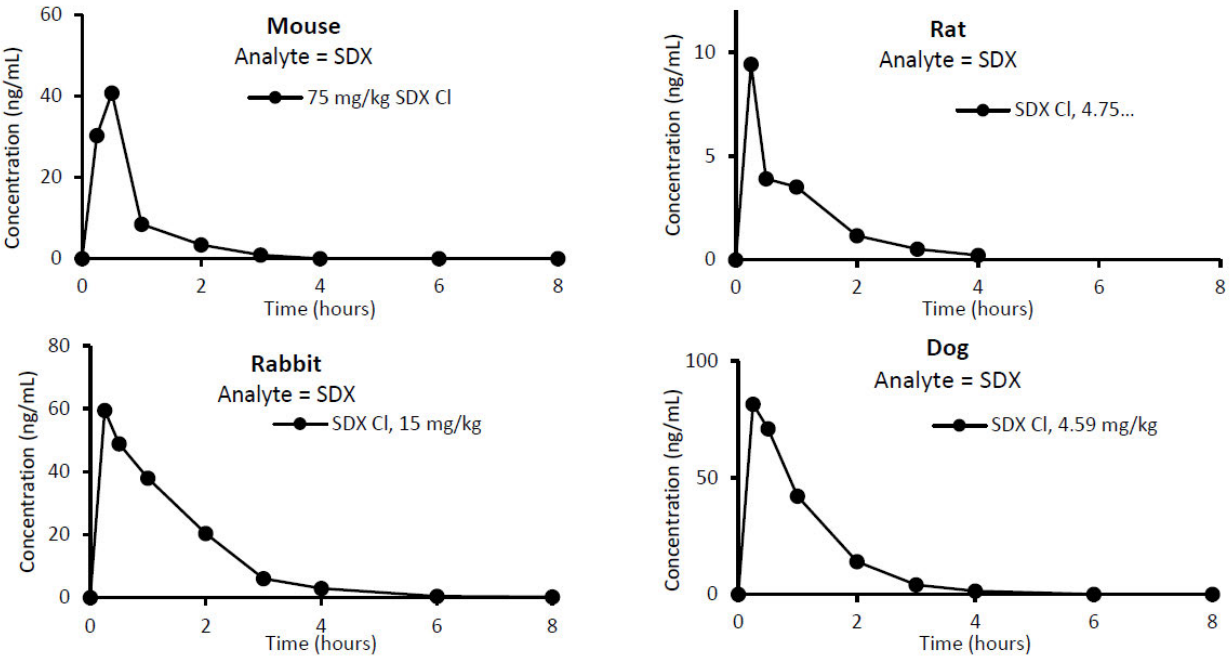
Table 43: Endogenous Levels, Dietary Intake, and Drug Doses for Formaldehyde, Serine, and Niacin

Amount in SDX at MRHD	Endogenous Levels	Dietary Intake	Drug dose or levels released
Formaldehyde 3.1 mg released	steady state ~2.6 mg/kg[1]	Estimated to be 1.5 - 14 mg/day[1]	5.1 - 59.1 mg released in drugs approved for children
L-Serine 11 mg (Applicant estimated serum levels at C_{max}: 1.75 µmol/L)	Serum concentration in healthy volunteers: 175 µmol/L[2]	Examples 1 large egg: 291 mg serine[3] 1 oz cheddar cheese: 390 mg serine[4]	
Niacin 12.9 mg		Average daily recommended amount for age 4 - 13 years: 8 - 12 mg/day Daily upper limits from supplements for age 4 - 13 years: 15 - 20 mg[5]	

[1]Dhareshwar SS, Stella VJ. J Pharm Sci. 2008; 97:4184-4193.
[2]Hashimoto K, Fukushima T, Shimizu E, et al. Arch Gen Psychiatry. 2003 Jun; 60(6):572-576
[3]https://fdc.nal.usda.gov/fdc-app.html#/food-details/747997/nutrients
[4]https://fdc.nal.usda.gov/fdc-app.html#/food-details/170899/nutrients
[5]https://ods.od.nih.gov/factsheets/Niacin-Consumer/

