A Multicenter, Dose-Optimized, Open-Label Safety Study with KP415 in Children with Attention-Deficit/Hyperactivity Disorder

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Sponsor & Principal Investigator Approval / Signature Page

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Study Phase	Phase 3
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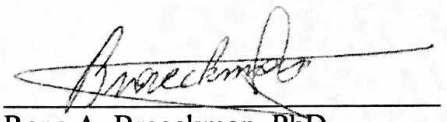

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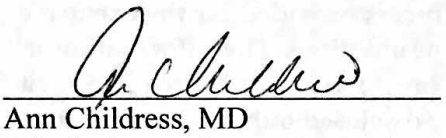
14 May 2019
Date



Ann Childress, MD
Principal Investigator, Center for Psychiatry and Behavioral Medicine. Inc.

14 May 2019
Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADHD	Attention-deficit hyperactivity disorder
ADHD-RS-5	Attention-deficit hyperactivity disorder rating scale 5
ADL	Activity of Daily Living
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
β-hCG	Beta human chorionic gonadotropin
BLQ	Below the limit of quantification
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impressions–Severity
CGI-I	Clinical Global Impressions–Improvement
CI	Confidence Interval
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CSHQ	Children's Sleep Habits Questionnaire
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DEA	Drug Enforcement Agency
DMDD	Disruptive Mood Dysregulation Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ER	Extended Release
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimation Equation
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hydroxypropyl methylcellulose
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IR	Immediate Release
IRB	Institutional Review Board

ITT	Intent-to-Treat
IUD	Intrauterine device
LLN	Lower Limit of Normal
LS	Least-square
MedDRA	Medical Dictionary of Regulatory Activities
MAO	Monoamine Oxidase
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MPH	Methylphenidate
NCE	New Chemical Entity
ODD	Oppositional Defiant Disorder
OTC	Over the Counter
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q1	25^{th} Percentile (1^{st} Quartile)
Q3	75^{th} Percentile (3^{rd} Quartile)
QTcF	Time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle, corrected for heart rate with Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOE	Schedule of Events
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
$T_{1/2}$	Apparent plasma terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
T_{max}	Time to achieve the maximum observed plasma concentration

PROTOCOL SYNOPSIS

TITLE	A Multicenter, Dose-Optimized, Open-Label Safety Study with KP415 in Children with Attention-Deficit/Hyperactivity Disorder
SPONSOR	KemPharm, Inc.
PROTOCOL NUMBER	KP415.S01
INVESTIGATIONAL PRODUCT	The KP415 product (capsule) contains KP415 (a prodrug of d-methylphenidate, d-MPH) and immediate-release d-MPH.
NAME OF ACTIVE INGREDIENT	The chemical name of the KP415 prodrug is 3-(((S)-1-carboxy-2-hydroxyethyl)carbamoyl)-1-((((*R*)-2-((*R*)-2-methoxy-2-oxo-1-phenylethyl)piperidine-1-carbonyl)oxy)methyl)pyridine-1-ium chloride (single d-methylphenidate 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).
ROUTE	Oral
NUMBER OF SITES	Approximately 20 sites in the United States of America
STUDY DESIGN	The study is a multicenter, dose-optimized, open-label safety study with KP415 in children with Attention-Deficit/Hyperactivity Disorder (ADHD). Eligible subjects for the current study will be either subjects who completed Study KP415.E01 or new subjects who did not previously receive KP415. Study participation: • **Rolled-Over Subjects:** For subjects rolled over from Study KP415.E01, the study will consist of a Screening Phase, Treatment Phase and a Follow-Up Visit. These subjects will be enrolled in the Screening Phase of the current study within 45 days after the last dose of study drug in Study KP415.E01. The roll-over window, dose-to-dose between both studies (i.e., gap between the last dose in Study KP415.E01 [Visit 6] and the first dose in the current study [Visit 5]) is maximum 45 days. Subjects are allowed to enter Screening (Visit 1B) on the same day as the Follow-Up Visit in Study KP415.E01, or later. Subjects not rolled over from Study KP415.E01 within 45 days of the last dose of study drug, may be enrolled in the current study as new subjects (they will need to start with Screening followed by the Dose Optimization Phase – see

	New Subjects below). These subjects will be considered new subjects and will undergo all the visits and procedures of new subjects (starting with Visit 1A as the Screening Visit). For roll-over subjects, the Investigator has the option to use the clinical chemistry and hematology results from the Follow-Up Visit in Study KP415.E01 (Visit 7) in lieu of collecting new blood samples at Screening (Visit 1B) in the current study, as long as the clinical chemistry and hematology data from the E01 study were collected within 30 days of Screening (Visit 1B) in the current study. For all roll-over subjects who are children of childbearing potential, a blood sample for the measurement of a serum pregnancy test is needed at Visit 1B. For other assessments required at Visit 1B (C-SSRS, for example), the Visit 7 assessments from the E01 study (if collected) can be used as long as Visit 1B is conducted on the same day as Visit 7 in the E01 study. • **New Subjects:** For new subjects (not previously treated with KP415 during the last 45 days), the study will consist of a Screening Period, a Dose Optimization Phase, a Treatment Phase and a Follow-Up Visit. The study design and procedures in the Treatment Phase and Follow-Up Visit are the same for new subjects and rolled-over subjects. **All subjects will receive unblinded (open-label) active drug in all phases of the study wherein study drug is administered.** The phases of the study are as follows: • **Screening Period:** New Subjects will undergo a screening period up to 30 days prior to entering into the Dose Optimization Phase. Rolled-over subjects will undergo a screening period up to 30 days prior to entering into the Treatment Phase. • **Dose Optimization Phase (for new subjects only):** During the Dose Optimization Phase, subjects will be titrated to doses of 20, 30, or 40 mg KP415 capsules based on individual tolerability and best dose-response in the opinion of the Investigator. • **Treatment Phase:** Eligible subjects will receive single daily doses of KP415 for 360 ±20 days, approximately 12 months. The starting dose of KP415 given in the Treatment Phase will be the same as the optimized dose of

	KP415 in Study KP415.E01 for rolled-over subjects or at the end of the Dose Optimization Phase for new subjects. During the Treatment Phase, the dose of KP415 may be changed based on individual tolerability and best dose-response (to either 20, 30, or 40 mg KP415 capsules). Safety, efficacy and sleep behavior assessments will be performed. After subjects complete approximately 180 days (approximately 6 months) of the Treatment Phase, an interim analysis will be conducted to evaluate safety parameters. • **Follow-Up Visit:** 3 ±2 days after administration of the last dose of the Treatment Phase, subjects will enter a Follow-Up Visit to evaluate safety parameters.
STUDY STOPPING RULES	The study will be stopped for any of the following reasons, whichever comes first: 1. An interim analysis of the safety data will be conducted after approximately all subjects remaining in the study have completed 180 days (approximately 6 months) of treatment. After the completion of the interim analysis, based on the acceptance of the clinical and nonclinical safety database from the current study and other studies, the Sponsor may stop the study. Treatment in the current study will continue as planned while the interim analysis is conducted. If the decision is made to stop the study, all subjects remaining in the study will undergo the EOT Visit (with safety evaluations including fasting safety labs and ECGs) and a Follow-Up Visit. 2. After all subjects have completed 360 days (approximately 1 year) of treatment.
PRIMARY OBJECTIVE	To determine the safety and tolerability of KP415 in treating children with ADHD.
SECONDARY OBJECTIVES	To determine efficacy and changes in sleep behavior during KP415 treatment in children with ADHD.
NUMBER OF SUBJECTS	Approximately 250 subjects will be enrolled in the Treatment Phase of the study. Subjects will be rolled over from Study KP415.E01 and to reach the targeted number of subjects, new subjects will be enrolled as well. Subjects who fail Screening and new subjects who terminate early during the Dose Optimization Phase may be replaced. Subjects who terminate early in the Treatment Phase will not be replaced.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria for Subjects Rolled Over from Study KP415.E01 (at Screening Visit 1B, except when noted otherwise)** 1. Subjects must have completed the Double-Blind Treatment Phase of Study KP415.E01, and must have

	received the last dose of KP415 in Study KP415.E01 (Visit 6) within 45 days prior to the first dose in the current study (Visit 5). Subjects who completed Study KP415.E01 but received their last dose of study drug more than 45 days prior to Visit 5 are eligible in the current study as New Subjects (but not as rolled-over subjects). Subjects who completed Study KP415.E01 and start the current study outside the 45-day roll-over window will be considered New Subjects and will undergo all the visits and procedures of new subjects (starting with Visit 1A as the Screening Visit). 2. Subjects rolled-over from Study KP415.E01 needed to be at least 6 years old and less than 13 years old at the start of the Dose Optimization Phase in Study KP415.E01. By the time they are rolled over into the current study, some may be 13 years old. 3. Female subjects must agree, when they are of childbearing potential at Screening or when they become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. Male subjects with female partners must agree, when their partners are of childbearing potential at Screening or when their partners become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. Childbearing potential is defined as follows: Girls under the age of 12 who have not had their first period will be considered “not of child-bearing potential”. Girls of 12 years and older (including girls who will become 12 years or older during the study) will be considered “of child-bearing potential”, even if they have not yet had their first period. Irrespective of age, girls who have had their first period, will be considered “of child-bearing potential”. 4. Subject must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and clinical laboratory values

	(hematology, chemistry, and urinalysis) at the Follow-Up Visit of Study KP415.E01. If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject can be included only if the Investigator determines the deviations to be not clinically relevant. 5. At least one parent/legal guardian of the subject must voluntary give written permission for him/her to participate in the study. 6. Subject must give written or verbal assent prior to study participation. For verbal assent, the procedure will be documented and signed by a witness. A parent or guardian may not be the witness for a child's verbal assent document. 7. Subject must be able and willing to wash out current stimulant ADHD medications (if applicable, if taking ADHD medications between studies), including herbal medications from 5 days prior to the start of the Treatment Phase (Visit 5), and abstain from taking these to the end of the Follow-Up Visit or Early Termination; and wash out non-stimulant ADHD medications (if applicable) from 14 days prior to the start of the Treatment Phase (Visit 5), and abstain from taking these to the end of the Follow-Up Visit or Early Termination. 8. Subject, subject's parent/legal guardian and caregiver (if applicable) must understand and be willing and able to comply with all study procedures and visit schedule. If the subject is cared for by a caregiver for relevant parts of any period between study visits, and if in this case, in the opinion of the Investigator, the caregiver of the subject is more suitable for certain assessments, the caregiver will need to agree to the applicable procedures and visits. 9. Subject, parent/legal guardian and caregiver (if applicable) must be able to speak and understand English, and be able to communicate satisfactorily with the Investigator and study coordinator. 10. Subject must be able to swallow size 3 capsules as demonstrated by easily swallowing a size 3 placebo capsule at Screening, unless the subject participated in the KP415.E01 study previously, or unless the subject agrees to take the contents of the capsule

	sprinkled on a small amount of applesauce or in a small amount of water. **Inclusion Criteria for New Subjects (at Screening Visit 1A, except when noted otherwise)** 1. Subject must be at least 6 years old and less than 13 years old at the start of the Dose Optimization Phase (Visit 2). 2. Subject must have a body weight of at least 21 kg at Screening. 3. Female subjects must agree, when they are of childbearing potential at Screening or when they become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. Male subjects with female partners must agree, when their partners are of childbearing potential at Screening or when their partners become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. Childbearing potential is defined as follows: Girls under the age of 12 who have not had their first period will be considered “not of child-bearing potential”. Girls of 12 years and older (including girls who will become 12 years or older during the study) will be considered “of child-bearing potential”, even if they have not yet had their first period. Irrespective of age, girls who have had their first period, will be considered “of child-bearing potential”. 4. Subject must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis) at Screening. If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject can be included only if the Investigator determines the deviations to be not clinically relevant.

	5. At least one parent/legal guardian of the subject must voluntary give written permission for him/her to participate in the study. 6. Subject must give written or verbal assent prior to study participation. For verbal assent, the procedure will be documented and signed by a witness. A parent or guardian may not be the witness for a child's verbal assent document. 7. Subject must meet Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). If the MINI-KID assessment is available from a previous study with KP415, it does not need to be repeated. 8. Subject must have a score of at least 3 (mildly ill) on the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale at Visit 2. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout. 9. Subject must be able and willing to wash out current stimulant ADHD medications, including herbal medications from 5 days prior to the start of the Dose Optimization Phase (Visit 2), and abstain from taking these to the end of the Follow-Up Visit or Early Termination; and wash out non-stimulant ADHD medications from 14 days prior to the start of the Dose Optimization Phase (Visit 2), and abstain from taking these to the end of the Follow-Up Visit or Early Termination. 10. An ADHD-Rating Scale-5 (ADHD-RS-5) total score of at least 28 at Visit 2. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout. 11. Subject, subject's parent/legal guardian and caregiver (if applicable) must understand and be willing and able to comply with all study procedures and visit schedule. If the subject is cared for by a caregiver for relevant parts of a school day, and if in this case, in the opinion of the Investigator, the caregiver of the subject is more suitable for certain assessments, the caregiver will need to agree to the applicable procedures and visits.

	12. Subject, parent/legal guardian and caregiver (if applicable) must be able to speak and understand English, and be able to communicate satisfactorily with the Investigator and study coordinator. 13. Subject must be able to swallow size 3 capsules as demonstrated by easily swallowing a size 3 placebo capsule at Screening, unless the subject participated in the KP415.E01 study previously, or unless the subjects agrees to take the contents of the capsule sprinkled on a small amount of apple sauce or in a small amount of water. **Exclusion Criteria for Subjects Rolled Over from Study KP415.E01 (at Screening Visit 1B, except when noted otherwise)** 1. If female, must not be pregnant or breastfeeding, and if of childbearing potential, must have a negative pregnancy test at the start of the Screening Phase (Visit 1B). In addition, a positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 12.9.** 2. Based on the medical history evaluated at Screening (Visit 1B), subject with any new clinically significant chronic medical condition that, in the judgment of the Investigator, may interfere with the participant's ability to participate in the study, or that may affect safety and/or the results of the study. 3. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug. 4. Subjects are using or planning to use prohibited drugs during the trial as specified in the protocol. 5. Subject has a positive urine MPH screen at Visit 5. 6. Subject, parent/legal guardian and caregiver (if applicable at the Investigator's discretion) has commitments during the study that would interfere with attending study visits. 7. Subject or subject's family anticipates a move outside the geographic range of the investigative site during the study period, or plans extended travel inconsistent with the recommended visit interval during study duration.

	8. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study. **Exclusion Criteria for New Subjects (at Screening Visit 1A, except when noted otherwise)** 1. Subjects who have received study drug (KP415 or placebo for KP415) in Study KP415.E01 during the 45 days prior to the Treatment Phase. Subjects who have received KP415 in Study KP415.E01 less than 45 days prior to the Treatment Phase are eligible to be enrolled in the current study as roll-overs (but not as new subjects). 2. If female, must not be pregnant or breastfeeding, and if of childbearing potential, must have a negative pregnancy test at the start of the Screening Phase (Visit 1A). In addition, a positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 12.9.** 3. Subject with any clinically significant chronic medical condition that, in the judgment of the Investigator, may interfere with the participant's ability to participate in the study. 4. Subject has any diagnosis of bipolar I or II disorder, major depressive disorder, conduct disorder, obsessive-compulsive disorder, any history of psychosis, autism spectrum disorder, disruptive mood dysregulation disorder (DMDD), intellectual disability, Tourette's Syndrome, confirmed genetic disorder with cognitive and/or behavioral disturbances. Subjects with oppositional defiant disorder (ODD) are permitted to enroll in the study as long as ODD is not the primary focus of treatment, and, in the opinion of the Investigator, the ODD is mild to moderate, and eligible subjects with ODD are appropriate and cooperative during Screening. 5. Subject has generalized anxiety disorder or panic disorder that has been the primary focus of treatment at any time during the 12 months prior to Screening or that has required pharmacotherapy any time during the 6 months prior to Screening. 6. Subject has evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder,

	potential CNS related disorders that might occur in childhood (e.g., Duchenne Muscular dystrophy, myasthenia gravis, or other neurologic or serious neuromuscular disorders), or history of persistent neurological symptoms attributable to serious head injury. A past history of febrile seizure, drug-induced seizure, or alcohol withdrawal seizure is allowed. Subject taking anticonvulsants for seizure control currently or within the past 2 years before Screening are not eligible for study participation. 7. Subject has a current (last month) psychiatric diagnosis other than specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders. Subjects allowed to enroll with any of these DSM disorders will require written justification from the Investigator documenting why the conditions will not interfere with participation and to emphasize that ADHD is the primary indication. 8. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug. 9. Subject has any clinically significant unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular (including cardiomyopathy, serious arrhythmias, structural cardiac disorders, or severe hypertension), gastrointestinal, respiratory, hepatic, or renal systems, or a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion of study drug. Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the medical monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if controlled) must be discussed with the medical monitor during Screening.