ADME

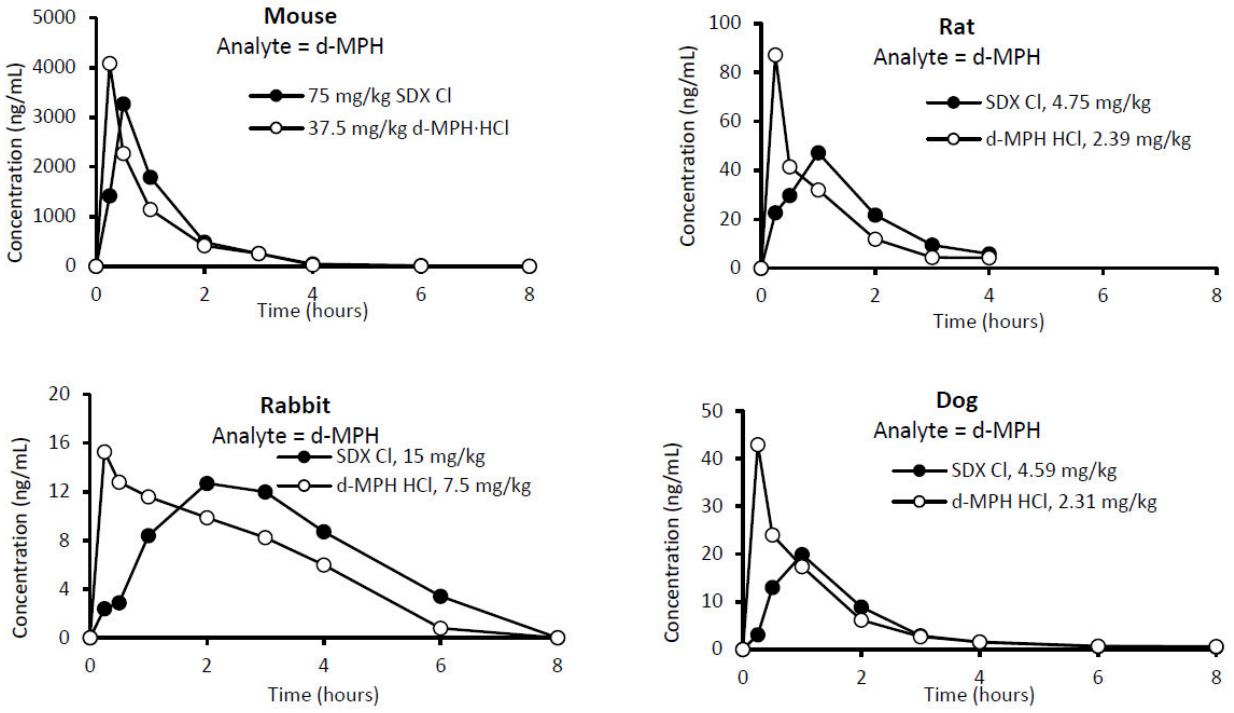
Figure 18: Mean Plasma Concentration-Time Profiles of SDX Following Single Oral Doses of SDX Cl in Mice, Rats, Rabbits, and Dogs (Males and Females Combined)



Source: Upper left panel: 0841MK19.001 study report, Appendix IV-Figure 1; Upper right panel: KP415-PK-001 study report, Figure 4; Lower left panel: 4005904 study report, Figure 1; Lower right panel: 0832DK19.004, Table 3

Source: Applicant's Figure, Nonclinical Overview, p. 9

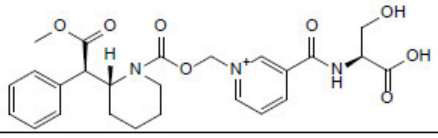
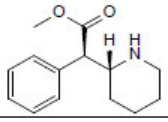
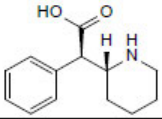
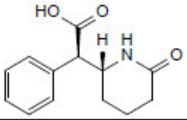
Figure 19: Mean Plasma Concentration-Time Profiles of d-MPH Following Single Oral Doses of SDX Cl or d-MPH Cl in Mice, Rats, Rabbits, and Dogs (Males and Females Combined)