	10. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant. 11. Subject has a history of, or currently has a malignancy, except for non-melanomatous skin cancer. 12. Subject has uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) ≤0.8 x the lower limit of normal (LLN) or ≥1.25 x the upper limit of normal (ULN) for the reference laboratory at Screening. For subjects who previously participated in Study KP415.E01, this condition does not need to be re-evaluated. 13. Subjects with a history of substance abuse or treatment (including alcohol) within 1 year prior to Screening. 14. Subject shows evidence of substance or alcohol use or is currently using tobacco or other nicotine-containing products, or has a positive urine alcohol or urine drug screen at Screening. Subjects with a positive urine drug screen may be allowed to continue in the study, provided that the Investigator determines that the positive test is a result of taking prescribed medications, and subject is willing to wash out the current medication as required. 15. Subject has participated in any other clinical study with an investigational drug/product within 90 days prior to Screening, or is currently participating in another clinical trial, with the exception of any trial with KP415, as follows: Subjects who participated in Study KP415.E01 and completed the last dose in Study KP415.E01 more than 45 days before the Treatment Phase in the current study, are eligible as new subjects in the current study. Subjects who completed other studies with KP415 (for example, the single-dose pharmacokinetic study KP415.105) may be enrolled in the current study as new subjects after a minimum 5-day washout period between the last dose of KP415 and Screening in the current study. 16. Subject has taken ADHD medications from more than one class within 30 days prior to Screening. Subjects on a stable dose of one ADHD medication with occasional use of ADHD medications from another class are eligible at the discretion of the Investigator. 17. Subjects with demonstrated lack of response or

	intolerability to adequate dose and duration of treatment with methylphenidate products. Judgment of adequate dose and duration is at the discretion of the Investigator. 18. Subjects are using or planning to use prohibited drugs during the trial as specified in the protocol. 19. Subject has a positive urine MPH screen at Visit 2. 20. Subject has a history of severe allergies or adverse drug reactions to more than one class of medications. 21. Subject has a history of allergic reaction or a known or suspected sensitivity to methylphenidate or any substance that is contained in the study drug. 22. Subject, parent/legal guardian and caregiver (if applicable at the Investigator's discretion) has commitments during the study that would interfere with attending study visits. 23. Subject or subject's family anticipates a move outside the geographic range of the investigative site during the study period, or plans extended travel inconsistent with the recommended visit interval during study duration. 24. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study. **Eligibility Criteria (end of Dose Optimization Phase, new subjects only)** Subjects will need to meet the following additional eligibility criteria at the end of the Dose Optimization Phase in order to enter into the Treatment Phase: 1. A reduction of ≥30% in ADHD-RS-5 from baseline (Visit 2) during the Dose Optimization Phase. 2. A CGI-I score of 1 or 2 at the end of the Dose Optimization Phase. 3. Acceptable tolerability of the optimized KP415 dose experienced during the Dose Optimization Phase. **Rescreening** New subjects who are screened outside the screening window may be rescreened for participation at a later time. New subjects who received any dose of study drug and are terminated early or are not eligible to continue in the Treatment Phase, are not eligible to participate later in the study (and will not be rescreened).

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	The KP415 capsules contain two active pharmaceutical ingredients: d-methylphenidate (d-MPH) hydrochloride as the immediate release (IR) d-MPH component, and KP415 prodrug as the extended release (ER) d-MPH component. In terms of d-MPH equivalent amounts, all capsule strengths contain 30% of d-MPH (IR component) and 70% of d-MPH from the KP415 prodrug (ER component). The total equivalent amount of d-MPH in each capsule strength (used as daily doses in this study), and the amounts of both APIs are listed in the following table.

Total d-MPH dose [1] (mg)	d-MPH [2] (mg)	KP415 Prodrug [3] (mg)
20	6	28 (14)
30	9	42 (21)
40	12	56 (28)

1. Based on the d-MPH amount plus the equivalent amount of d-MPH as KP415 prodrug.
2. The dose of d-MPH is expressed in terms of d-methylphenidate hydrochloride.
3. The dose of KP415 prodrug is expressed in terms of KP415 chloride. The amount of d-MPH hydrochloride equimolar to each KP415 prodrug dose is listed between parentheses.

The KP415 prodrug is not yet a scheduled controlled substance; however, methylphenidate is a Schedule II substance under the Controlled Substances Act. As a result of the d-MPH content in the KP415 capsules, the drug product used in this study is a Schedule II product. Therefore, study sites are required to have the appropriate permit from the Drug Enforcement Agency (DEA) to receive, store, ship and dispense the KP415 product according to all local, state, and federal regulations for Schedule II substances.

All subjects will receive unblinded (open-label) active drug in all phases of the study wherein study drug is administered, as follows:

- In the Dose Optimization Phase (new subjects only), daily treatments of 20, 30 and 40 mg open-label KP415 capsules will be administered (one capsule/day), for the titration to an optimal daily KP415 dose.
- In the Treatment Phase, daily treatments of open-label KP415 capsules will be administered (one capsule/day), at a daily dose of KP415 that is the same as the optimal dose of KP415 at the end of the Dose Optimization Phase, either 20, 30, or 40 mg KP415 capsules. However, during the Treatment Phase, the Investigator will evaluate

	the tolerability and dose-response on an ongoing basis, and based on this evaluation, may change the dose of KP415. At any time, the daily oral dose of KP415 will be either 20, 30, or 40 mg. All study drugs will be given orally with up to 210-240 mL water. Additional water may be given if needed. The capsule needs to be swallowed whole (without crushing, cutting, crushing, chewing, opening, or dissolving) or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water.
ADHD SEVERITY/EFFICACY EVALUATION CRITERIA	The following scales will be used to assess the changes in ADHD severity: • ADHD-Rating Scale-5 (ADHD-RS-5): The ADHD-RS-5 is an 18-item scale (DuPaul 2016) based on Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association 2013) criteria of ADHD that rates symptoms on a 4-point scale. Each item is scored using a combination of severity and frequency ratings from a range of 0 (reflecting no symptoms or a frequency of never or rarely) to 3 (reflecting severe symptoms or a frequency of very often), so that the total ADHD-RS-5 scores range from 0 to 54. The 18 items can be divided into two 9-item subscales: One for hyperactivity/impulsivity and the other for inattentiveness. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver at each visit. • Clinical Global Impressions–Severity (CGI-S): The CGI-S is a clinician-rated scale that evaluates the severity of psychopathology (ADHD symptoms in the study) on a scale from 1 (not at all ill) to 7 (among the most severely ill) (Busner and Targum 2007). • Clinical Global Impressions–Improvement (CGI-I): The CGI-I is a clinician-rated scale that evaluates the improvement of psychopathology (ADHD symptoms in the study) on a scale from 1 (very much improved) to 7 (very much worse). During the Dose Optimization Phase (new subjects only), the ADHD-RS-5, CGI-I and CGI-S scale assessments are the main efficacy response variables (in conjunction with tolerability and safety) to guide dose optimization. During the Treatment Phase, the ADHD-RS-5 and CGI-S scale assessments are the efficacy variables to evaluate the changes in ADHD severity over time, and may be used (in

	conjunction with tolerability and safety) to adjust the dose of study drug.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	**Rolled-Over Subjects:** Subjects rolled over from Study KP415.E01 will participate in the study as outpatients for up to 416 days, including up to 30 days of Screening, 1 day for Visit 5, up to 380 days (360 ±20 days) in the Treatment Phase and a Follow-Up Visit up to 5 days (3 ±2 days) after the administration of the last dose of the Treatment Phase. Subjects who completed Study KP415.E01 and start the current study outside the 45-day roll-over window will be considered new subjects and will undergo all the visits and procedures of new subjects. The roll-over window (for Rolled-Over Subjects), dose-to-dose between both studies (i.e., gap between the last dose in Study KP415.E01 [Visit 6] and the fist dose in the current study [Visit 5]) is maximum 45 days. **New Subjects:** New subjects will participate in the study as outpatients for up to 440 days including up to 30 days of Screening, 1 day for Visit 2, up to 23 days (20 ±3 days) in the Dose Optimization Phase, 1 day for Visit 5, up to 380 days (360 ±20 days) in the Treatment Phase and a Follow-Up Visit up to 5 days (3 ±2 days) after the administration of the last dose of the Treatment Phase. If the study is stopped earlier based on the study stopping rules, all or some subjects may participate in the study for shorter durations than those listed above.
MEDICATION RESTRICTIONS	Rolled-over subjects will be prohibited/limited to receive certain medications in the trial, as follows: • Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Treatment Phase (Visit 5) to the end of the Follow-Up Visit or Early Termination Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dextromethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall®. • Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Treatment Phase (Visit 5) to the end of the Follow-Up Visit or Early Termination Visit. These include: Atomoxetine, guanfacine, clonidine; and SSRIs such as fluoxetine and paroxetine. • The following medications are prohibited from 14 days prior to the start of the Treatment Phase (Visit 5) to the

	end of the Follow-Up Visit or Early Termination Visit: o Tricyclic antidepressants. o Monoamine oxidase inhibitors (MAOIs). o Mood stabilizers (e.g., lithium, valproate, quetiapine). o Antipsychotics (e.g., risperidone, olanzapine). o Coumarin anticoagulants. o Anticonvulsants. o Halogenated anesthetics. o Phenylbutazone o Coumarin anticoagulants • Sedative hypnotics/sleep enhancers (with the exception of melatonin) are prohibited from 14 days prior to the start of the Treatment Phase (Visit 5) to the end of the Follow-Up Visit or Early Termination Visit. • Melatonin is allowed if subjects have taken it for more than 30 days before the start of the Treatment Phase (Visit 5) and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. **New subjects will be prohibited/limited to receive certain medications in the trial, as follows:** • Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dextromethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall®. • Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit. These include: Atomoxetine, guanfacine, clonidine; and SSRIs such as fluoxetine and paroxetine. • The following medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit: o Tricyclic antidepressants. o Monoamine oxidase inhibitors (MAOIs). o Mood stabilizers (e.g., lithium, valproate, quetiapine).

	○ Antipsychotics (e.g., risperidone, olanzapine). ○ Coumarin anticoagulants. ○ Anticonvulsants. ○ Halogenated anesthetics. ○ Phenylbutazone • Sedative hypnotics/sleep enhancers (with the exception of melatonin) are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit. • Melatonin is allowed if subjects have taken it for more than 30 days before the start of the Dose Optimization Phase (Visit 2) and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to Visit 2 to the end of the Follow-Up Visit or Early Termination Visit. **Allowed medications for all enrolled subjects:** Medications allowed during the course of the study include nasal steroids, bronchodilators, acetaminophen and nonsteroidal anti-inflammatory medications; non-sedating antihistamines such as cetirizine, loratadine, and fexofenadine; mometasone; and approved courses of prescription and nonprescription medications for the treatment of acute illnesses. If subjects participated in a previous study with KP415 (including Study KP415.E01), they are allowed to take any medications (including ADHD medications) after completing the previous study with KP415 and before starting the current study, except for the medications and the time intervals specified in this protocol.
SAFETY ENDPOINTS	• The occurrence of Treatment-Emergent Adverse Events (TEAEs) will be assessed starting following the first dose of study drug, and ending with the Follow-Up Visit or Early Termination Visit. • Physical examinations will be performed at the first visit (at Screening, before the first dose of study drug), after approximately 6 months of treatment (Visit 11), and at the end of the Treatment Phase (Visit 17, EOT) or at Early Termination. • Clinical laboratory tests will be performed at the first visit (at Screening, before the first dose of study drug), after approximately 6 months of treatment (Visit 11), and at the end of the Treatment Phase (Visit 17, EOT) or at Early Termination. • ECG parameters will be collected at the first visit (at

	Screening, before the first dose of study drug), after approximately 6 months of treatment (Visit 11), and at the end of the Treatment Phase (Visit 17, EOT) or at Early Termination. • Vital signs, height, weight, and BMI will be collected at each visit. • A C-SSRS will be performed at each study visit.
EFFICACY ENDPOINTS	During the Dose Optimization Phase (new subjects only): • CGI-S will be assessed at each visit (Screening to Visit 5). ADHD-RS-5 will administered at Visits 2 through 5. CGI-I will be assessed at Visits 3, 4, and 5 (since CGI-I is an ADHD improvement assessment, it will not be assessed at Screening and at Visit 2). During the Treatment Phase (all subjects): • ADHD-RS-5 and CGI-S will be assessed at each visit (Visit 5 to Visit 17, EOT).
SLEEP BEHAVIOR ENDPOINT	The modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be used to assess the sleep behavior in the Dose Optimization Phase for new subjects (Visit 2) and in the Treatment Phase for all subjects (Visit 5 to Visit 17). The baseline will be measured before the first dose of study drug, at Visit 2 for new subjects and at Visit 5 for roll-over subjects.
ANALYSIS POPULATIONS	• **Treatment-Phase Safety Population:** All enrolled subjects in the Treatment Phase who received at least one dose of study medication in the Treatment Phase and had at least one post-dose safety assessment in the Treatment Phase. • **Efficacy Population:** All enrolled subjects who received at least 30 days of study medication in the Treatment Phase, who had adequate data to assess the change from baseline of the efficacy parameters and who had no protocol deviations that could affect the efficacy parameters. • **Dose-Optimization Safety Population:** All enrolled subjects in the Dose Optimization Phase ("New Subjects") who received at least one dose of study medication in the Dose Optimization Phase and had at least one post-dose safety assessment in the Dose Optimization Phase.
STATISTICAL ANALYSES	The primary focus of the statistical analyses are the safety assessments during the Treatment Phase. The secondary focus of the statistical analyses is the efficacy assessments during

	the Treatment Phase. The safety and efficacy parameters during the Dose Optimization Phase (for new subjects only) will be summarized descriptively. **Primary Endpoint (Safety in the Treatment Phase):** The frequencies of adverse events (AEs), changes in clinical laboratory assessments, physical examinations, changes in weight, height and BMI, vital signs, ECG parameters, and the frequency of suicidal ideation or behavior (assessed using the C-SSRS) will be analyzed in the *Treatment-Phase Safety Population*. The baseline for the safety parameters will be measured at Visit 1A and 1B. **Secondary Endpoint (Efficacy in the Treatment Phase):** Changes in ADHD-RS-5, CGI-S and CSHQ will be analyzed in the *Efficacy Population*. The baseline for ADHD-RS-5, CGI-S and CSHQ will be measured at Visit 5 for roll-over subjects and at Visit 2 for new subjects. **Descriptive Analyses (Safety and Efficacy in the Dose Optimization Phase):** The safety and efficacy parameters during the Dose Optimization Phase (from Screening to Visit 5) will be summarized descriptively in the *Dose-Optimization Safety Population*. **Subgroup Analyses:** Subgroup analyses will include safety, efficacy and CSHQ endpoints by study site, dose (including cumulative dose), duration of treatment, previous treatment, age, and gender.
STUDY PROCEDURES	The study procedures are outlined in the Schedule of Events (**Section 1**).

1. SCHEDULE OF EVENTS

1.1. Screening (all subjects) and Dose Optimization Phase (new subjects only)

ASSESSMENTS	*NEW* SCREENING PHASE [22] *ROLLOVER*		OPEN-LABEL DOSE OPTIMIZATION PHASE [21, 22] (*NEW SUBJECTS ONLY*)					
Study Day	-30 to -1	-30 to -1	0	1-6 (±3 Days)	7 (±3 Days)	8-13 (±3 Days)	14 (±3 Days)	15-20 (±3 Days)
Visit Number	1A	1B[24]	2		3		4	
Parental Permission/Written or Verbal Assent	X	X						
ADHD Diagnosis and Confirmation [1]	X							
Capsule Swallowing Test [2]	X							
Inclusion/Exclusion	X	X	X		X		X	
Demographics	X	X						
Medical History [3]	X	X	X					
Physical Examination	X	X						
Body Weight, Height, BMI [4]	X	X						
Vital Signs [5]	X	X	X		X		X	
12-Lead ECG [6]	X	X						
Chemistry/Hematology/Urinalysis (under fasting conditions)	X	X						
Urine Alcohol/Drugs of Abuse Screen [7]	X	X						
Urine MPH Screen [8]	X		X					
Pregnancy Test [9]	X	X	X					
C-SSRS [10]	X	X	X		X		X	
Washout ADHD Meds [11]			X					
Open-Label KP415 Dosing [12]				X	X	X	X	X
Drug Accountability & Compliance Assessment [13]					X		X	
ADHD-RS-5 [14]			X		X		X	
MINI-KID [15]	X							
CGI-S [16]	X		X		X		X	
CGI-I [17]					X		X	
CSHQ [18]			X					
Adverse Events [19]				X	X	X	X	X
Concomitant Medications [20]	X		X		X		X	

BMI = Body Mass Index; ECG = Electrocardiogram; MPH = methylphenidate; see footnotes for other abbreviations.

1. ADHD Diagnosis based on the Statistical Manual of Mental Disorders - Fifth Edition (DSM-5)

criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).

2. Capsule Swallowing Test: Subjects must be able to comply with one of the following:
    a) Subjects will take a size 3 capsule with up to 240 mL of water at Screening. The capsule may not contain any active drug substance. Subjects must be able to easily swallow the size 3 capsule to be eligible for further study participation. This is not required for subjects who have previously participated in the KP415.E01 study.
    b) If subjects are unable to demonstrate that they can swallow size 3 capsules, they must agree to take the capsule contents sprinkled over a small amount of applesauce or added to a small amount of water during the study.

   Any of the methods of administration may be used on any day of the study, but if subjects plan to take study drug as the whole capsule, subjects will need to have demonstrated that they are able to swallow size 3 capsules at Screening or any time during the study (or have been previously participated in Study KP415.E01).
3. Medical History: A complete medical history including chronic conditions, relevant surgical procedures (with start date), history of drug and alcohol use. As part of Medical History for Visit 1B (and with more details captured in the database), record treatment with study drug in Study KP415.E01 with regards to dose, duration, date of last dose (Visit 6 in Study KP415.E01), last visit in Study KP415.E01 (Visit 7 in Study KP415.E01), etc.
4. Height will be recorded in centimeters (cm) with the subject's shoes removed. Body weight will be measured in kilograms (kg); subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.
5. Vital sign measurements will be obtained after the subject has been seated for at least 3 minutes. Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. Vital signs will be collected once at each visit.
6. Electrocardiogram (ECG): A 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF). For roll-over subjects, if the Screening Visit (Visit 1B) occurs on the same day as the Follow-Up Visit (Visit 7) of Study KP415.E01, one ECG will be obtained to be used in both studies. If Visit 1B occurs later, after Visit 7 in E01, a new ECG will be obtained at Visit 1B as baseline for the current study.
7. Urine Screen for Alcohol and Drugs of Abuse: Urine samples will be tested for alcohol, and drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone) at Screening (Visit 1A or 1B). If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for ADHD medications such as amphetamines and methamphetamines. All ADHD medications must be washed out by Visit 2 for new subjects and Visit 5 for roll-over subjects.
8. Urine Screen for Methylphenidate (MPH): For new subjects, urine samples will be tested for MPH at Screening (Visit 1A) and Visit 2. A urine dipstick (e.g., NarcoCheck®) will be used to screen for the presence of MPH in the urine. If a subject's current ADHD medication at Screening contains MPH, the urine screen at Screening (Visit 1A, new subjects) may test positive for MPH. All ADHD medications must be washed out by Visit 2 for new subjects and Visit 5 for roll-over subjects (MPH urine screen must test negative).
9. Pregnancy Test: performed for female subjects of childbearing potential. A serum β-hCG pregnancy test will be performed at Screening. A urine pregnancy test will be performed at Visit 2. A positive pregnancy test at Screening or before the last dose of study drug will exclude a subject from further

participation in the study.