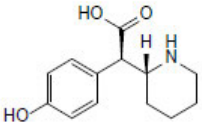
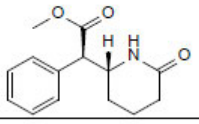
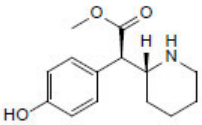
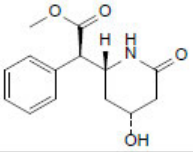
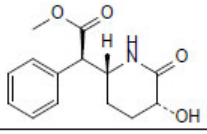
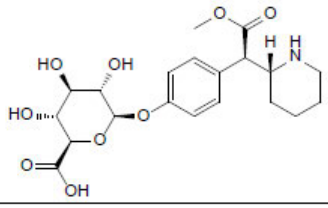
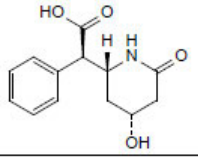
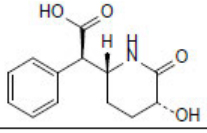


Source: Upper left panel: 0841MK19.001 study report, Appendix IV-Figure 1; Upper right panel: KP415-PK-001 study report, Figure 1; Lower left panel: 4005904 study report, Figure 3; Lower right panel: 0832DK19.004 study report, Table 1 and Table 2

Source: Applicant's Figure, Nonclinical Overview, p. 9

Table 44: Proposed Structures of Metabolites Identified in Rat Urine, Feces, and Plasma

ID	Name	M/z	Proposed Structure	Matrix
KP415 Prodrug	SDX	500		Plasma, feces
M2a	d-MPH	234		Plasma
M3a	RA	220		Plasma, urine, feces
M4a	6-oxo-RA	234		Plasma, urine feces

ID	Name	M/z	Proposed Structure	Matrix
M5	p-hydroxy-RA	236		Feces
M7a	6-oxo-MPH	248		Plasma
M8a/M8d	p-hydroxy-MPH	250		Urine, feces
M14a	4-hydroxy-6-oxo-MPH	264		Plasma
M14b	5-hydroxy-6-oxo-MPH	264		Plasma
M17	UA	266	UA	Plasma, urine
M26	p-glucuronide-MPH	426		Plasma, urine, feces
M34	5-hydroxy-6-oxo-RA	250		Plasma
M35	4-hydroxy-6-oxo-RA	250		Plasma, urine, feces

Source: Applicant's Figure, Pharmacokinetics Written Summary, pp. 51-52

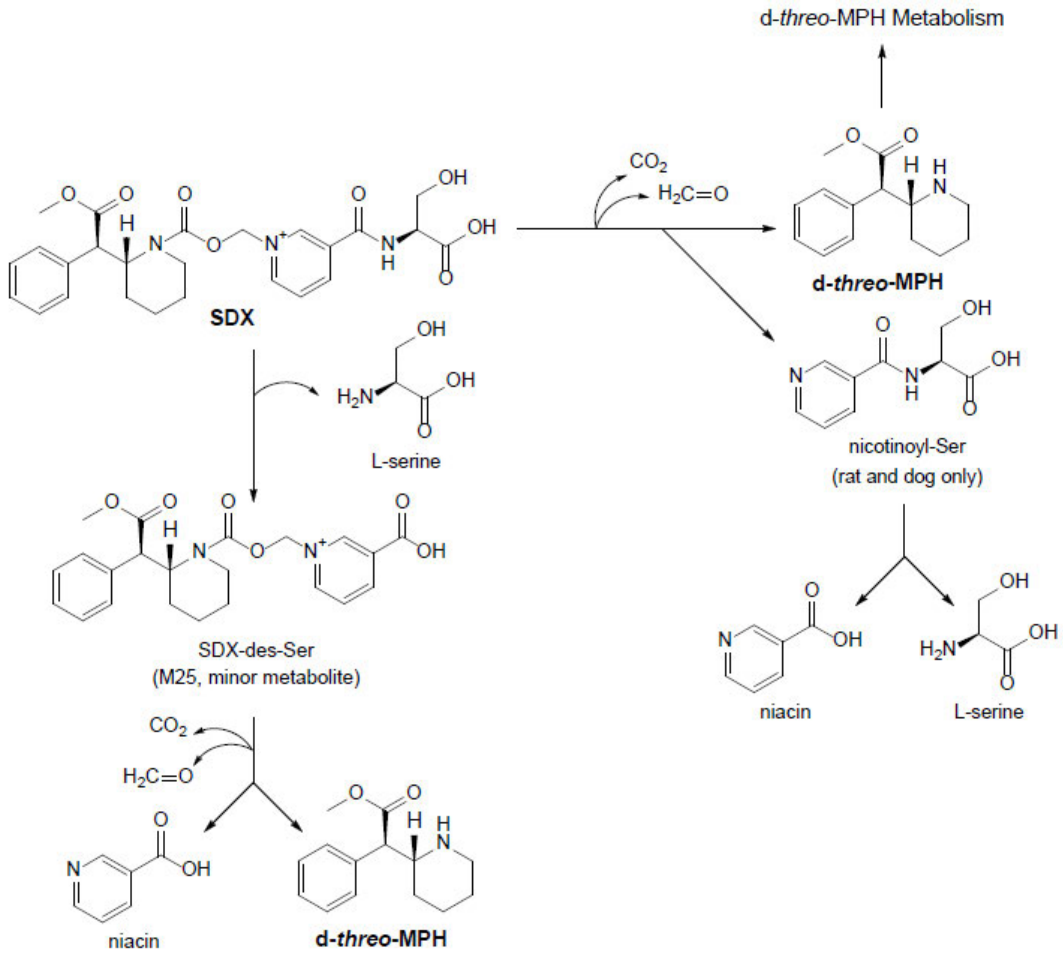
Potential metabolites of SDX (M1, M25, M33, and RA) were quantified by LC-MSMS from pooled plasma samples from the 28-day repeat dose toxicity study in rat, the 28-day repeat dose toxicity study in dogs, and a Phase 1 clinical PK study in humans (Study No. KP415-MP-001; Table 45).