10. Columbia Suicide Severity Rating Scale (C-SSRS): The "Children's Baseline/Screening" version will be assessed at Screening, and the "Children's Since Last Visit" version will be assessed at all other visits. Subjects who have, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study.
11. All Subjects must wash out ADHD medications prior to Visit 2. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 2 for new subjects and prior to Visit 5 for rolled-over subjects to the end of the Follow-Up Visit or Early Termination Visit. Before or on the day during the screening period that subjects will need to start the washout of their ADHD medications (for example, 5 days before Visit 2 for stimulants), study site staff will contact the subject's parent/guardian by phone to remind them of the washout ("washout phone call").
    Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit. Other prohibited medications with their associated time windows when they are prohibited are listed in the protocol.
12. KP415 Dose Optimization: Subjects will begin taking open-label KP415 at home the morning following Visit 2. The starting dose of KP415 (Days 1-7 ±3 days) will be 30 mg/day. KP415 dose adjustments, if needed, will be performed at approximately weekly intervals between visits (at Visits 3 and 4). Actual visit dates may deviate from exactly being spaced 7 days apart such that the total duration of the Dose Optimization Phase is 3 weeks (21 days) ±3 days. The daily doses of KP415 used in the Dose Optimization Phase will be 20, 30, and 40 mg (dose optimization range of ≥20 and ≤40 mg). At Visits 3 and 4, based on the CGI scores, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic responses and tolerability to treatment and decide whether the current KP415 dose should be increased, decreased, or remain the same for the next week of dosing. If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their KP415 dose may be adjusted before the next scheduled visit. Unscheduled visits between Visits 2, 3, and 4 are allowed as needed, at the discretion of the Investigator.
13. Drug Accountability & Compliance Assessment: All study drug will be recorded by each site's pharmacy staff member or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site.
14. ADHD-Rating Scale-5 (ADHD-RS-5) assessment: 1 assessment at the indicated visits.
15. Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID): For confirmation of ADHD diagnosis at Screening.
16. Clinical Global Impressions–Severity (CGI-S) scale assessment: 1 assessment at the indicated visits.
17. Clinical Global Impressions–Improvement (CGI-I) scale assessment: 1 assessment at the indicated visits.
18. Children's Sleep Habits Questionnaire (CSHQ) assessment: 1 assessment at Visit 2.
19. Adverse Events: To be assessed and recorded in the eCRF following the first dose of open-label drug (KP415), on Day 1, through either Follow-Up or Early Termination. Subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
20. Concomitant Medications: new and/or changed medications and dose, medical treatments and/or therapies will be recorded at Screening through either Follow-Up or Early Termination.
21. Actual visit dates in the Dose Optimization Phase may deviate from exactly being spaced 7 days apart such that the total duration of the Dose Optimization Phase ranges between 18 and 24 days (21 ±3 days). Any allowed deviation (up to 3 days in total) of the targeted 21-day Dose Optimization Phase will be carried over into the actual days for the subsequent visits.
22. Subjects who meet withdrawal criteria post-dose during the Dose Optimization Phase (after at least one dose of study drug is administered) will complete Early Termination procedures as listed in the

Schedule of Events in **Section 1.3**. This includes subjects who do not meet the eligibility criteria to continue in the Treatment Phase. At the discretion of the Investigator, ensuring the safety of the subjects, any Early Termination procedures that were already performed on the same day as part of the procedures of the Dose Optimization Phase, do not need to be repeated. Subjects who withdraw early from the study and complete the ET procedures will not return for a Follow-Up Visit. Therefore, the ET Visit is the End-of-Study (EOS) for these subjects.

23. The procedures at Screening are different between subjects rolled over from Study KP415.E01 and new subjects. Therefore, the Screening Visit for roll-over subjects is designated as Visit 1B, and for new subjects is designated Visit 1A. Visits 2, 3 and 4 are not needed for subjects rolled over from Study KP415.E01 because their optimum dose was determined in the Dose Optimization Phase of Study KP415.E01. Therefore, rolled-over subjects from Study KP415.E01 will start with Visit 1B as the first visit of the current study, followed by Visit 5 as the next visit (rolled-over subjects will not have Visits 2, 3 and 4).
24. The Screening Visit for rolled-over subjects (Visit 1B) may occur on the same day as the EOS (Visit 7, Follow-Up) in Study KP415.E01 or later, and must occur within 30 days before Visit 5 in the current study. For roll-over subjects, the Investigator has the option to use the clinical laboratory (clinical chemistry, hematology and urinalysis) results from the Follow-Up Visit in Study KP415.E01 (Visit 7) in lieu of collecting new blood samples at Screening (Visit 1B) in the current study, as long as the clinical laboratory samples from the E01 study were collected within 30 days prior to Screening (Visit 1B) in the current study. For all roll-over subjects who are children of childbearing potential, a blood sample for the measurement of a serum pregnancy test is needed at Visit 1B. For other assessments required at Visit 1B (C-SSRS, for example), the Visit 7 assessments from the E01 study (if collected) can be used as long as Visit 1B is conducted on the same day as Visit 7 in the E01 study. Visit 7 clinical laboratory samples collected during KP415.E01 (also used as the Visit 1B results) are not required to be collected under fasting conditions. During Visit 1B of the current study, the study site will document whether these samples were collected under fasting/non-fasting conditions, and this will be recorded in the database.

1.2. Treatment Phase (First 6 Months; All Subjects)

ASSESSMENTS	OPEN-LABEL TREATMENT PHASE [19]												
Study Day	0	1-29 (±5 days)	30 (±5 days)	31-59 (±5 days)	60 (±5 days)	61-89 (±5 days)	90 (±5 days)	91-119 (±5 days)	120 (±5 days)	121-149 (±5 days)	150 (±5 days)	151-179 (±5 days)	180 (±5 days)
Visit Number	5		6		7		8		9		10		11
Inclusion/Exclusion	X												
Medical History [1]	X												
Physical Examination [2]													X
Body Weight, Height, BMI [3]	X		X		X		X		X		X		X
Vital Signs [4]	X		X		X		X		X		X		X
12-Lead ECG [5]													X
Chemistry/Hematology/Urinalysis													X
Urine MPH Screen (roll-overs) [6]	X												
Pregnancy Test [7]	X		X		X		X		X		X		X
C-SSRS [8]	X		X		X		X		X		X		X
Prohibited Medications [9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility Criteria (new subjects) [10]	X												
Enrollment in Treatment Phase [11]	X												
Open-Label KP415 Dosing [12]		X	X	X	X	X	X	X	X	X	X	X	X
Drug Accountability & Compliance Assessment	X [22]		X		X		X		X		X		X
ADHD-RS-5 [13]	X		X		X		X		X		X		X
CGI-S [14]	X		X		X		X		X		X		X
CGI-I [15]	X												
CSHQ [16]	X		X		X		X		X		X		X
Adverse Events [17]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications [18]	X		X		X		X		X		X		X
Interim Analysis [23]													X

EOS = End of Study; ET = Early Termination; BMI = Body Mass Index; ECG = Electrocardiogram; see footnotes for other abbreviations. See

Section 1.3 for all footnotes.

1.3. Treatment Phase (Second 6 Months), and Early Termination and Follow-Up Visits (All Subjects)

ASSESSMENTS	OPEN-LABEL TREATMENT PHASE [19]												ET [21] (EOS)	FOLLOW-UP (EOS)
Study Day	181-209 (±5 days)	210 (±5 days)	211-239 (±5 days)	240 (±5 days)	241-269 (±5 days)	270 (±5 days)	271-299 (±5 days)	300 (±5 days)	301-229 (±5 days)	330 (±5 days)	331-359 (±5 days)	360 [20] (±5 days)	-	343-383 (±2 days) [19]
Visit Number		12		13		14		15		16		17	-	18
Physical Examination [2]												X	X	
Body Weight, Height, BMI [3]		X		X		X		X		X		X	X	X
Vital Signs [4]		X		X		X		X		X		X	X	X
12-Lead ECG [5]												X	X	
Chemistry/Hematology/Urinalysis (under fasting conditions)												X	X	
Pregnancy Test [7]		X		X		X		X		X		X	X	X
C-SSRS [8]		X		X		X		X		X		X	X	X
Prohibited Medications [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Open-Label KP415 Dosing [12]	X	X	X	X	X	X	X	X	X	X	X	X		
Drug Accountability & Compliance Assessment		X		X		X		X		X		X	X	
ADHD-RS-5 [13]		X		X		X		X		X		X		
CGI-S [14]		X		X		X		X		X		X		
CGI-I [15]														
CSHQ [16]		X		X		X		X		X		X		
Adverse Events [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications [18]		X		X		X		X		X		X	X	X

EOS = End of Study; ET = Early Termination; BMI = Body Mass Index; ECG = Electrocardiogram; see footnotes for other abbreviations.

1. Medical History: A complete medical history including chronic conditions, relevant surgical procedures (with start date), history of drug and alcohol use.
2. Physical examination at Visit 11, and at Visit 17 (EOT) or at Early Termination (if possible).
3. Body weight, height and BMI at each visit. Height will be recorded in centimeters (cm) with the subject's shoes removed. Body weight will be measured in kilograms (kg); subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.
4. Vital sign measurements will be obtained after the subject has been seated for at least 3 minutes. Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. Vital signs will be collected once at each visit.
5. Electrocardiogram (ECG): A 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF).
6. Urine Screen for Methylphenidate (MPH): Urine samples will be tested for MPH at Visit 5 for roll-over subjects. A urine dipstick (e.g., NarcoCheck®) will be used to screen for the presence of MPH in the urine. All ADHD medications must be washed out by Visit 5 for roll-over subjects. Subjects with a positive MPH urine screen at Visit 5 will be excluded from further participation in the study or may be retested at a later date, and may be enrolled if the MPH urine screen retest is negative as long as the Screening Window is adhered to.
7. A urine pregnancy test will be performed for female subjects of childbearing potential at all visits during the Treatment Phase, and at Early Termination or Follow-Up. A positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study.
8. Columbia Suicide Severity Rating Scale (C-SSRS): The "Children's Since Last Visit" version will be assessed at all visits the Treatment Phase, and at Early Termination or Follow-Up. Subjects who have, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study.
9. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 5 to the end of the Follow-Up Visit or Early Termination Visit.
   Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Other prohibited medications with their associated time windows when they are prohibited are listed in the protocol body text.
10. At Visit 5, for new patients, the Investigator will evaluate the eligibility criteria based on assessments in the Dose Optimization Phase, for continuation into the subsequent Treatment Phase. For subjects eligible for the Treatment Phase, the optimal daily KP415 dose will be used as the daily KP415 dose in the Treatment Phase. This is not needed for subjects rolled over from Study KP415.E01 because their optimum dose was determined in the Dose Optimization Phase of Study KP415.E01. Rolled-over subjects from Study KP415.E01 will start with Visit 1B as the first visit of the current study, followed by Visit 5 as the next visit (rolled-over subjects will not have Visits 2, 3, and 4).
11. Enrollment in the Treatment Phase: Subjects able to tolerate at least 20 mg/day of KP415 and with an adequate dose-response will be enrolled into the Treatment Phase. The determination of tolerability and adequate dose-response will be determined in Study KP415.E01 for subjects rolled over from Study KP415.E01 (they will need to have completed Study KP415.E01), or at the end of the Dose Optimization Phase in the current study for new subjects. Subjects rolled over from Study KP415.E01 will be enrolled in the Treatment Phase of the current study (Visit 5)

within 45 days after the last dose of study drug in Study KP415.E01 (Visit 6 in Study KP415.E01). New subjects will continue to the Treatment Phase immediately after the end of the Dose Optimization Phase in the current study. Subjects not rolled over from Study KP415.E01 within 45 days of the last dose of study drug, may be enrolled in the current study as new subjects (they will need to start with Screening and Dose Optimization Phase). At the start of the Treatment Phase (Visit 5), the appropriate open-label study drug to be taken at home once-a-day in the morning on each of the days of the Treatment Phase until the next visit will be dispensed to the subjects.

12. Study Drug Administration: All subjects eligible to participate in the Treatment Phase will receive non-blinded oral capsules with active KP415 drug (one capsule). The dose level is an optimized KP415 dose of 20, 30, or 40 mg determined at the end of the Dose Optimization Phase in Study KP415.E01 for rolled-over subjects from Study KP415.E01, or as determined at the end of the Dose Optimization Phase in the current study for new subjects.
    Based on individual tolerability and dose-response during the Treatment Phase, at the discretion of the Investigator, the KP415 dose may be changed (increased or decreased, but one of the 3 dose levels of 20, 30, or 40 mg KP415 capsules). All study drugs will be given orally. Subjects will take study drug (one capsule/day) in the morning at home under supervision of their parent or legal guardian. The final dose of study drug will be administered on the last day of the Treatment Phase (Day 360 ±20 days; Visit 17). If the study is stopped earlier based on the stopping rules, the last day of the Treatment Phase (Visit 17) may occur earlier than Day 360 for some or all subjects. Study drug will be taken orally with up to 210-240 mL of water. The capsule needs to be swallowed whole (without crushing, cutting, crushing, chewing, opening, or dissolving) or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water.
13. ADHD-Rating Scale-5 (ADHD-RS-5) assessment: 1 assessment at the indicated visits.
14. Clinical Global Impressions–Severity (CGI-S) scale assessment: 1 assessment at the indicated visits.
15. Clinical Global Impressions–Improvement (CGI-I) scale assessment: 1 assessment at Visit 5 for new subjects only.
16. Children's Sleep Habits Questionnaire (CSHQ) assessment: 1 assessment at the indicated visits.
17. Adverse Events: To be assessed and recorded in the eCRF following the first dose of open-label drug (KP415), through either Early Termination or Follow-Up. Subject's parent/guardian will be instructed to contact the study site for the reporting of AEs while away from the study site.
18. Concomitant Medications: new and/or changed medications and dose, medical treatments and/or therapies will be recorded at Visit 5 through either Follow-Up or Early Termination.
19. To allow flexibility in scheduling visits, actual visit dates for individual subjects in the Treatment Phase may deviate from exactly being spaced 30 days apart (up to 30 ±5 days from the previous visit) such that the total duration of the Treatment Phase may be in the range of 360 ±20 days (340-380 days from Visit 5 to Visit 17). The Follow-Up Visit (3 days after the last dose) therefore falls between Day 343 and Day 383, but has its own window of ±2 days added.
20. The end of the Treatment Phase is on Day 360 ±20 days (Visit 17), after all post-dosing procedures are completed.
21. Subjects who meet withdrawal criteria post-dose during the Treatment Phase (after at least one dose of study drug is administered) will complete Early Termination procedures. At the discretion of the Investigator, ensuring the safety of the subjects, any Early Termination procedures that were already performed on the same day as part of the procedures of the Treatment Phase, do not need to be repeated. Subjects who withdraw early from the study and complete the ET procedures will not return for a Follow-Up Visit. Therefore, the ET Visit is the End-of-Study (EOS) for these subjects.
22. Drug Accountability & Compliance Assessment: All study drug will be recorded by each site's pharmacy staff member or Investigator-

delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site at each visit for subjects receiving study drug since the previous visit (including drug accountability at Visit 5 for drug returned from the last week of the Dose Optimization Phase, by new subjects).

23. An interim analysis of the safety data will be conducted after approximately all subjects remaining in the study have completed 180 days (approximately 6 months) of treatment. After the completion of the interim analysis, based on the acceptance of the clinical and nonclinical safety database from the current study and other studies, the Sponsor may stop the study. Treatment in the current study will continue as planned while the interim analysis is conducted. If the decision is made to stop the study, all subjects remaining in the study will undergo the EOT Visit (with safety evaluations including fasting safety labs and ECGs) and a Follow Up Visit.

2. BACKGROUND

2.1. Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is a common neurobehavioral disorder that occurs in 6-8% of children and 4-5% of adults worldwide (Wilens 2008). The 3 main symptoms of ADHD include inattention, hyperactivity, and impulsivity. ADHD is theorized to result from a deficiency of neurotransmission of dopamine and norepinephrine either through the insufficient sensitivity of the receptors or amount of dopamine produced. The most common and effective therapeutics for the treatment of ADHD are CNS stimulants, which contain amphetamine or methylphenidate (MPH). Amphetamine-containing products include brand names such as Adderall®, Dexedrine®, Dextrostat®, and Vyvanse®. Methylphenidate containing products include Metadate®, Concerta®, Daytrana®, Ritalin®, Methylin®, Quilivant®, and Focalin®. Positive effects on behavior and academic productivity are well established for stimulant medications such as MPH (Wilens and Biederman 1992). Several studies have shown that, in children with ADHD, MPH improves classroom functioning, notably by decreasing disruptive behavior and increasing academic productivity, accuracy and improvement in teacher ratings. In addition, MPH has been shown to improve performance in children for several cognitive tasks, including measures of attention and memory.

2.2. KP415: A Prodrug Conjugate of d-Methylphenidate

KemPharm is developing KP415 as an extended release (ER) prodrug of d-threo-MPH HCl. Chemically, KP415 consists of a single d-threo-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 covalent linkage makes KP415 a new chemical entity (NCE). Results from preliminary in vivo studies in rats have shown that the prodrug has unique pharmacokinetic (PK) properties that suggest it will have reduced intranasal and intravenous abuse potential.

As a prodrug, KP415 represents a potential abuse-deterrent form of MPH with abuse-deterrent properties that are imparted at the molecular level. Some of the KP415 attributes that make it worthy of further development are highlighted below:

- KP415 has negligible pharmacological activity at key receptors that are responsible for the efficacy of d-MPH for the treatment of ADHD.
- When administered intranasally or intravenously in rats, KP415 resulted in d-MPH plasma concentrations that are significantly reduced when compared to d-MPH HCl.
- KP415 exhibits chemical stability when subjected to certain hydrolytic conditions with the intention to extract methylphenidate.