Table 45: PK of Potential SDX Metabolites in Pooled Rat, Dog, and Human Plasma Samples

Analyte	Species	Day	AUC (ng.h/mL)	Cmax (ng/mL)	Tmax (h)
N-nicotinoyl-L-Serine (M1)	Rat	1	1353.28	255	2
		28	734.68	184	0.5
	Dog	1	2805.25	885	2
		28	5575.45	1900	1
	Human	1	BLQ	BLQ	BLQ
SDX-des-Ser (M25)	Rat	1	BLQ	BLQ	BLQ
		28	BLQ	BLQ	BLQ
	Dog	1	BLQ	BLQ	BLQ
		28	BLQ	BLQ	BLQ
	Human	1	BLQ	BLQ	BLQ
SDX acid (M33)	Rat	1	3.96	2.34	1
		28	7.13	5.13	0.25
	Dog	1	10.2	1.53	0.5
		28	3.93	1.74	1
	Human	1	BLQ	BLQ	BLQ
Ritalinic acid (RA)	Rat	1	5302.94	787	2
		28	4854.58	873	1
	Dog	1	1700.99	135	2
		28	2890.08	275	2
	Human	1	642.38	36.5	10

BLQ = below level of quantification

Figure 20: Proposed Metabolic Pathway of SDX



Source: Applicant's Figure, Pharmacokinetics Written Summary, p. 55

Reproductive and Developmental Toxicology

Cross-Species Comparison: Because of the species difference for PK/TK for SDX and d-MPH release, the Applicant conducted a cross-species analysis for humans, dogs, rats, and rabbits using single-dose data from multiple clinical studies, 14-day and 1-month rat and dog repeat dose-studies, and a single-dose PK study in rabbit. Relative exposure ratios (RR) between species using dose normalized AUC values were used to help determine the most appropriate species (Table 46). The results showed that, exposures to SDX relative to d-MPH in humans is lower than in rabbits and dogs, but higher than in rats, suggesting that rabbits and dogs are better models than rats for assessing SDX toxicity. Comparing dogs and rabbits, suggest that even though dogs have greater SDX exposures than rabbits they have even greater d-MPH exposures compared to rabbits. This suggested that rabbits may tolerate higher doses of SDX per body weight (or surface area) than dogs if comparable d-MPH exposure produces comparable pharmacodynamic responses in dogs and rabbits.

Table 46: Mean Relative Ratios (RR) of Dose-Normalized Exposure to SDX and d-MPH Obtained from Cross-Species Comparisons between Humans, Dogs, Rats, and Rabbits