3. OVERVIEW OF CLINICAL STUDIES WITH KP415

The pharmacology, metabolism and toxicology of methylphenidate are well established (Challman and Lipsky 2000, Leonard 2004). Methylphenidate is a CNS stimulant approved for the treatment of ADHD and narcolepsy. Methylphenidate inhibits the reuptake of dopamine and norepinephrine, increased dopaminergic and noradrenergic activity in the prefrontal cortex may explain its efficacy in ADHD.

Common side effects of methylphenidate include nervousness, agitation, anxiety, sleep problems (insomnia), stomach pain, decreased appetite, weight loss, nausea, vomiting, dizziness, palpitations, headache, vision problems, increased heart rate, increased blood pressure, sweating, skin rash, psychosis, and numbness, tingling, or cold feeling in hands or feet. When abused, methylphenidate produces toxicity similar to other CNS stimulant overdoses (Morton and Stockton 2000). Supra-therapeutic doses have shown to cause delirium, hallucinations, bruxism (jaw-grinding), and trismus (jaw clenching) (Morton and Stockton 2000).

3.1. Study KP415.101

This Phase 1 proof-of-concept trial (Study KP415.101) was designed to assess the PK of 32 mg of KP415 API (liquid, dissolved in water) compared with 36 mg of Concerta® (tablet) after oral administration under fasted conditions. Twenty-four (24) healthy adult volunteers were enrolled in this open-label, single-dose, two-treatment, two-period PK trial. Dosing levels in each treatment were not molar equivalent amounts of d-MPH: 36 mg Concerta® contained approximately 12% more d-MPH than 32 mg of the KP415 prodrug API (standalone KP415).

KP415 API prodrug effectively released the active d-MPH into the bloodstream which is consistent with previously collected preclinical data. After KP415 API prodrug dosing, the mean peak concentration (C_{max}) of d-MPH was 2.9 ng/mL at a median T_{max} of 8 hr compared to 8.0 ng/mL at 6 hr after Concerta®.

The mean systemic exposure ($AUC_{0\text{-}last}$) for d-MPH was 44 ng•hr/mL after KP415 API prodrug versus 97 ng•hr/mL after Concerta® dosing. The mean total systemic exposure ($AUC_{0\text{-}inf}$) for d-MPH was 100 ng•hr/mL after KP415 API prodrug versus 102 ng•hr/mL after Concerta® dosing. The mean terminal elimination plasma half-life ($T_{1/2}$) of d-MPH was 25 hr after KP415 API prodrug versus 4 hr after Concerta®.

After oral dosing of standalone KP415, it appears that that there is rapid absorption of prodrug followed by slow release of d-MPH resulting in a gradual onset followed by a slow extended release of d-MPH. The later T_{max} and longer $T_{1/2}$ for d-MPH after KP415 dosing indicate that KP415 as a prodrug of d-MPH has extended-release (ER) properties that support a once-per-day dosing schedule for an ADHD indication. The ER properties inherent in the KP415 prodrug molecule can subsequently provide sustained d-MPH exposure, as desired for a once-per-day treatment of ADHD

in adults. No l-MPH levels were detected after KP415 dosing and very low l-MPH levels were measured after Concerta® dosing.

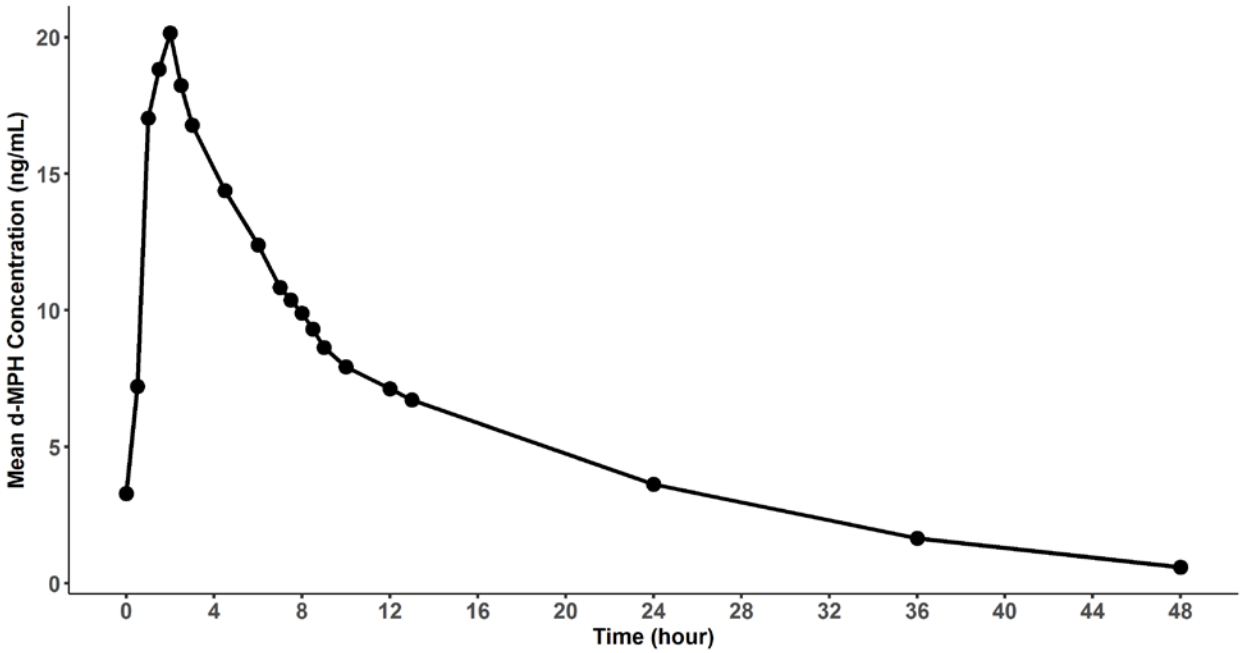
Both treatments were generally well-tolerated. There were no apparent changes in vital signs and ECG parameters between treatments. Safety laboratory values were approximately the same after the treatment phase versus those measured at Screening.

3.2. Study KP415.109

This Phase 1 open-label PK study included a treatment group wherein healthy adult volunteers were dosed for 7 days with oral daily doses of 12 mg d-MPH API (immediate release component) and 56 mg KP415 prodrug API, each administered as an oral liquid in water immediately after each other. The total daily equivalent d-MPH dose was 40 mg. This dose was the same as the highest dose that will be used in the current protocol.

The mean d-MPH plasma concentrations on Day 7 of Study KP415.109 are presented in Figure 1. The mean d-MPH trough concentration (C_{min}; pre-dose on Day 7) was 3.3 ng/mL and the mean d-MPH peak concentration (C_{max} on Day 7) was 20.9 ng/mL at a median T_{max} of 1.5 hr. The mean systemic exposure over the dosing interval ($AUC_{0\text{-}24hr}$) for d-MPH was 208 ng•hr/mL and the mean terminal elimination plasma half-life ($T_{1/2}$) of d-MPH was 8.9 hr. The mean accumulation ratios (Day 7/Day 1 ratios) for C_{min}, C_{max} and $AUC_{0\text{-}24hr}$ were 1.31, 1.20 and 1.34, respectively. The combination of 70%/30% KP415/d-MPH resulted in early peak d-MPH exposure followed by sustained d-MPH exposure, as desired for chronic, once-per-day treatment of ADHD in a pediatric population. The efficacy and safety of this combination in children 6-12 years old with ADHD will be studied in the study presented in this protocol.

Figure 1: Mean (N=10) d-Methylphenidate (d-MPH) Concentrations after the 7th Oral Daily Dose of 12 mg d-MPH and 56 mg KP415 Prodrug (Together Equivalent to 40 mg d-MPH)



4. STUDY RATIONALE

The safety of KP415 has been investigated in pharmacokinetic studies with healthy adult volunteers after daily oral doses of up to 7 days. In addition, the efficacy and safety in children 6-12 years old with ADHD is being investigated in Study KP415.E01. Study KP415.E01 is a multicenter, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy laboratory classroom study with KP415 with daily oral KP415 administration up to 4 weeks. The rationale of the current study is to investigate the safety and tolerability of daily oral KP415 doses for a longer duration. In addition, the current study will also determine the efficacy and sleep behavior of KP415 in treating children with ADHD. For ease of enrollment and to extend the duration of dosing already available from Study KP415.E01, the study population will include subjects rolled over from 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).

5. STUDY OBJECTIVES

5.1. Primary Objective

To determine the safety and tolerability of KP415 in treating children with ADHD.

5.2. Secondary Objectives

To determine the efficacy and changes in sleep behavior during KP415 treatment in children with ADHD.

6. INVESTIGATIONAL PLAN

6.1. Study Design

The study is a multicenter, multiple-dose, dose-optimized, open-label safety study with KP415 administered orally in children with Attention-Deficit/Hyperactivity Disorder (ADHD). Approximately 20 sites in the United States of America will take part in the study.

6.1.1. Definition of "Rolled-Over Subjects" or "New Subjects"

Eligible subjects for the current study will be either **"Rolled-Over Subjects"** or **"New Subjects"**, defined as follows:

- **Rolled-Over Subjects** are those who successfully completed Study KP415.E01 and rolled over (i.e., received first dose in the current study) within 45 days of the last dose of study drug in Study KP415.E01. The roll-over window (for Rolled-Over Subjects), dose-to-dose between both studies (i.e., gap between the last dose in Study KP415.E01 [Visit 6] and the first dose in the current study [Visit 5]) is maximum 45 days. For roll-over subjects, the Investigator has the option to use the clinical chemistry and hematology results from the Follow-Up Visit in Study KP415.E01 (Visit 7) in lieu of collecting new blood samples at Screening (Visit 1B) in the current study, as long as the clinical chemistry and hematology data from the E01 study were collected within 30 days of Screening (Visit 1B) in the current study. For all roll-over subjects who are children of childbearing potential, a blood sample for the measurement of a serum pregnancy test is needed at Visit 1B. For other assessments required at Visit 1B (C-SSRS, for example), the Visit 7 assessments from the E01 study (if collected) can be used as long as Visit 1B is conducted on the same day as Visit 7 in the E01 study.

- **New Subjects** are those who did not participate in Study KP415.E01 or completed the last dose in Study KP415.E01 more than 45 days before the first dose in the current study. Subjects who completed other studies with KP415 (for example, the single-dose pharmacokinetic study KP415.105) may be enrolled in the current study as new subjects after a minimum 5-day washout period between the last dose of KP415 and Screening in the current study.

Rolled-over subjects and new subjects will need to meet their respective inclusion/exclusion criteria listed in **Section 7.2**.

6.1.2. Study Participation

The study visits, treatment and procedures leading up to the Treatment Phase are different for rolled-over and new subjects, as follows:

- Rolled-Over Subjects: For subjects rolled over from Study KP415.E01, the study will consist of a Screening Phase, Treatment Phase and a Follow-Up Visit. These subjects will be enrolled in the Treatment Phase of the current study (first dose at Visit 5) within 45 days after the last dose of study drug in Study KP415.E01. The roll-over window (for Rolled Over Subjects), dose-to-dose between both studies (i.e., gap between the last dose in Study KP415.E01 [Visit 6] and the first dose in the current study [Visit 5]) is maximum 45 days. Subjects are allowed to enter Screening (Visit 1B) on the same day as the Follow-Up Visit in Study KP415.E01, or later. Subjects not rolled over from Study KP415.E01 within 45 days of the last dose of study drug, may be enrolled in the current study as new subjects (they will need to start with Screening followed the by Dose Optimization Phase – see New Subjects below). These subjects will be considered New Subjects and will undergo all the visits and procedures of New Subjects (starting with Visit 1A as the Screening Visit). For roll-over subjects, the Investigator has the option to use the clinical chemistry and hematology results from the Follow-Up Visit in Study KP415.E01 (Visit 7) in lieu of collecting new blood samples at Screening (Visit 1B) in the current study, as long as the clinical chemistry and hematology data from the E01 study were collected within 30 days of Screening (Visit 1B) in the current study. For all roll-over subjects who are female subjects of childbearing potential, a blood sample for the measurement of a serum pregnancy test is needed at Visit 1B. For other assessments required at Visit 1B (C-SSRS, for example), the Visit 7 assessments from the E01 study (if collected) can be used as long as Visit 1B is conducted on the same day as Visit 7 in the E01 study.

- **New Subjects:** For new subjects, the study will consist of a Screening Period, a Dose Optimization Phase, a Treatment Phase and a Follow-Up Visit.

The study design and procedures in the Treatment Phase, the Follow-Up Visit and the Early Termination Visit are the same for new subjects and rolled-over subjects.

6.1.3. Study Phases and Treatment

All subjects will receive unblinded (open-label) active drug (KP415 capsules) in all phases of the study wherein study drug is administered.

The phases of the study are as follows:

- **Screening Period**: New Subjects will undergo a screening period up to 30 days prior to entering into the Dose Optimization Phase. Rolled-over subjects will undergo a screening

period up to 30 days prior to entering into the Treatment Phase.

- **Dose Optimization Phase (for new subjects only)**: During the Dose Optimization Phase, subjects will be titrated to doses of 20, 30 or 40 mg KP415 capsules based on individual tolerability and best dose-response in the opinion of the Investigator.

- **Treatment Phase**: Eligible subjects will receive single daily oral doses of KP415 for approximately 360 days (approximately 12 months), or for a shorter duration if the study is stopped earlier (see **Section 8.6** for the study stopping rules). The starting dose of KP415 given in the Treatment Phase will be the same as the optimized dose of KP415 determined and used in Study KP415.E01 for rolled-over subjects, or determined at the end of the Dose Optimization Phase for new subjects. During the Treatment Phase, the dose of KP415 may be changed based on individual tolerability and best dose-response (to either 20, 30 or 40 mg KP415 capsules). Safety, efficacy and sleep behavior assessments will be performed.

- **Follow-Up Visit**: 3 ±2 days after administration of the last dose of the Treatment Phase, subjects will enter a Follow-Up Visit to evaluate safety parameters.

6.2. Study Duration

Rolled-Over Subjects: Subjects rolled over from Study KP415.E01 will participate in the study as outpatients for up to 416 days, including up to 30 days of Screening, 1 day for Visit 5, up to 380 days (360 ±20 days) in the Treatment Phase and a Follow-Up Visit up to 5 days (3 ±2 days) after the administration of the last dose of the Treatment Phase. Subjects who completed Study KP415.E01 and start the current study outside the 45-day roll-over window will be considered new subjects and will undergo all the visits and procedures of new subjects.

New Subjects: New subjects will participate in the study as outpatients for up to 440 days including up to 30 days of Screening, 1 day for Visit 2, up to 23 days (20 ±3 days) in the Dose Optimization Phase, 1 day for Visit 5, up to 380 days (360 ±20 days) in the Treatment Phase and a Follow-Up Visit up to 5 days (3 ±2 days) after the administration of the last dose of the Treatment Phase.

If the study is stopped earlier based on the study stopping rules (see **Section 8.6**), all or some subjects may participate in the study for shorter durations than those listed above.

7. SUBJECT SELECTION

7.1. Number of Subjects

Approximately 250 subjects will be enrolled in the Treatment Phase of the study. Subjects will be rolled over from Study KP415.E01 and to reach the targeted number of subjects, new subjects will be enrolled as well. Subjects who fail Screening and new subjects who terminate early during the Dose Optimization Phase may be replaced. Subjects who terminate early in the Treatment Phase

will not be replaced.

7.2. Study Population

Subjects rolled over from Study KP415.E01 or new subjects with ADHD who meet the inclusion/exclusion criteria listed below. See **Section 6.1.1** for the definitions of rolled-over subjects and new subjects.

7.2.1. Inclusion Criteria for Subjects Rolled Over from Study KP415.E01

(To be evaluated at Screening Visit 1B, except when noted otherwise)

A subject will be eligible for inclusion in the study if all the following criteria apply:

1. Subjects must have completed the Double-Blind Treatment Phase of Study KP415.E01, and must have received the last dose of KP415 in Study KP415.E01 (Visit 6) within 45 days prior to the first dose in the current study (Visit 5). Subjects who completed Study KP415.E01 but received their last dose of study drug more than 45 days prior to Visit 5 are eligible in the current study as New Subjects (but not as rolled-over subjects). Subjects who completed Study KP415.E01 and start the current study outside the 45-day roll-over window will be considered New Subjects and will undergo all the visits and procedures of new subjects (starting with Visit 1A as the Screening Visit).

2. Subjects rolled-over from Study KP415.E01 needed to be at least 6 years old and less than 13 years old at the start of the Dose Optimization Phase in Study KP415.E01. By the time they are rolled over into the current study, some may be 13 years old.

3. Female subjects must agree, when they are of childbearing potential at Screening or when they become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. Male subjects with female partners must agree, when their partners are of childbearing potential at Screening or when their partners become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. "Of childbearing potential" is defined in **Section 12.9**. Acceptable forms of birth control are listed in **Section 10.3**.

4. Subject must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis) at the Follow-Up Visit of Study KP415.E01. If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference

range, then the subject can be included only if the Investigator determines the deviations to be not clinically relevant.

5. At least one parent/legal guardian of the subject must voluntary give written permission for him/her to participate in the study.

6. Subject must give written or verbal assent prior to study participation. For verbal assent, the procedure will be documented and signed by a witness. A parent or guardian may not be the witness for a child's verbal assent document.

7. Subject must be able and willing to wash out current stimulant ADHD medications (if applicable, if taking ADHD medications between studies), including herbal medications from 5 days prior to the start of the Treatment Phase (Visit 5), and abstain from taking these to the end of the Follow-Up Visit or Early Termination; and wash out non-stimulant ADHD medications (if applicable) from 14 days prior to the start of the Treatment Phase (Visit 5), and abstain from taking these to the end of the Follow-Up Visit or Early Termination.

8. Subject, subject's parent/legal guardian and caregiver (if applicable) must understand and be willing and able to comply with all study procedures and visit schedule. If the subject is cared for by a caregiver for relevant parts of any period between study visits, and if in this case, in the opinion of the Investigator, the caregiver of the subject is more suitable for certain assessments, the caregiver will need to agree to the applicable procedures and visits.

9. Subject, parent/legal guardian and caregiver (if applicable) must be able to speak and understand English, and be able to communicate satisfactorily with the Investigator and study coordinator.