	Mean RR (Range)[a]			
	Method = BW[b]		Method = BSA[c]	
Comparison	Analyte = SDX	Analyte = d-MPH	Analyte = SDX	Analyte = d-MPH
Human vs Dog	2.8 (1.9 - 4.8)	9.4 (5.9 - 23.6)	1.5 (1.1 - 2.7)	5.2 (3.3 - 13)
Human vs Rat	172 (145 - 211)	14 (9.9 - 24)	28 (23 - 34)	2.2 (1.6 - 3.8)
Human vs Rabbit[d]	13	71	4.2	23
Dog vs Rat	62 (30 - 109)	1.5 (0.42 - 4.0)	18 (8.8 - 32)	0.43 (0.12 - 1.2)
Dog vs Rabbit	4.7 (2.7 - 6.6)	7.5 (3.0 - 12)	2.7 (1.6 - 3.9)	4.4 (1.8 - 7.0)
Rat vs Rabbit	0.08 (0.06 - 0.09)	5.1 (3.0 - 7.2)	0.15 (0.12 - 0.18)	10 (6.0 - 14)

[a] RR = relative ratios of AUC/dose between species; AUC_{last} used for animal exposure (less data available for AUC_{inf}); AUC_{inf} used for human exposure to avoid overestimating the safety margin; Range indicates the lowest and highest exposure ratio observed across animal studies

[b] Doses were compared based on body weight (mg/kg)

[c] Doses were compared based on body surface (mg/m^2)

d Since only data for a one study was available at the time, no range could be calculated

Studies included for the analysis: rat: 14-day (4005106) and 28-day (4005540) repeated dose toxicity studies; dogs: 14-day (4005107) and 28-day (4005541) repeated dose toxicity studies; rabbits: single dose PK study (4005904); humans: KP415.101, KP415.102, KP415.108 (fasted subjects only [Treatment A]), KP415.109 (only for RR of SDX).

Combined male and female data were used except for rabbits for which only data in male animals were available at the time.

Since only single dose data were available for rabbits and most human studies at the time, Day 1 (single dose) exposure data were used for all studies with repeated dose administration for better comparison.

Source: Toxicokinetic Reports of studies 0437RK19.007, 0436RK19.003, 0437DK19.006, 0436DK19.004, and KP415.101 CSR, KP415.102 CSR, KP415.108 CSR, and KP415.109 CSR.

Source: Applicant's Figure, Toxicology Written Summary, p. 42

Oral Gavage Embryo-Fetal Developmental Toxicity and Toxicokinetic Study with KP415 in Rabbits/Study No. 8381422

Cesarean Section Data

Table 47: Cesarean Section Findings from Rabbit Embryo-Fetal Development Study

Parameter	0 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Total pregnancy rate	21/22	22/22	23/23	22/22
Mean corpora lutea	9	10	10	11
Mean implantation sites	9	10	9	10
Preimplantation loss (%)	7.3	6.8	7.4	10.5
Postimplantation loss (%)	6.3	3	4.5	4.1
Mean live fetuses	8	9	9	9
Mean total resorptions	1	0	0	0
Mean early resorptions	0	0	0	0
Mean late resorptions	0	0	0	0
Abortions	0	1	0	0
Mean sex rate (% males)	43	48	52	48
Mean fetus weight (g)	41.3	38.8	39.1	38.7
Mean uterus weight (g)	490	525	506	520

F_1 Offspring

Table 48: Offspring Data from Rabbit Embryo-Fetal Development Study

Parameter	0 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Total number of litters examined	21	21	22	22
Number of fetuses examined	172	196	194	204
Fetuses with malformations (litters)	7(4)	7(6)	5(4)	10(10)
Fetuses with visceral variations (litters)	35(15)	35(15)	29(13)	25(15)
Fetuses with skeletal variations (litters)	109(18)	144(20)	127(22)	132(22)
Fetuses with external variations (litters)	--	--	--	1(1)

Table 49: Summary of Malformations (litter/fetuses) Observed in Rabbit Embryo-Fetal Development Study

Malformation	0 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg
Omphalocele	1/1			
Head, acephaly	1/1			
Limb, hyperflexion	1/1			1/1
Adrenal, supernumerary				1/1
Blood vessel, aorta - dilated		1/1	1/1	

Blood vessel, pulmonary trunk - atretic			1/1	
Diaphragm, hernia		1/1		
Gall Bladder, absent	1/1			2/2
Heart, ventricle - large			1/1	
Heart, ventricle - small			1/1	
Heart, ventricular septum defect		1/1	1/1	
Kidney, absent				1/1
Kidney, large	1/1			
Liver, abnormal lobulation		1/2		
Ureter, absent				1/1
Vas deferens, absent				1/1
Skull, absent	1/1			
Skull, mandible/zygomatic arch fused			1/2	
Sternebrae, fused	3/6	3/3	2/2	6/7
Caudal vertebra, fused				1/1
Lumbar centrum, fused				1/1