10. Subject must be able to swallow size 3 capsules as demonstrated by easily swallowing a size 3 placebo capsule at Screening, unless the subject participated in the KP415.E01 study previously, or unless the subjects agrees to take the contents of the capsule sprinkled on a small amount of applesauce or in a small amount of water.

7.2.2. Inclusion Criteria for New Subjects

(To be evaluated at Screening Visit 1A, except when noted otherwise)

A subject will be eligible for inclusion in the study if all the following criteria apply:

1. Subject must be at least 6 years old and less than 13 years old at the start of the Dose Optimization Phase (Visit 2).

2. Subject must have a body weight of at least 21 kg at Screening.

3. Female subjects must agree, when they are of childbearing potential at Screening or when they become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. Male subjects with female partners must agree, when their partners are of childbearing potential at Screening or when their partners become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken. "Of childbearing potential" is defined in **Section 12.9**. Acceptable forms of birth control are listed in **Section 10.3**.

4. Subject must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical and neurological examinations, vital signs, ECGs, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis) at Screening. If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject can be included only if the Investigator determines the deviations to be not clinically relevant.

5. At least one parent/legal guardian of the subject must voluntary give written permission for him/her to participate in the study.

6. Subject must give written or verbal assent prior to study participation. For verbal assent, the procedure will be documented and signed by a witness. A parent or guardian may not be the witness for a child's verbal assent document.

7. Subject must meet Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). If the MINI-KID assessment is available from a previous study with KP415, it does not need to be repeated.

8. Subject must have a score of at least 3 (mildly ill) on the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale at Visit 2. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout.

9. Subject must be able and willing to wash out current stimulant ADHD medications, including herbal medications from 5 days prior to the start of the Dose Optimization Phase (Visit 2), and abstain from taking these to the end of the Follow-Up Visit or Early Termination; and wash out non-stimulant ADHD medications from 14 days prior to the start of the Dose Optimization Phase (Visit 2), and abstain from taking these to the end of the Follow-Up Visit or Early Termination.

10. An ADHD-Rating Scale-5 (ADHD-RS-5) total score of at least 28 at Visit 2. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout.

11. Subject, subject's parent/legal guardian and caregiver (if applicable) must understand and be willing and able to comply with all study procedures and visit schedule. If the subject is cared for by a caregiver for relevant parts of a school day, and if in this case, in the opinion of the Investigator, the caregiver of the subject is more suitable for certain assessments, the caregiver will need to agree to the applicable procedures and visits.

12. Subject, parent/legal guardian and caregiver (if applicable) must be able to speak and understand English, and be able to communicate satisfactorily with the Investigator and study coordinator.

13. Subject must be able to swallow size 3 capsules as demonstrated by easily swallowing a size 3 placebo capsule at Screening, unless the subject participated in the KP415.E01 study previously, or unless the subjects agrees to take the contents of the capsule sprinkled on a small amount of apple sauce or in a small amount of water.

7.2.3. Exclusion Criteria for Subjects Rolled Over from Study KP415.E01

(To be evaluated at Screening Visit 1B, except when noted otherwise)

A subject who meets any of the following exclusion criteria will not be enrolled into the study:

1. If female, must not be pregnant or breastfeeding, and if of childbearing potential, must have a negative pregnancy test at the start of the Screening Phase (Visit 1B). In addition, a positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 12.9.**

2. Based on the medical history evaluated at Screening (Visit 1B), subject with any new clinically significant chronic medical condition that, in the judgment of the Investigator, may interfere with the participant's ability to participate in the study, or that may affect safety and/or the results of the study.

3. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug.

4. Subjects are using or planning to use prohibited drugs during the trial as specified in the protocol.

5. Subject has a positive urine MPH screen at Visit 5.

6. Subject, parent/legal guardian and caregiver (if applicable at the Investigator's discretion) has commitments during the study that would interfere with attending study visits.

7. Subject or subject's family anticipates a move outside the geographic range of the investigative site during the study period, or plans extended travel inconsistent with the recommended visit interval during study duration.

8. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

7.2.4. Exclusion Criteria for New Subjects

(To be evaluated at Screening Visit 1A, except when noted otherwise)

A subject who meets any of the following exclusion criteria will not be enrolled into the study:

1. Subjects who have received study drug (KP415 or placebo for KP415) in Study KP415.E01 during the 45 days prior to the Treatment Phase. Subjects who have received KP415 in Study KP415.E01 less than 45 days prior to the Treatment Phase are eligible to be enrolled in the current study as roll-overs (but not as new subjects).

2. If female, must not be pregnant or breastfeeding, and if of childbearing potential, must have a negative pregnancy test at the start of the Screening Phase (Visit 1A). In addition, a positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 12.9.**

3. Subject with any clinically significant chronic medical condition that, in the judgment of the Investigator, may interfere with the participant's ability to participate in the study.

4. Subject has any diagnosis of bipolar I or II disorder, major depressive disorder, conduct disorder, obsessive-compulsive disorder, any history of psychosis, autism spectrum disorder, disruptive mood dysregulation disorder (DMDD), intellectual disability, Tourette's Syndrome, confirmed genetic disorder with cognitive and/or behavioral disturbances. Subjects with oppositional defiant disorder (ODD) are permitted to enroll in the study as long as ODD is not the primary focus of treatment, and, in the opinion of the Investigator, the ODD is mild to moderate, and eligible subjects with ODD are appropriate and cooperative during Screening.

5. Subject has generalized anxiety disorder or panic disorder that has been the primary focus of treatment at any time during the 12 months prior to Screening or that has required pharmacotherapy any time during the 6 months prior to Screening.

6. Subject has evidence of any chronic disease of the central nervous system (CNS) such as

tumors, inflammation, seizure disorder, vascular disorder, potential CNS related disorders that might occur in childhood (e.g., Duchenne Muscular dystrophy, myasthenia gravis, or other neurologic or serious neuromuscular disorders), or history of persistent neurological symptoms attributable to serious head injury. A past history of febrile seizure, drug-induced seizure, or alcohol withdrawal seizure is allowed. Subject taking anticonvulsants for seizure control currently or within the past 2 years before Screening are not eligible for study participation.

7. Subject has a current (last month) psychiatric diagnosis other than specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders. Subjects allowed to enroll with any of these DSM disorders will require written justification from the Investigator documenting why the conditions will not interfere with participation and to emphasize that ADHD is the primary indication.

8. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on a history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug.

9. Subject has any clinically significant unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular (including cardiomyopathy, serious arrhythmias, structural cardiac disorders, or severe hypertension), gastrointestinal, respiratory, hepatic, or renal systems, or a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion of study drug. Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the medical monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if controlled) must be discussed with the medical monitor during Screening

10. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant.

11. Subject has a history of, or currently has a malignancy, except for non-melanomatous skin cancer.

12. Subject has uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) $\leq$0.8 x the lower limit of normal (LLN) or $\geq$1.25 x the upper limit of normal (ULN) for the reference laboratory at Screening. For subjects who previously participated in Study KP415.E01, this condition does not need to be re-evaluated.

13. Subjects with a history of substance abuse or treatment (including alcohol) within 1 year prior to Screening.

14. Subject shows evidence of substance or alcohol use or is currently using tobacco or other nicotine-containing products, or has a positive urine alcohol or urine drug screen at Screening. Subjects with a positive urine drug screen (including urine MPH screen) at Screening may be allowed to continue in the study, provided that the Investigator determines that the positive test is a result of taking prescribed medications, and subject is willing to wash out the current medication as required.

15. Subject has participated in any other clinical study with an investigational drug/product within 90 days prior to Screening, or is currently participating in another clinical trial, with the exception of any trial with KP415, as follows: Subjects who participated in Study KP415.E01 and completed the last dose in Study KP415.E01 more than 45 days before the Treatment Phase in the current study, are eligible as new subjects in the current study. Subjects who completed other studies with KP415 (for example, the single-dose pharmacokinetic study KP415.105) may be enrolled in the current study as new subjects after a minimum 5-day washout period between the last dose of KP415 and Screening in the current study.

16. Subject has taken ADHD medications from more than one class within 30 days prior to Screening. Subjects on a stable dose of one ADHD medication with occasional use of ADHD medications from another class are eligible at the discretion of the Investigator.

17. Subjects with demonstrated lack of response or intolerability to adequate dose and duration of treatment with methylphenidate products. Judgment of adequate dose and duration is at the discretion of the Investigator.

18. Subjects are using or planning to use prohibited drugs during the trial as specified in the protocol.

19. Subject has a positive urine MPH screen at Visit 2.

20. Subject has a history of severe allergies or adverse drug reactions to more than one class of medications.

21. Subject has a history of allergic reaction or a known or suspected sensitivity to methylphenidate or any substance that is contained in the study drug.

22. Subject, parent/legal guardian and caregiver (if applicable at the Investigator's discretion) has commitments during the study that would interfere with attending study visits.

23. Subject or subject's family anticipates a move outside the geographic range of the

investigative site during the study period, or plans extended travel inconsistent with the recommended visit interval during study duration.

24. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

7.2.5. Eligibility Criteria for Treatment Phase

(To be evaluated at the end of the Dose Optimization Phase, for new subjects only)

Subjects will need to meet the following additional eligibility criteria at the end of the Dose Optimization Phase in order to enter into the Treatment Phase:

1. A reduction of ≥30% in ADHD-RS-5 from baseline (Visit 2) at the end of the Dose Optimization Phase.

2. A CGI-I score of 1 or 2 at the end of the Dose Optimization Phase.

3. Acceptable tolerability of the optimized KP415 dose experienced during the Dose Optimization Phase.

8. STUDY TREATMENTS

8.1. KP415 Dose Optimization (new subjects only)

In the Dose Optimization Phase, daily treatments of 20, 30 and 40 mg open-label KP415 capsules will be administered (one capsule/day in the morning), for the titration to an optimal daily KP415 dose based on tolerability and best individual dose-response in the opinion of the Investigator. Study drug will be taken orally in the morning at home or, at the visit days, may be taken at the study site. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

Subjects will begin taking open-label KP415 at home the morning following Visit 2. The starting dose of KP415 (Days 1-7 ±3 days) will be 30 mg/day. KP415 dose adjustments, if needed, will be performed at approximately weekly intervals between visits (at Visits 3 and 4). Actual visit dates may deviate from exactly being spaced 7 days apart such that the total duration of the Dose Optimization Phase ranges between 18 and 24 days (21 ±3 days). The daily doses of KP415 used in the Dose Optimization Phase will be 20, 30, and 40 mg (dose optimization range of ≥20 and ≤40 mg). At Visits 3 and 4, based on the CGI scores, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic responses and tolerability to treatment and decide whether the current KP415 dose should be increased, decreased, or remain the

same for the next week of dosing. If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their KP415 dose may be adjusted before the next scheduled visit. Unscheduled visits between Visits 2, 3, 4, and 5 are allowed as needed, at the discretion of the Investigator.

At Visit 5 (start of the Treatment Phase), the Investigator will evaluate the eligibility criteria (see **Section 7.2.5**) for continuation into the Treatment Phase. For subjects eligible for the Treatment Phase, the optimal daily KP415 dose will be used as the daily KP415 dose during the Treatment Phase.

8.2. Study Drug Administration in the Treatment Phase

All subjects will be administered one unblinded KP415 capsule once daily in the Treatment Phase. The dose of KP415 will be determined by the optimal dose of KP415 at the end of the Dose Optimization Phase, either 20, 30, or 40 mg/day KP415. Study drug will be taken orally in the morning at home or, at the visit days, may be taken at the study site. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

8.3. Treatment Assignment

Dose Optimization Phase (new subjects only): All eligible subjects will start on a dose of 30 mg/day open-label KP415 and the KP415 dose will be titrated to either 20, 30 or 40 mg/day based on tolerability and best individual dose-response in the opinion of the Investigator.

Treatment Phase (all subjects): Rolled-over subjects from Study KP415.E01, and new subjects who completed the Dose Optimization Phase (and passed the eligibility criteria for the Treatment Phase, **Section 7.2.5**), will be enrolled at Visit 5 (start of the Treatment Phase) for treatment with the optimized dose of KP415 capsules. During the Treatment Phase, at the Investigator' discretion, based on individual tolerability and dose response, the daily dose of KP415 may be changed to any of the allowed dose levels (20, 30, or 40 mg/day).

8.4. Blinding

This is an open-label study. Study treatments will not be blinded.

8.5. Compliance

All study drug will be recorded by each site's pharmacy staff member or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site.

Acceptable Compliance is defined as 80-100% (inclusive). If Compliance between subsequent scheduled visits of the Treatment Phase (Visits 6 through 16) is outside this acceptance range, or

cannot be determined (when, for example, the subject did not return unused study drug), the Investigator or designee will counsel the parent/legal guardian. If a subject is noncompliant more than once, the Investigator will discuss the subject's noncompliance with the Medical Monitor.

8.6. Study Stopping Rules

The study will be stopped for any of the following reasons, whichever comes first:

1. An interim analysis of the safety data will be conducted after approximately all subjects remaining in the study have completed 180 days (approximately 6 months) of treatment. After the completion of the interim analysis, based on the acceptance of the clinical and nonclinical safety database from the current study and other studies, the Sponsor may stop the study. Treatment in the current study will continue as planned while the interim analysis is conducted. If the decision is made to stop the study, all subjects remaining in the study will undergo the EOT Visit (with safety evaluations including fasting safety labs and ECGs) and a Follow-Up Visit.

2. After all subjects have completed 360 days (approximately 1 year) of treatment.

9. STUDY PROCEDURES

For all subjects, the study will include a Screening Phase, Treatment Phase and a Follow-Up Visit. For new subjects only, after the Screening Phase and before entering the Treatment Phase, there will be a Dose Optimization Phase. Subjects rolled over from Study KP415.E01 (within the 45-day window) will have a Screening Visit followed by a Treatment Phase (no Dose Optimization Phase) because eligibility assessments and dose optimization were completed in Study KP415.E01. A table with the Schedule of Events (SOE) representing the required testing procedures to be performed is included in **Section 1**. Following is a list of these procedures and assessments:

9.1. Screening Procedures (Visit 1A - New Subjects Only)

The procedures at Screening are different between subjects rolled over from Study KP415.E01 and new subjects. Therefore, the Screening Visit for new subjects is designated Visit 1A (current section), and for roll-over subjects, is designated as Visit 1B (see **Section 9.2**).

Subjects will complete the screening visit (Visit 1A) within 30 days of starting the Dose Optimization Phase (Visit 2). Prior to conducting any study-related activities including screening procedures, written or verbal assent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the parent/legal guardian.

The following procedures will be performed at the Screening Visit:

1. Permission and HIPAA authorization by one parent/legal guardian of the subject.

2. Written or verbal assent by the subject. For verbal assent, the procedure will be documented and signed by a witness. A parent or guardian may not be the witness for a child's verbal assent document.

3. ADHD Diagnosis and Confirmation based on the Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).

4. Perform the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale assessment. Subjects must have a CGI-S score of at least 3 (mildly ill) for further study participation.

5. Subject demographics including date of birth, sex, race, and ethnicity.

6. Administer a size 3 placebo capsule orally with up to 240 mL of water (Capsule Swallowing Test). The capsule may not contain any active drug substance. Subjects must be able to easily swallow the size 3 capsule to be eligible for further study participation. This is not required for subjects who have previously participated in the KP415.E01 study, or for subjects who are planning to take the study drug as the capsule contents sprinkled over a small amount of applesauce or added to a small amount of water. Subjects will be instructed how to take the study medication while at home. See **Appendix A** for detailed instructions.

7. Review of inclusion/exclusion criteria to determine study eligibility.

8. Record medical history including chronic conditions, relevant surgical procedures (with start date), medications, and history of alcohol and recreational drug use.

9. A complete physical examination.

10. Body weight, height, and BMI.

11. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

12. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, “Children’s Baseline/Screening” version. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on a history of attempted suicide and the C-SSRS assessment, will be excluded from enrollment in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

13. 12-lead electrocardiogram (ECG) after subject has been in supine position for a minimum of 3 minutes.

14. Clinical laboratory tests (chemistry, hematology and urinalysis) will be obtained under fasting conditions. Clinical laboratory measurements may be repeated at the discretion of the Investigator.

15. At Screening, urine samples will be tested for alcohol and drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone). If the urine test is positive for alcohol or drugs of abuse at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for ADHD medications such as amphetamines and methamphetamines. All ADHD medications must be washed out by Visit 2. Subjects with a positive MPH urine screen at Visit 2 will be excluded from further participation in the study or may be retested at a later date, and may be enrolled if the MPH urine screen retest is negative, as long as the Screening Window is adhered to.

16. At Screening, urine samples will be tested for methylphenidate. If the urine test is positive for methylphenidate at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for methylphenidate. All ADHD medications must be washed out by Visit 2.

17. Serum β-human chorionic gonadotropin (β-hCG) pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.

18. Review of concomitant medications, treatment and/or therapies including treatment for ADHD.

After subjects complete the screening procedures and are considered eligible to take part in the clinical study, they will be instructed to return to the clinic at Visit 2 to begin the Dose Optimization Phase. In addition, if applicable, they will be given the date on which to begin wash out of any ADHD and other medications prior to Visit 2. See **Section 10.2** for the medications that are prohibited and their associated time frames, including the days that they are prohibited before Visit 2, i.e., washout days for subjects taking the medications.

Before or on the day during the screening period that subjects will need to start the washout of their ADHD medications (for example, 5 days before Visit 2 for stimulants), study site staff will contact the subject's parent/guardian by phone to remind them of the washout ("washout phone call").

Rescreening: New subjects who are screened outside the screening window may be rescreened for participation at a later time. New subjects who received any dose of study drug and are terminated early or are not eligible to continue in the Treatment Phase, are not eligible to participate later in the study (and will not be rescreened).

9.2. Screening Procedures (Visit 1B - Rolled-Over Subjects Only)

The procedures at Screening are different between subjects rolled over from Study KP415.E01 and new subjects. Therefore, the Screening Visit for rolled-over subjects is designated as Visit 1B (current section), and for new subjects is designated Visit 1A (see **Section 9.1**).