A 6-Month Study of KP415 Administered by Oral (Stomach Tube) Administration in Juvenile Rabbits with a 1-Month Recovery Period/Study No. 20144952

Mortality

Table 50: Summary of Premature Mortalities for All Groups

Subset	Mode of Death	Dose Group									
		0 mg/kg/day (KP415)		75 mg/kg/day (KP415)		150 mg/kg/day (KP415)		300 mg/kg/day KP415)		75 mg/kg/day (d-MPH HCl)	
		M	F	M	F	M	F	M	F	M	F
Main Study	FD	4	-	3	1	2	1	3	2	5	2
	UE	-	1	-	-	-	2	-	-	4	-
Recovery Phase	FD	-	-	1	1	1	1	-	2	2	1
	UE	1	-	-	-	-	-	-	1	-	-
Toxicokinetic Study	FD	1	-	1	-	-	-	-	3	-	2
	UE	-	-	-	-	-	-	-	-	-	-
Dose Replacement	FD	1	1	1	1	2	1	1	1	1	1
	UE	1	-	1	-	-	-	-	-	-	2
Total Mortality		**8**	**2**	**7**	**3**	**5**	**5**	**4**	**9**	**12**	**8**

FD = Found Dead; UE = Unscheduled Euthanasia; - = no deaths occurred; M = male; F = female.

Source: Applicant's Table, Study No. 20144952, p. 57

Table 51: Cause of Death for Premature Mortalities in Chronic Juvenile Animal Study in Rabbits

Cause of Death	Dose Group									
	0 mg/kg/day (KP415)		75 mg/kg/day (KP415)		150 mg/kg/day (KP415)		300 mg/kg/day (KP415)		75 mg/kg/day (d-MPH HCl)	
	M	F	M	F	M	F	M	F	M	F
Unknown[a]	-	-	-	-	1	-	-	3	-	-
Undetermined[b]	-	-	2	-	-	-	1	1	5	2
Gavage-related	7	2	5	2	3	3	2	2	6	3
Probable gavage-related	1	-	-	1	1	2	1	3	1	-
Secondary to enteric parasitism	-	-	-	-	-	-	-	-	-	1
Total Mortality	**8**	**2**	**7**	**3**	**5**	**5**	**4**	**9**	**12**	**7**

- = no deaths occurred; M = male; F = female.
[a] Rabbits that did not have tissues examined microscopically due to original assignment to the toxicokinetic phase and/or dose replacement subset (no tissues were collected or retained).
[b] As determined by the microscopic examination of the retained tissues.

Source: Applicant's Table, Study No. 20144952, p.58

Histopathology

Liver

Minimal-to-moderate hepatocellular pigmentation occurred in a dose-dependent manner in test article-dosed groups (Table 52) and was still observed after the recovery period (Table 53). Hepatocellular pigmentation was also seen in a small number of male and female control animals at the end of dosing and in d-MPH dosed animals at the end of dosing and after the recovery period. The incidence and severity were similar for MD and d-MPH females (150 mg/kg KP415 is equimolar to 75 mg/kg d-MPH HCl); however, were lower for d-MPH males compared to all dose groups at the end of dosing but were similar at the end of the recovery period. According to the Applicant the "…pigmentation was characterized by subtle, punctate, finely granular, goldenbrown, circumscribed, non-refractile cytoplasmic structures that were approximately 0.25-1 µm in size; this intracellular pigmented material was most common in periportal hepatocytes but could occasionally be found widespread throughout all hepatocellular zones, particularly with increasing severity grade." There was no evidence of other hepatocellular findings (including degeneration, necrosis, or hypertrophy) and there were no changes in liver weights or clinical chemistry parameters which correlated to the pigmentation.

Table 52: Summary of Liver Histopathology Findings at the End of Dosing (PND 197) in Chronic Juvenile Animal Study

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	75	150	300	75	0	75	150	300	75
No. Animals Examined	10	10	10	10	7	10	10	10	10	10
Liver (No. Examined)										
Pigment, hepatocellular	(1)[a]	(4)	(5)	(9)	(2)	(2)	(5)	(7)	(10)	(7)
Minimal	1	4	4	7	2	2	5	6	4	6
Mild	0	0	1	2	0	0	0	1	6	1

[a] Numbers in parentheses represent the number of animals with the finding.