Screening Window:
The Screening Visit for rolled-over subjects (Visit 1B) may occur on the same day as the EOS (Visit 7, Follow-Up) in Study KP415.E01, or later, and must occur within 30 days before Visit 5 in the current study. The roll-over window (for Rolled-Over Subjects), dose-to-dose between both studies (i.e., gap between the last dose in Study KP415.E01 [Visit 6] and the fist dose in the current study [Visit 5]) is maximum 45 days.

Prior to conducting any study-related activities including screening procedures, written or verbal assent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the parent/legal guardian.

The following procedures will be performed at the Screening Visit:

1. Permission and HIPAA authorization by one parent/legal guardian of the subject.

2. Written or verbal assent by the subject. For verbal assent, the procedure will be documented and signed by a witness. A parent or guardian may not be the witness for a child's verbal assent document.

3. Subject demographics including date of birth, sex, race, and ethnicity.

4. Review of inclusion/exclusion criteria to determine study eligibility, including the successful completion of Study KP415.E01.

5. Record medical history including chronic conditions, relevant surgical procedures (with start date), medications, and history of alcohol and recreational drug use.

6. As part of Medical History (and with more details captured in the database), record treatment with study drug in Study KP415.E01 with regards to dose, duration, date of last dose (Visit 6 in Study KP415.E01), last visit in Study KP415.E01 (Visit 7 in Study KP415.E01), etc.

7. A complete physical examination.

8. Body weight, height, and BMI.

9. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

10. Perform the C-SSRS assessment, "Children's Baseline/Screening" version. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on a history of attempted suicide and the C-SSRS assessment, will be excluded from enrollment in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator. For roll-over subjects, if the Screening Visit (Visit 1B) occurs on the same day as the Follow-Up Visit (Visit 7) of Study KP415.E01, one C-SSRS will be obtained to be used in both studies. If Visit 1B occurs later, after Visit 7 in E01, a new C-SSRS will be obtained at Visit 1B for the current study.

11. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes. For roll-over subjects, if the Screening Visit (Visit 1B) occurs on the same day as the Follow-Up Visit (Visit 7) of Study KP415.E01, one ECG will be obtained to be used in both studies. If Visit 1B occurs later, after Visit 7 in E01, a new ECG will be obtained at Visit 1B as baseline for the current study.

12. Clinical laboratory tests (chemistry, hematology and urinalysis) will be obtained under fasting conditions (or under non-fasting conditions for the special case explained below). For roll-over subjects, the Investigator has the option to use the clinical laboratory results from the Follow-Up Visit in Study KP415.E01 (Visit 7) in lieu of collecting new blood samples at Screening (Visit 1B) in the current study, as long as the clinical laboratory samples from the E01 study were collected within 30 days prior to Visit 1B. If clinical laboratory measurements from Visit 7 of study KP415.E01 are being utilized, then fasting is not required; however, the site must record whether the samples were collected under fasting/non-fasting conditions. Clinical laboratory measurements may be repeated at the discretion of the Investigator.

13. At Screening, urine samples will be tested for alcohol and drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone). If the urine test is positive for alcohol or drugs of abuse at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for ADHD medications such as amphetamines and methamphetamines. All ADHD medications must be washed out by Visit 5 (rolled-over subjects will not have Visits 2, 3 and 4), and the urine test must be negative for further study participation.

14. Serum β-hCG pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.

15. Subjects will be instructed how to take the study medication at home. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See Appendix A for detailed instructions. Any of the methods of administration may be used on any day of the study.

After roll-over subjects complete the screening procedures and are considered eligible to take part in the clinical study, they will be instructed to return to the clinic at Visit 5 to begin the Treatment Phase. Visits 2, 3, and 4 are not needed for subjects rolled over from Study KP415.E01 because their optimum dose was determined in the Dose Optimization Phase of Study KP415.E01. Therefore, rolled-over subjects from Study KP415.E01 will start with Visit 1B as the first visit of the current study, followed by Visit 5 as the next visit (rolled-over subjects will not have Visits 2, 3 and 4).

If applicable, roll-over subjects will be given the date on which to begin wash out of any ADHD and other medications prior to Visit 5. See **Section 10.1** for the medications that are prohibited and their associated time frames, including the days that they are prohibited before Visit 5, i.e., washout days for subjects taking the medications.

Before or on the day during the screening period that subjects will need to start the washout of their ADHD medications (for example, 5 days before Visit 5 for stimulants), study site staff will contact the subject's parent/guardian by phone to remind them of the washout ("washout phone call").

Rescreening: Subjects that successfully completed Study KP415.E01 but are unable to be screened within the screening window for roll-over subjects may be screened as new subjects. Rolled-over subjects who received any dose of study drug in the current study but are terminated early, are not eligible to participate later in the study (and will not be rescreened).

9.3. Dose Optimization Phase (Visit 2-4; New Subjects Only)

Subjects who meet the inclusion/exclusion criteria during Screening, will enter into the Dose Optimization Phase (Visits 2, 3, and 4). The subjects will undergo the following procedures during these visits.

9.3.1. Visit 2

The following procedures will be performed at Visit 2:

1. Review of inclusion/exclusion criteria to determine whether subjects continue to meet

study eligibility.

2. Update medical history.

3. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

4. Perform the C-SSRS, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on the C-SSRS assessment, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

5. Perform the ADHD-RS-5 score assessment (baseline assessment). Subjects needs to have an ADHD-RS-5 total score of at least 28 for further study participation. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout of at least 5 days.

6. Perform the clinician-administered CGI-S scale assessment (baseline assessment). Subjects must have a CGI-S score of at least 3 (mildly ill) for further study participation. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout of at least 5 days.

7. Perform the CSHQ. The Investigator or designee will fill in the CSHQ questionnaire based on an interview with the parent/guardian/caregiver. For subjects requiring washout of ADHD medications, the scoring will be based on the subject's sleep behavior on the days after washout for at least 5 days before Visit 2.

8. Urine Screen for MPH: Urine samples will be tested for MPH at Visit 2 for new subjects. A urine dipstick (e.g., NarcoCheck®) will be used to screen for the presence of MPH in the urine. All ADHD medications must be washed out by Visit 2 (MPH urine screen must test negative). New subjects with a positive MPH urine screen at Visit 2 will be excluded from further participation in the study or may be retested at a later date, and may be enrolled if the MPH urine screen retest is negative, as long as the Screening Window is adhered to.

9. Urine pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential. A positive pregnancy test at Screening will exclude a subject from further participation in the study.

10. Review of concomitant medications, treatment and/or therapies.

11. Provide subject with the starting dose of 30 mg KP415 capsules to begin the Dose

Optimization Phase (Days 1-7 ±3 days). KP415 dose adjustments, if needed, will be performed at approximately weekly intervals between visits (at Visits 3 and 4). Actual visit dates may deviate from exactly being spaced 7 days apart such that the total duration of the Dose Optimization Phase ranges between 18 and 24 days (21 ±3 days). Subjects will be instructed to take study drug every morning while at home under the supervision of their parent/legal guardian/caregiver. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

9.3.2. Visit 3 (Day 7 ±3 days)

The following procedures will be performed at Visit 3:

1. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance (See **Section 8.5**).

2. Review of inclusion/exclusion criteria to determine whether subjects continue to meet study eligibility.

3. Update medical history.

4. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

5. Perform the C-SSRS, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

6. Perform the ADHD-RS-5 score assessment.

7. Perform the clinician-administered CGI-S scale assessment.

8. Perform the CGI-I scale assessment.

9. KP415 dosing and dose adjustments, if needed, will be performed at weekly intervals ± 3 days. At Visit 3 based on the CGI, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic responses and tolerability to treatment, and decide whether the current KP415 dose should be increased, decreased, or remain the same for the next week of titration. At any day during

the Dose Optimization Phase, the daily dose will be either 20, 30 or 40 mg KP415 capsules. Subjects will be instructed to take study drug every morning while at home. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

10. Assessment and review of Adverse Events, and the subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.

11. Review of concomitant medications, treatment and/or therapies.

9.3.3. Visit 4 (Day 14 ±3 days)

The following procedures will be performed at Visit 4:

1. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance.

2. Review of inclusion/exclusion criteria to determine whether subjects continue to meet study eligibility.

3. Update medical history.

4. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

5. Perform the C-SSRS, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

6. Perform the ADHD-RS-5 score assessment. This assessment may be obtained by phone within 48 hours before the visit.

7. Perform the clinician-administered CGI-S scale assessment. This assessment may be obtained by phone within 48 hours before the visit.

8. Perform the CGI-I scale assessment. This assessment may be obtained by phone within 48 hours before the visit.

9. KP415 dosing and dose adjustments, if needed, will be performed at weekly intervals

±3 days. At Visit 4, based on the CGI, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic responses and tolerability to treatment, and decide whether the current KP415 dose should be increased, decreased, or remain the same for the next week of titration. At any day during the Dose Optimization Phase, the daily dose will be either 20, 30 or 40 mg KP415 capsules. Subjects will be instructed to take study drug every morning while at home under the supervision of their parent/legal guardian/caregiver. Additional water may be given if needed. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

10. Assessment and review of Adverse Events, and the subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.

11. Review of concomitant medications, treatment and/or therapies.

9.4. Treatment Phase (Visits 5 to 17; All Subjects)

Subjects who meet the inclusion/exclusion criteria will enter into the Treatment Phase (Visits 5-17). The subjects will undergo the following procedures during these visits.

9.4.1. Visit 5

Rolled-over subjects who have taken ADHD medications (other than study drug in Study KP415.E01) between KP451.E01 and Visit 5 of the current study, will need to wash out their ADHD medications for at least 5 days before Visit 5. For these subjects, if possible, study site staff will contact the parent/guardian 5 days before Visit 5 to remind them that subjects must abstain of taking study drug on the 5 days before Visit 5.

The following procedures will be performed at Visit 5:

1. If applicable, record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance. This only applies to new subjects who received study drug at home between Visits 4 and 5, as part of the Dose Optimization Phase.

2. Review of inclusion/exclusion criteria to determine whether subjects continue to meet study eligibility.

3. Update medical history.

4. Body weight, height, and BMI.

5. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

6. Urine Screen for MPH (roll-over subjects only): Urine samples will be tested for MPH at Visit 5 for roll-over subjects. A urine dipstick (e.g., NarcoCheck®) will be used to screen for the presence of MPH in the urine. All ADHD medications must be washed out by Visit 5 for roll-over subjects (new subjects will not be tested since they will have received study drug in the preceding Dose Optimization Phase). Roll-over subjects with a positive MPH urine screen at Visit 5 will be excluded from further participation in the study or may be retested at a later date, and may be enrolled if the MPH urine screen retest is negative, as long as the Screening Window is adhered to.

7. Urine pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.

8. Perform the C-SSRS assessment, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on the C-SSRS assessment, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

9. Perform the ADHD-RS-5 score assessment.

10. Perform the clinician-administered CGI-S scale assessment.

11. For new subjects only, perform the CGI-I scale assessment. This assessment at the end of the Dose Optimization Phase is used to evaluate eligibility criteria for the Treatment Phase of new subjects (see **Section 7.2.5**).

12. Perform the CSHQ. The Investigator or designee will fill in the CSHQ questionnaire based on an interview with the parent/guardian/caregiver. The scoring will be based on the subject's sleep behavior on the days before Visit 5 (and after washout of ADHD medications, if applicable). This assessment will be used as the baseline to assess sleep behavior.

13. For new subjects only, the Investigator will evaluate the eligibility criteria (see **Section 7.2.5**) based on the data from the Dose Optimization Phase for continuation into the Treatment Phase. For subjects eligible for the Treatment Phase, the previously determined optimal daily KP415 dose will be used as the daily KP415 dose in the Treatment Phase.

14. Eligible subjects will be enrolled in the Treatment Phase, and their appropriate dose of unblinded study drug (KP415 capsules) to be taken at home once-a-day in the morning on each of the following 30 days (Days 1-30 ±5 days) will be dispensed to the subjects. Subjects will be instructed to take study drug every morning while at home under the supervision of their parent/legal guardian/caregiver. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

15. Assessment and review of Adverse Events, and the subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.

16. Review of concomitant medications, treatment and/or therapies.

9.4.2. Treatment During At Home Periods

On days of the Treatment Phase between visits, subjects will take unblinded study drug at home under supervision of parent or legal guardian. Study drug will be taken daily in the morning while at home. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions. Any of the methods of administration may be used on any day of the study.

Subject's parent/guardian will contact the study site for the reporting of AEs during the dosing periods at home. Subjects will need to adhere to all medication restrictions and general restrictions (see **Section 10**).

9.4.3. Visit 6 through Visit 16

The following procedures will be performed during each of the Visits 6-16 (inclusive), except when noted otherwise:

1. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance (See **Section 8.5**).

2. Update medical history.

3. A complete physical examination (**at Visit 11 only**).

4. Body weight, height, and BMI.

5. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

6. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes **(at Visit 11 only)**.

7. Clinical laboratory tests (chemistry, hematology and urinalysis) **(at Visit 11 only)** under fasting conditions.

8. Perform the C-SSRS assessment, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

9. Urine pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.

10. Perform the ADHD-RS-5 score assessment.

11. Perform the clinician-administered CGI-S scale assessment.

12. Perform the CSHQ. The Investigator or designee will fill in the CSHQ questionnaire based on an interview with the parent/guardian/caregiver.

13. If needed, perform a KP415 dose adjustments: based on the CGI-S, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic responses and tolerability to treatment, and decide whether the current KP415 dose should be increased, decreased, or remain the same. At any day during the Treatment Phase, the daily dose will be either 20, 30 or 40 mg KP415 capsules.

14. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Other prohibited medications with their associated time windows when they are prohibited are listed in **Section 10**.

15. The appropriate dose of unblinded study drug (KP415) to be taken at home once-a-day in the morning on each day until the next visit will be dispensed to the subjects.

16. Assessment and review of Adverse Events, and the subject's parent/guardian will be

instructed to contact the study site for the reporting of AEs during the dosing periods at home.

17. Review of concomitant medications, treatment and/or therapies.

9.4.4. Visit 17 (EOT Visit)

The following procedures will be performed at the End-of-Treatment Visit (EOT, Visit 17) after administration of the last dose of study drug:

1. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance.
2. Update medical history.
3. A complete physical examination.
4. Body weight, height, and BMI.
5. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).
6. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes.
7. Clinical laboratory tests (chemistry, hematology and urinalysis) under fasting conditions.
8. Urine pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential.
9. Perform the C-SSRS assessment, "Children's Since Last Visit" version. If a subject has clinically significant suicidal ideation, in the opinion of the Investigator, based on the C-SSRS assessment, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
10. Perform the ADHD-RS-5 score assessment.
11. Perform the clinician-administered CGI-S scale assessment.
12. Perform the CSHQ. The Investigator or designee will fill in the CSHQ questionnaire based on an interview with the parent/guardian/caregiver.
13. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 5 to the end of the Follow-Up

Visit or Early Termination Visit. Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Other prohibited medications with their associated time windows when they are prohibited are listed in **Section 10**.

14. Assessment and review of Adverse Events.

15. Review of concomitant medications, treatment and/or therapies.

9.5. Unscheduled Visits

At the discretion of the Investigator, subjects may be asked to come to the clinical site for an unscheduled visit. Subjects will need to bring their unused study drug to the visit.

Unscheduled visits can occur at any time during the Dose Optimization Phase (new subjects only) or the Treatment Phase. Examples of reasons to conduct an unscheduled visit:

- If subjects experience an Adverse Event during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, further in-person medical evaluation and review may be performed.

- If subjects experience symptoms of intolerance during the at-home treatment with study drug or have complaints about increases in ADHD symptoms, they must contact the clinical site, and, at the discretion of the Investigator, their KP415 dose may be adjusted before the next scheduled visit.

The following procedures will occur at the Unscheduled Visit:

1. Record the number of administered capsules of unblinded study drug for drug accountability and compliance. For this purpose, subjects will be asked to bring their unused medication to the clinical site.

2. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

3. Assessment and review of Adverse Events.

4. Review of concomitant medications, treatment and/or therapies.

The following procedures will occur at the Unscheduled Visit, <u>each at the discretion of the Investigator</u>:

1. Evaluations for safety, as needed (for example, to evaluate and review Adverse Events):

a. Physical examination
b. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes
c. C-SSRS, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on the C-SSRS assessment, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
d. Clinical laboratory assessments

2. If, at the discretion of the Investigator, an unscheduled evaluation of the changes in ADHD symptoms is needed, for a potential unscheduled dose level change of study drug:

    a. If needed, perform an assessment of ADHD severity. This may include an ADHD-RS-5 and/or CGI-S scale assessment, and/or, during the Dose Optimization Phase (new subjects only), a CGI-I scale assessment.
    b. If needed, perform a KP415 dose adjustment: based on the ADHD severity assessment, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic response and tolerability to treatment, and decide whether the current KP415 dose should be increased, decreased, or remain the same. On any day during the study, the daily dose will be either 20, 30 or 40 mg KP415 capsules. See **Section 11.5.4** for drug dispensing and drug return procedures at unscheduled visits.

If a subject meets any of the withdrawal criteria during the Unscheduled Visit, the subject will be withdrawn, and Early Termination procedures will be completed (see **Section 9.6**).

9.6. Early Termination Visit

Early Termination (ET) from the study is defined as withdrawal during the Dose Optimization Phase (new subjects only) or Treatment Phase (all subjects) after at least one dose of study drug is administered. For subjects who withdraw early from the study, the Investigator should make every effort to perform all ET procedures before discharging the subject from the research clinic.

The following procedures will be performed at ET visits:

1. If appropriate, record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance.

2. Update medical history.

3. Complete physical examination.

4. Body weight, height, and BMI.

5. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after subject has been sitting for a minimum of 3 minutes.

6. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes.

7. Clinical laboratory tests (chemistry, hematology and urinalysis).

8. Urine pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential.

9. Assessment of the C-SSRS, "Children's Since Last Visit" version. If a subject has, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on the C-SSRS assessment, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

10. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Other prohibited medications with their associated time windows when they are prohibited are listed in **Section 10**.

11. Review of concomitant medications, treatment and/or therapies.

12. Assessment and review of Adverse Events.

At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day as part of the study phase from where the subject enters ET, do not need to be repeated.