Source: Applicant's Table, Study No. 20144952, p.69

Table 53: Summary of Liver Histopathology Findings after the Recovery Period (PND 224) in Chronic Juvenile Animal Study

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	75	150	300	75	0	75	150	300	75
No. Animals Examined	3	3	3	3	3	3	3	3	3	3
Liver (No. Examined)	3	3	3	3	3	3	3	3	3	3
Pigment, hepatocellular	(0)[a]	(2)	(2)	(3)	(2)	(0)	(2)	(2)	(3)	(3)
Minimal	0	2	2	2	1	0	2	1	1	3
Mild	0	0	0	1	1	0	0	1	2	0

[a] Numbers in parentheses represent the number of animals with the finding.

Source: Applicant's Table, Study No. 20144952, p.70

To evaluate the punctate granular pigmentation within hepatocytes, staining for iron (Perl's Prussian Blue), bile (Hall's Bilirubin), and lipofuscin (Schmorl's) was conducted on a subset of animals at the end of dosing and after the recovery period (n = 3/control, HD, and d-MPH groups; Table 54 and Table 55). There was no staining of punctate liver granules for iron or bile. There was partial staining of punctate liver granules by Schmorl's stain. Granules varied from light blue to dark blue and there was heterogeneity of staining, where some granules did not stain and other granules stained light-to-dark blue (some were adjacent within the same cell). According to the Applicant, this equivocal staining pattern may suggest, but is not definitive for lipofuscin. The staining pattern was similar for all dose groups evaluated (except male controls at the end of dosing).

Table 54: Summary of Liver Special Staining at the End of Dosing (PND 197) in Chronic Juvenile Animal Study

	Males (PND 197)					Females (PND 197)				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	75	150	300	75	0	75	150	300	75
No. Animals Examined	3	0	0	3	3	3	0	0	3	3
Liver – Schmorl's SS (No. Examined)	3	-	-	3	3	3	-	-	3	3
Increased intensity	(0)[a]	-	-	(3)	(3)	(3)	-	-	(3)	(3)
Minimal	0	-	-	1	2	1	-	-	1	0
Mild	0	-	-	2	1	2	-	-	2	3
Liver – Hall's SS (No. Examined)	3	-	-	3	3	3	-	-	3	3
No Visible Lesions	(3)	-	-	(3)	(3)	(3)	-	-	(3)	(3)
Liver – Perl's SS (No. Examined)	3	-	-	3	3	3	-	-	3	3
No Visible Lesions	(3)	-	-	(3)	(3)	(3)	-	-	(3)	(3)

[a] Numbers in parentheses represent the number of animals with the finding.

Source: Applicant's Table, Study No. 20144952, p.72

Table 55: Summary of Liver Special Staining after the Recovery Period (PND 224) in Chronic Juvenile Animal Study

	Males (PND 224)					Females (PND 224)				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	75	150	300	75	0	75	150	300	75
No. Animals Examined	3	0	0	3	3	3	0	0	3	3
Liver – Schmorl's SS (No. Examined)	3	-	-	3	3	3	-	-	3	3
Increased intensity	(2)[a]	-	-	(3)	(3)	(1)	-	-	(3)	(3)
Minimal	0	-	-	3	1	0	-	-	0	1
Mild	2	-	-	0	2	1	-	-	3	2
Liver – Hall's SS (No. Examined)	3	-	-	3	3	3	-	-	3	3
No Visible Lesions	(3)	-	-	(3)	(3)	(3)	-	-	(3)	(3)
Liver – Perl's SS (No. Examined)	3	-	-	3	3	3	-	-	3	3
No Visible Lesions	(3)	-	-	(3)	(3)	(3)	-	-	(3)	(3)

[a] Numbers in parentheses represent the number of animals with the finding.

Source: Applicant's Table, Study No. 20144952, p.72

Because the hepatocellular pigmentation occurred at low incidence and severity in controls and at lower to similar incidence and/or severity in d-MPH comparators, the Applicant considers this to be a test article-related exacerbation of a background finding.

Reviewer's comments: *From the data provided, it is also unclear to me that the pigmentation is test article-related because of the similar findings in d-MPH females and lower to similar findings in d-MPH males. In addition, it does not appear that this pigmentation is adverse*

because there are no other hepatocellular findings or changes in liver weights or clinical chemistry parameters.

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/s/

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03/01/2021 02:22:39 PM

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