Subjects will be discharged from the study clinic when the Investigator determines that the subjects are medically stable and, if possible, after all ET procedures are completed.

Subjects who withdraw early from the study and complete the above ET procedures will not return for a Follow-Up Visit. Therefore, the ET Visit is the EOS for these subjects.

9.7. Follow-Up Visit

Subjects who complete the Treatment Phase will return in 3 ±2 days after the administration of the last dose of study drug for the Follow-Up Visit.

The following procedures will be completed during the Follow-Up Visit:

1. Update medical history.

2. Body weight, height, and BMI.

3. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

4. Urine pregnancy test for all female subjects of childbearing potential. See **Section 12.9** for the definition of childbearing potential.

5. Assessment of the C-SSRS, "Children's Since Last Visit" version. If a subject has, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on the C-SSRS assessment, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

6. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit. Other prohibited medications with their associated time windows when they are prohibited are listed in **Section 10**.

7. Review of concomitant medications, treatment and/or therapies.

8. Assessment and review of adverse events.

The Follow-Up Visit is the EOS for subjects who will undergo the Follow-Up procedures.

9.8. End of Study (EOS)

The End of Study (EOS) is either the Follow-Up Visit for subjects who complete the Treatment Phase, or the Early Termination Visit for subjects who withdraw early from the study.

10. CONCOMITANT MEDICATIONS AND RESTRICTIONS

Subjects will adhere to the following restrictions before and after administration of study drug, as specified:

10.1. Medication Restrictions for Rolled-Over Subjects

Rolled-over subjects will be prohibited/limited to receive certain medications in the trial, as follows:

- Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Treatment Phase (Visit 5) to

the end of the Follow-Up Visit or Early Termination Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dextromethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall®.

- Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Treatment Phase (Visit 5) to the end of the Follow-Up Visit or Early Termination Visit. These include: Atomoxetine, guanfacine, clonidine; and SSRIs such as fluoxetine and paroxetine.

- The following medications are prohibited from 14 days prior to the start of the Treatment Phase (Visit 5) to the end of the Follow-Up Visit or Early Termination Visit:

    - Tricyclic antidepressants.
    - Monoamine oxidase inhibitors (MAOIs).
    - Mood stabilizers (e.g., lithium, valproate, quetiapine).
    - Antipsychotics (e.g., risperidone, olanzapine).
    - Coumarin anticoagulants.
    - Anticonvulsants.
    - Halogenated anesthetics.
    - Phenylbutazone

- Sedative hypnotics/sleep enhancers (with the exception of melatonin) are prohibited from 14 days prior to the start of the Treatment Phase (Visit 5) to the end of the Follow-Up Visit or Early Termination Visit.

- Melatonin is allowed if subjects have taken it for more than 30 days before the start of the Treatment Phase (Visit 5) and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to the start of Visit 5 to the end of the Follow-Up Visit or Early Termination Visit.

  If subjects participated in a previous study with KP415 (including Study KP415.E01), they are allowed to take any medications (including ADHD medications) after completing the previous study with KP415 and before starting the current study, except for the medications and the time intervals specified in this protocol.

10.2. Medication Restrictions for New Subjects

- Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dextromethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall®.

- Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit. These include: Atomoxetine, guanfacine, clonidine; and SSRIs such as fluoxetine and paroxetine.

- The following medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit:

    - Tricyclic antidepressants.
    - Monoamine oxidase inhibitors (MAOIs)
    - Mood stabilizers (e.g., lithium, valproate, quetiapine)
    - Antipsychotics (e.g., risperidone, olanzapine)
    - Coumarin anticoagulants
    - Anticonvulsants
    - Halogenated anesthetics
    - Phenylbutazone

- Sedative hypnotics/sleep enhancers (with the exception of melatonin) are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Follow-Up Visit or Early Termination Visit.

- Melatonin is allowed if subjects have taken it for more than 30 days before the start of the Dose Optimization Phase (Visit 2) and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to Visit 2 to the end of the Follow-Up Visit or Early Termination Visit.

Medications allowed during the course of the study include nasal steroids, bronchodilators, acetaminophen and nonsteroidal anti-inflammatory medications; non-sedating antihistamines such as cetirizine, loratadine, and fexofenadine; mometasone; and approved courses of prescription and nonprescription medications for the treatment of acute illnesses.

10.3. Birth Control

Female subjects must agree, when they are of childbearing potential at Screening or when they become of childbearing potential during the study to use one of the following forms of birth control from screening until 14 days after the last dose of study drug has been taken, unless a different timeframe is listed below:

a. Double barrier (diaphragm with spermicide; condoms with spermicide)

b. Intrauterine device (IUD)

c. Total abstinence (must agree to use a double barrier method if they become sexually

active between Screening and 14 days after the last dose of study drug).

d. Implanted or intrauterine hormonal contraceptives in use for at least 3 consecutive months prior to Screening.

e. Oral, patch, or injected contraceptives, or vaginal hormonal device (i.e., NuvaRing®), in use for at least 3 consecutive months prior to Screening.

Male subjects with female partners must agree, when their partners are of childbearing potential at Screening or when their partners become of childbearing potential during the study, to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 14 days after the last dose of study drug has been taken.

"Of childbearing potential" is defined in **Section 12.9**.

11. INVESTIGATIONAL PRODUCT

11.1. Active Pharmaceutical Ingredients

The chemical name of the KP415 prodrug is 3-(((S)-1-carboxy-2-hydroxyethyl)carbamoyl)-1-((((R)-2-((R)-2-methoxy-2-oxo-1-phenylethyl)piperidine-1-carbonyl)oxy)methyl)pyridine-1-ium chloride. It is a single d-methylphenidate 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.

11.2. Clinical Trial Material

The capsules of study drug (KP415 capsules) with contain two active pharmaceutical ingredients: d-methylphenidate hydrochloride as the immediate release (IR) d-methylphenidate component, and KP415 prodrug as the extended release (ER) d-methylphenidate component. In terms of d-MPH equivalent amounts, all capsule strengths contain 30% of d-MPH (IR component) and 70% of d-MPH from the KP415 prodrug. The total equivalent amount of d-methylphenidate (d-MPH) in each capsule strength (used as daily doses in this study), and the amounts of both APIs are listed in the following table.

Total d-MPH dose [1] (mg)	**d-MPH [2] (mg)**	**KP415 Prodrug [3] (mg)**
20	6	28 (14)
30	9	42 (21)
40	12	56 (28)

1. Based on the d-MPH amount plus the equivalent amount of d-MPH as KP415 prodrug.
2. The dose of d-MPH is expressed in terms of d-methylphenidate hydrochloride.
3. The dose of KP415 prodrug is expressed in terms of KP415 chloride. The amount of d-MPH hydrochloride equimolar to each KP415 prodrug dose is listed between parentheses.

The KP415 prodrug is not yet a scheduled controlled substance; however, methylphenidate is a Schedule II substance under the Controlled Substances Act. As a result of the d-MPH content in the KP415 capsules, the drug product used in this study is a Schedule II product. Therefore, study sites are required to have the appropriate permit from the Drug Enforcement Agency (DEA) to receive, store, ship and dispense the KP415 product according to all local, state, and federal regulations for Schedule II substances.

Unblinded capsules with 20, 30, and 40 mg KP415 product will be used in the study. All study drug will be supplied by the Sponsor (or designee). The Sponsor (or designee) will supply sufficient quantities of KP415 to allow for completion of the study. The study drug shipment(s) will be shipped to each site after site activation (i.e., after all required regulatory documentation has been received by the Sponsor or designee and a contract has been executed). The lot numbers of study drug supplied will be recorded in the study report.

All other drug products needed for the conduct of the study (such as allowed medications to treat Adverse Events, including acetaminophen and nonsteroidal anti-inflammatory medications) will be commercially available products obtained by each research site.

11.3. Pharmaceutical Formulation

KP415 will be provided in size 3 capsules consisting of a color-coded (by strength) hydroxypropyl methylcellulose (HPMC) capsule shell with text indicating the name (KP415) and the strength (either 20 mg, 30 mg or 40 mg). Besides KP415 drug substance, each capsule of study drug contains the following inactive ingredients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate.

11.4. Packaging and Labeling

The KP415 capsules will be packaged and labeled appropriately, according to the appropriate FDA regulations.

11.4.1. Dose Optimization Phase

Unblinded KP415 capsules will be dispensed to the subjects as bottles with 10 capsules. One bottle contains enough drug supply for one subject, for at least 7 days of dosing in the Dose Optimization Phase (1 capsule/day) and 3 extra capsules to cover the potential loss of capsules or extra dosing days before the next visit. Each bottle will be dispensed with instructions on how to administer study drug.

11.4.2. Treatment Phase

Unblinded KP415 capsules will be dispensed to the subjects as bottles with 35 capsules. One bottle contains enough drug supply for one subject, for at least 30 days of dosing in the Treatment Phase (1 capsule/day) and 5 extra capsules to cover the potential loss of capsules or extra dosing days before the next visit. Each bottle will be dispensed with instructions on how to administer study drug.

11.5. Dispensing and Drug Return Procedures

11.5.1. General Dispensing and Drug Return Procedures

Unblinded bottles of drug supply (KP415 capsules) will be dispensed at each visit of the study with enough capsules for treatment until the next visit. The assigned study drug will consist of one of the following: 20, 30 or 40 mg KP415 capsules.

At each visit, a bottle will be dispensed to the subject's parent or guardian with instructions when and how to administer study drug while at home, under supervision of parent or legal guardian. At the day of each visit, subjects may take their dose of study drug at home before coming to the study site or subjects will be administered study drug at the study site. Subjects will be instructed to take study drug every morning while at home under the supervision of their parent/legal guardian/caregiver. The capsule needs to be swallowed whole, or may be taken by sprinkling the contents of the capsule over a small amount of applesauce, or putting the contents in a small amount of water. See **Appendix A** for detailed instructions.

At each visit, subjects will return to the study site with unused study drug, and site personnel will record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance.

In the event that subjects report lost study drug during the at-home dosing periods, they will be instructed to contact the study site as soon as possible after the loss. Lost drug supply may be replaced with the appropriate new bottle.

The Investigator will not supply study drug to anyone other than those named as sub-investigators on FDA Form 1572, designated site staff, and subjects in the study.

11.5.2. Dispensing in Dose Optimization Phase (Visit 2, 3, and 4)

Unblinded bottles of drug supply will be dispensed at each visit as follows:

- **Visit 2:** Subjects will be dispensed an unblinded bottle with 10 capsules of 30 mg KP415 product (starting dose for Dose Optimization).

- **Visit 3:** Subjects will return to the research clinic after 7 ±3 days for Visit 3 with unused study drug, and will be dispensed either a bottle with 30 mg KP415 capsules (same daily dose as Week 1), with 20 mg KP415 capsules (dose level decrease from Week 1), or with 40 mg KP415 capsules (dose level increase from Week 1).

- **Visit 4:** Subjects will return to the research clinic after 7 ±3 days for Visit 4 with unused study drug, and will be dispensed either a bottle with 20, 30 or 40 mg KP415 capsules (same daily dose as Week 2, or either a dose level decrease or increase from Week 2).

11.5.3. Dispensing in Treatment Phase (Visits 5 to 16)

Unblinded bottles of drug supply will be dispensed at each visit as follows:

- **Visit 5:** Subjects will be dispensed an unblinded bottle with 35 capsules of the optimized dose of KP415 (either 20 mg, 30 mg or 40 mg capsules). For rolled-over subjects from Study KP415.E01, the optimized dose as determined in Study KP415.E01 will be used. For new subjects, the optimized dose will be determined at the end of the Dose Optimization Phase in the current study.

- **Visit 6 to Visit 16:** Subjects will return to the research clinic with unused study drug, and will be dispensed a new bottle with 35 capsules of either 20 mg, 30 mg or 40 mg KP415 product. Since the Investigator may increase or decrease the dose of KP415 during the Treatment Phase, based on individual tolerability and dose response, the capsule strengths dispensed at Visit 6 to Visit 16 may be different from the previous visit.

11.5.4. Dispensing at Unscheduled Visits

At unscheduled visits (see **Section 9.5**), if needed, the Investigator may decide to change the daily KP415 dose. In this case, a new bottle with capsules of either 20 mg, 30 mg or 40 mg KP415 product will be dispensed to the subjects, and unused study drug previously dispensed will need to be returned. The same dispensing and drug return procedures (see **Section 11.5.1**) will be followed as for scheduled visits.

11.6. Storage of Study Drug

Study drug will be stored at controlled room temperature 20°-25°C (68°-77°F) with excursions allowed between 15° and 30°C (59° and 86°F). Transient spikes up to 40°C are permitted as long as they do not last for more than 24 hours. Study drug will be stored at the study site in a safe, secure area with limited, controlled access for Schedule II substances in accordance with all local, state, and federal regulations. Investigational products must not be frozen. The Investigator will ensure that adequate precautions are taken, including storage of the study drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of

distribution.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product.

11.7. Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject, in both the Dose Optimization Phase and the Treatment Phase, will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

12. SAFETY AND EFFICACY ASSESSMENTS

12.1. Medical History

A complete medical history will be obtained at the Screening Visit including the recording of demographic data (date of birth, sex, age, race, ethnicity), collection of previous surgeries, medications and chronic conditions, past or present illnesses or dysfunctions, substance/drug abuse, and history of allergies or idiosyncratic responses to drugs. Medical history (changes from screening) will be updated at subsequent visits after the Screening Period.

12.2. Physical Examination

For all subjects, a complete physical examination will be completed at Screening, after approximately 6 months of treatment (Visit 11), after the last dose of study drug (Visit 17, EOT), and at Early Termination (if possible). The complete physical examination will include a review of the subject's general appearance, skin, head and neck (eyes, ears, nose, mouth, and throat), lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, lungs, abdomen and a brief examination of the neurological system.

Body weight, height and BMI will be determined at all visits to follow the growth of the subjects. Height will be recorded in centimeters (cm) with the subject's shoes removed. Body weight will be measured in kilograms (kg); subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.

12.3. ADHD Diagnosis and Severity Assessments

For new subjects at Screening, eligible subjects must meet the inclusion criteria for a primary diagnosis of ADHD by Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or

hyperactive/impulsive presentation) per clinical evaluation and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).

Since rolled-over subjects from Study KP415.E01 will need to have that study completed, their ADHD diagnosis and diagnosis confirmation was conducted in Study KP415.E01.

For all subjects, the following scales will be used during the study to globally assess the changes in ADHD severity over time:

- **ADHD-Rating Scale-5 (ADHD-RS-5)**: The ADHD-RS-5 is an 18-item scale (DuPaul 2016) based on Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association 2013) criteria of ADHD that rates symptoms on a 4-point scale. Each item is scored using a combination of severity and frequency ratings from a range of 0 (reflecting no symptoms or a frequency of never or rarely) to 3 (reflecting severe symptoms or a frequency of very often), so that the total ADHD-RS-5 scores range from 0 to 54. The 18 items can be divided into two 9-item subscales: One for hyperactivity/impulsivity and the other for inattentiveness. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver at each visit in the Dose Optimization Phase.

- **Clinical Global Impressions–Severity (CGI-S)**: The CGI-S is a clinician-rated scale that evaluates the severity of psychopathology (ADHD symptoms in the study) on a scale from 1 (not at all ill) to 7 (among the most severely ill) (Busner and Targum 2007).

- **Clinical Global Impressions–Improvement (CGI-I)**: The CGI-I is a clinician-rated scale that evaluates the improvement of psychopathology (ADHD symptoms in the study) on a scale from 1 (very much improved) to 7 (very much worse).

During the Dose Optimization Phase (new subjects only), the ADHD-RS-5, CGI-I and CGI-S scale assessments are the main efficacy variables (in conjunction with tolerability and safety) to guide dose optimization. During the Treatment Phase, the ADHD-RS-5 and CGI-S scale assessments are the efficacy variables to evaluate the changes in ADHD severity over time, and may be used (in conjunction with tolerability and safety) to adjust the dose of study drug.

12.4. Children's Sleep Habits Questionnaire (CSHQ)

The modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be used to assess the sleep behavior during the Treatment Phase. The CSHQ is a retrospective, 33-item parent questionnaire to examine sleep behavior in small children (Owens 2000a, Owens 2000b). Items are rated on a 3-point scale of "Usually", "Sometimes" and "Rarely" for occurrences in a number of key sleep domains. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver at the visits in the Dose Optimization Phase for new subjects (Visit 2)

and in the Treatment Phase for all subjects (Visit 5 to Visit 17).

12.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, Pediatric Version) (Posner 2010). The "Children's Baseline/Screening" version will be assessed at Screening, and the "Children's Since Last Visit" version will be assessed at all visits of the Dose Optimization Phase (new subjects only), at all of the Treatment Phase visits, and at Follow-Up or Early Termination.

Subjects who, in the opinion of the Investigator, have clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

12.6. Vital Signs

Vital sign measurements will be obtained after the subject has been seated for 3 minutes. Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. Vital signs will be collected once at each visit. At the discretion of the Investigator, in order to ensure accuracy, out-of-range vital signs may be repeated once, at least 2 minutes after an abnormal finding.

12.7. 12-Lead Electrocardiogram

A 12-lead ECG will be obtained after the subject has been in a supine position for a minimum of 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF). ECGs will be obtained at Screening, after approximately 6 months of treatment (Visit 11), after the last dose of study drug (Visit 17, EOT), and at Early Termination (if possible). ECG recordings will be evaluated by skilled readers operating from a centralized ECG laboratory.

12.8. Clinical Laboratory Measurements

All clinical laboratory samples will be sent to a central laboratory for analysis. Up to approximately 40 mL of blood will be collected for clinical chemistries, hematology, and pregnancy test (if applicable) from each subject during the study. Clinical Laboratory Measurements will be performed at Screening, after approximately 6 months of treatment (Visit 11), after the last dose of study drug (Visit 17, EOT), and at Early Termination (if possible). Samples for Clinical Laboratory Measurements at Screening Visit 1A (new subjects), Visit 11, and Visit 17 (EOT) will be collected under fasting conditions.

The Clinical Laboratory evaluations will consist of the following:

- Total Hematology as well as differential and Coagulation: red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin, hematocrit and platelets, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT).

- Serum Chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase, bicarbonate, total bilirubin, blood urea nitrogen, phosphorus (inorganic) calcium, chloride, creatine phosphokinase, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, total protein, thyroid stimulating hormone (TSH), and uric acid. TSH will be measured at Screening only, for New Subjects only who did not previously participated in Study KP415.E01 (to evaluate the exclusion criterion for uncontrolled thyroid disease).

- Urinalysis: microanalysis for specific gravity, pH, protein, glucose, ketones, blood, nitrites, leukocytes. If positive for blood, protein or nitrites, a microscopic examination will be performed.

- Urine Screen for Alcohol Drugs of Abuse (new subjects only): At Screening (Visit 1), urine samples will be tested for alcohol and drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone). If the urine test is positive for alcohol and drugs of abuse at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for ADHD medications such as amphetamines and methamphetamines.

- Urine Screen for Methylphenidate: At Screening (Visit 1A, new subjects only), Visit 2 (new subjects only) and Visit 5 (roll-over subjects only), urine samples will be tested for methylphenidate. A urine dipstick (e.g., NarcoCheck®) will be used to screen for the presence of methylphenidate in the urine. If a subject's current ADHD medication at Screening (Visit 1A, new subjects) contains MPH, the urine screen at Screening may test positive for MPH.

12.9. Pregnancy Test

Pregnancy Tests will be performed for all female subjects of childbearing potential. A serum β-hCG pregnancy test will be performed at Screening. A urine pregnancy test will be performed at Visits 2 (new subjects), at Visit 5 to Visit 17, and at Follow-Up or Early Termination. A positive pregnancy test before the last dose of study drug will exclude a subject from further participation in the study. A positive urine pregnancy test will be confirmed with a serum β-hCG pregnancy test.

Childbearing potential is defined as follows: Girls under the age of 12 who have not had their first period will be considered "not of child-bearing potential". Girls of 12 years and older (including girls who will become 12 years or older during the study) will be considered "of child-bearing potential", even if they have not yet had their first period. Irrespective of age, girls who have had their first period, will be considered "of child-bearing potential".

12.10. Adverse Event Assessments

Adverse Events will be assessed and recorded from the first day of study drug administration through either Follow-Up or Early Termination. While subjects are at the research clinic after administration of study drug, AEs will be monitored continuously by study staff. During administration of study drug away from the research clinic, subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing period at home. In addition, study staff will inquire parent/guardian during the next study visit about AEs during the dosing period at home. Definitions and details of AE reporting and documentation are listed in **Section 16**. In cases in which the occurrence of an AE to the subject is unclear or for safety-related medical questions, the Medical Monitor should be consulted (for contact information, see **Page 2**).

13. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

13.1. Withdrawal of Subjects from the Study

A subject may be discontinued or choose to withdraw from study treatment at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent.
- Subject is not compliant with study procedures.
- Adverse event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study treatment.
- Lack of efficacy
- Protocol violation requiring discontinuation of study treatment.
- Lost to follow-up when there is no response to two attempts by phone and a registered letter to the subject. After these 3 failed attempts, the subject will be considered lost to follow-up.
- Sponsor request for early termination of the study.
- Positive pregnancy test (tested in females of childbearing potential) before the last dose of study drug.
- Out-of-range vital signs, at the discretion of the Investigator. In order to ensure accuracy, out-of-range vital signs may be repeated once, at least 2 minutes after an abnormal finding.
- For other reasons (e.g., significant protocol violation, non-compliance, overdose).

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and

treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

If a subject meets withdrawal criteria during the Dose Optimization Phase or the Treatment Phase, the subject will be withdrawn, and Early Termination procedures will be completed.

At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day as part of the procedures of the Dose Optimization Phase or the Treatment Phase do not need to be repeated.

13.2. Replacement of Subjects

Subjects who withdraw from the study during the Treatment Phase will not be replaced. Subjects who withdraw from the study during the Dose Optimization Phase may be replaced.

14. STUDY ENDPOINTS

This study is primarily a safety study in the target patient population after at least 6 months of daily oral doses of KP415 capsules. Therefore, the primary endpoint is the safety.

14.1. Safety Endpoints

- The occurrence of Treatment-Emergent Adverse Events (TEAEs) will be assessed starting following the first dose of study drug, and ending with the Follow-Up Visit or Early Termination Visit.

- Physical examinations will be performed at the first visit (at Screening, before the first dose of study drug), after approximately 6 months of treatment (Visit 11), and at the end of the Treatment Phase (Visit 17, EOT) or at Early Termination.

- Clinical laboratory tests will be performed at the first visit (at Screening, before the first dose of study drug), after approximately 6 months of treatment (Visit 11), and at the end of the Treatment Phase (Visit 17, EOT) or at Early Termination.

- ECG parameters will be collected at the first visit (at Screening, before the first dose of study drug), after approximately 6 months of treatment (Visit 11), and at the end of the Treatment Phase (Visit 17, EOT) or at Early Termination.

- Vital signs, height, weight, and BMI will be collected at each visit.

- A C-SSRS will be performed at each study visit.

14.2. Efficacy Endpoints

During the Dose Optimization Phase (new subjects only):

- CGI-S will be assessed at each visit (Screening to Visit 5). ADHD-RS-5 will be administered at Visits 2 through Visit 5. CGI-I will be assessed at Visits 3, 4, and 5 (since CGI-I is an ADHD improvement assessment, it will not be assessed at Screening and at Visit 2).

During the Treatment Phase (all subjects):

- ADHD-RS-5 and CGI-S will be assessed at each visit (Visit 5 to Visit 17, EOT).

14.3. Sleep Behavior Endpoint

The modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be used to assess the sleep behavior in the Dose Optimization Phase for new subjects (Visit 2) and in the Treatment Phase for all subjects (Visit 5 to Visit 17). The baseline will be measured before the first dose of study drug, at Visit 2 for new subjects and at Visit 5 for roll-over subjects.

15. STATISTICAL CONSIDERATIONS

This section summarizes the statistical considerations for this protocol. Details will be provided in the Statistical Analysis Plan (SAP) prior to the primary endpoint database lock of the trial.

15.1. Sample Size Calculation

No formal sample size calculations were conducted. It was determined that approximately 200 subjects are adequate to satisfy the primary objective of the study, which is to determine the safety and tolerability of KP415 in treating children with ADHD for at least 6 months. Assuming a maximum dropout rate of 20% over 6 months, approximately 250 subjects will be enrolled.

15.2. Populations for Analysis

Data will be analyzed in this study in the following analysis populations:

- ***Treatment-Phase Safety Population:*** All enrolled subjects in the Treatment Phase who received at least one dose of study medication in the Treatment Phase and had at least one post-dose safety assessment in the Treatment Phase.

- ***Efficacy Population:*** All enrolled subjects who received at least 30 days of study medication in the Treatment Phase, who had adequate data to assess the change from baseline of the efficacy parameters and who had no protocol deviations that could affect the efficacy parameters.

- ***Dose-Optimization Safety Population:*** All enrolled subjects in the Dose Optimization Phase ("New Subjects") who received at least one dose of study medication in the Dose Optimization Phase and had at least one post-dose safety assessment in the Dose Optimization Phase.

15.3. Statistical Analyses

15.3.1. General Approach

The primary focus of the statistical analyses are the safety assessments during the Treatment Phase. The secondary focus of the statistical analyses is the efficacy during the Treatment Phase. The safety and efficacy parameters during the Dose Optimization Phase (for new subjects only) will be summarized descriptively. The efficacy results will be judged with caution since this study is open label and has no control group.

Analysis Populations: All baseline analyses will be performed using the *Treatment-Phase Safety Population*. The primary safety analysis (during the Treatment Phase) will be performed using the *Treatment-Phase Safety Population*. The efficacy analyses and sleep behavior (CSHQ) across the Treatment Phase will use the *Efficacy Population*. Data from the Dose Optimization Phase (*Dose-Optimization Safety Population*) will be summarized descriptively.

Descriptive Statistics: For descriptive statistics, the following will be reported:

- Continuous data: n, mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum.
- Categorical data: n/N, percentage of total per arm and 95% confidence interval per category.

15.3.2. Attrition

The number of subjects enrolled and the number of subjects remaining in the study by month will be reported. The number of subjects who withdraw early from the study will be tabulated with the reason for early withdrawal. The main reasons overall for early withdrawal will be determined. For each main reason for early withdrawal, an assessment will be made when in the course of treatment most subjects withdrew early. Baseline variables and dose of study drug will be compared between subjects who withdrew early and subjects who completed the study.

15.3.3. Drug Exposure and Dosing Pattern

The mean daily dose of KP415 (mg), the mean daily dose of KP415 by body weight (mg/kg), and the mean daily dose of KP415 by body surface area (mg/m^2) will be calculated by month, and will be compared over time (percent change from starting dose in the Treatment Phase) to explore dose changes over the course of the study. The number of subjects who did not take study drug for any continuous period of ≥7, ≥14, ≥21, and ≥28 days in the Treatment Phase will be counted and

reported.

15.3.4. Primary Endpoint Analysis (Safety in the Treatment Phase)

The primary safety analysis will be conducted on the ***Treatment-Phase Safety Population***. The safety assessment will be based on adverse events, physical examinations, vital signs, height, weight, and BMI, ECG parameters, clinical laboratory tests and C-SSRS scores. The baseline for the safety parameters will be measured at Visit 1A and 1B.

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with new onset during the study between the initiation of study drug and 5 days after the last dose of study drug will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

TEAEs will be summarized by system organ class and preferred term, overall and by average dose. This will include overall incidence rates (regardless of severity and relationship to study drug) and incidence rates for moderate or severe adverse events. A summary of serious adverse events and adverse events leading to early discontinuation from the study will be summarized by average dose.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics overall and by average dose. Those subjects with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings. See **Section 16** for more information on safety data.

15.3.5. Secondary Endpoint Analyses (Efficacy and CSHQ in the Treatment Phase)

Changes in ADHD-RS-5, CGI-S and CSHQ will be analyzed in the *Efficacy Population*. The baseline for ADHD-RS-5, CGI-S and CSHQ will be measured at Visit 5 for roll-over subjects and at Visit 2 for new subjects.

15.3.6. Descriptive Analyses (Safety and Efficacy in the Dose Optimization Phase)

For new subjects only, the safety and efficacy parameters during the Dose Optimization Phase (*Dose-Optimization Safety Population*, from Screening to Visit 5) will be summarized descriptively. The baseline will be measured at Screening or at Visit 2 (before the first dose in the Dose Optimization Phase).

15.3.7. Abuse Potential Safety Analyses

In accordance with the 2017 FDA Guidance for Industry, Assessment of Abuse Potential of Drugs, the following analyses will be performed in the Treatment Phase:

- Systematic categorization and tabulation of AEs that are abuse potential-related, using the MedDRA Preferred Terms, including euphoria-related terms, terms of altered attention, cognition and mood, and dissociative/psychotic terms (FDA Guidance 2017, Sellers and Romach 2017). An analysis by dose, age, and gender; and by case, in order to understand the incident that led to the AEs, establish the time at which AEs appear following drug administration, the duration of the AEs, and which AEs overlap temporally.

- Analysis of subject's study drug accountability assessments that may provide information about the incidence of signals suggestive of abuse, such as substance use disorders, overdose, drug diversion or drug loss.

15.3.8. Baseline Descriptive Statistics

The key baseline characteristics (see the Statistical Analysis Plan (SAP) for list of baseline characteristics) will summarized descriptively.

15.3.9. Planned Interim Analysis

An interim analysis of the safety data will be conducted after approximately all subjects remaining in the study have completed 180 days (approximately 6 months) of treatment (Visit 11). The focus of the interim analysis are the safety assessments (primary endpoints, See **Section 15.3.5**) during the first 6 months of treatment in the Treatment Phase. The safety data will be analyzed with the same statistical methods as planned for the main analysis after completion of the study. The results from the interim safety analysis will be used to determine whether the study can be stopped (see **Section 8.6** for the stopping rules). All other endpoints (including the secondary endpoints) and assessments will also be analyzed as part of the interim analysis.

15.3.10. Subgroup Analyses

Subgroup analyses will include safety, efficacy and CSHQ endpoints by study site, dose (including cumulative dose), duration of treatment, previous stimulant exposure, age, gender, and race. Subgroup analyses will focus on the Treatment Phase. Subgroup analyses will be described in the SAP.

15.3.11. Tabulation of Individual Participant Data

All data will be listed. Listings will be sorted in the following order: treatment, subject ID, parameter (where applicable), and visit (where applicable). For TEAEs, a listing with date and type of each subject's TEAE will be provided. Details will be outlined in the SAP.

15.3.12. Exploratory Analyses

Exploratory analyses will be described in the SAP.

16. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

16.1. Adverse Events

16.1.1. Recording and Monitoring of Adverse Events

For the purpose of this clinical trial, all Adverse Events will be recorded and monitored for all enrolled subjects from the moment they receive the dose of study drug until they complete the study at the EOS (the Follow-Up visit or the Early Termination Visit).

16.1.2. Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient eCRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

16.1.3. AE Grading

Adverse Events shall be graded with regard to severity according to criteria defined in the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activity of Daily Living (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

16.1.4. AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following:

1. Definitely - Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

2. Probably - An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.

3. Possibly - An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.

4. Unrelated - An event that can be determined with certainty to have no relationship to the study drug.

16.2. Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Note that AEs of Grade 3 due to hospitalization or prolongation of a hospitalization, and Grade 4 and Grade 5 per CTCAE grading criteria are classified as SAEs.

16.2.1. Serious Adverse Event Reporting

Within 24 hours after a SAE detection, observation, or report of occurrence (regardless of the

relationship to test article), the investigator/qualified designee will complete a paper SAE/Overdosage report form with required information regarding the SAE and submit the completed form to Premier Research Pharmacovigilance. The data will also be entered into the appropriate module of the EDC as soon as possible after the paper form is sent to Premier Research Pharmacovigilance.

The site is to report SAEs in the EDC and at the same time report via SAE report paper form to the below contact info:

Premier Research Pharmacovigilance email address:
GlobalPV-US@premier-research.com
Fax Number: 215-972-8765

These SAE reports must contain the following information:

1. Study name/number
2. Study Drug
3. Investigator details (name, phone, fax, e-mail)
4. Subject Number
5. Subject Demographics
6. Clinical Event
7. Description
    a. Date of onset
    b. Treatment (drug, dose, dosage form)
    c. AE Relationship to study drug
    d. Action taken regarding study drug in direct relationship to the AE
    e. Criteria for "Serious" applicable to the AE
8. Cause of death (whether or not the death was related to study drug)
9. Autopsy findings (if available)

Any SAE that occurs during the study should be recorded by each clinical site, and reported to the Sponsor or designee.

SAEs considered definitely, probably, or possibly related to study drug shall also be classified by Sponsor as being "expected" or "unexpected." An unexpected event is one that is not listed in the investigator's brochure (KP415).

The person responsible for the study shall ensure the study has been carried out in accordance with local pharmacovigilance regulations.

All serious events reporting by Sponsor will adhere to 21 CFR 312.32 for IND drugs (7-day or 15-day alerts). Unexpected fatal or life-threatening SAEs considered related to the study drug should be reported to the FDA by Sponsor with an IND Safety report within 7 days. The Institutional Review Board (IRB) will be notified of the alert reports per FDA regulations.

16.3. Adverse Event Treatment and Follow-Up

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the electronic Case Report Form (eCRF). Treatment may be rendered on site under the direction of the Investigator as appropriate. Events requiring diagnostic evaluation or treatment beyond the scope of what is available and appropriate within the clinical research unit shall be referred in a timely basis to other care providers. Records of diagnostic and therapeutic interventions shall be requested in compliance with HIPAA requirements, and those received shall be retained in the subject's file.

For SAEs that occur during the study, the assessment, treatment, and follow up shall be performed for up to at least 30 days after last dose for events considered definitely, probably, or possibly related to study drug, and continued until resolved or clinically stable.

16.4. Overdosage

For the purposes of this clinical trial, overdosage is defined as the administration of a supratherapeutic dose, a daily dose of study drug larger than the highest dose used in the study, i.e., >40 mg KP415 product. Within 24 hours after overdosage detection the Investigator or designee will complete a paper SAE/Overdosage report form and submit it to Premier Research Pharmacovigilance (see contact information in **Section 16.2.1**). Premier Research will notify the sponsor before the end of the next business day after receipt of notification from the site. If the overdosage has an associated AE or SAE, the site is to report and document the event as listed in this protocol (see **Section 16.1** for AEs, and **Section 16.2** for SAEs).

Known signs and symptoms after acute overdosage of d-MPH, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, include vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes (Concerta® Extended Release Package Insert 2008, Focalin® Package Insert 2017, Focalin® XR Package Insert 2015, Ritalin® and Ritalin-SR® Package Insert 2015). Rhabdomyolysis has also been reported (Ritalin® and Ritalin-SR® Package Insert 2015).

Notifications of known incidences of subjects taking more than one capsule of study drug per day (irrespective of the dose size), which is considered misuse, will be provided by each study site to the Sponsor or designee.

17. PREGNANCY

If applicable (**see Section 13.1**), females with a positive pregnancy test will terminate the study early. Within 24 hours of becoming aware of pregnancy, the Investigator or designee will complete a paper pregnancy data collection form to be provided to Premier Research (see contact information

in **Section 16.2.1**). Additionally, the Investigator or designee will provide the paper pregnancy data collection form to the IRB within a time frame after the incident identification as required by the IRB. Premier Research will notify the sponsor before the end of the next business day after receipt of notification from the site.

The pregnancy must be followed up until completion of the pregnancy in order to determine the fetal outcome. Any birth defects will be reported as SAEs. Every infant must be followed for 2 months after delivery.

Pregnancy will not be considered an AE or SAE; any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or SAE. The site is to report and document AEs and SAEs as listed in this protocol (see **Section 16.1** for AEs, and **Section 16.2** for SAEs).

18. PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, Investigator, or Sponsor fails to adhere to significant protocol requirements that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare. Examples of protocol violations may include the following:

1. Inadequate or delinquent Informed Consent
2. Inclusion/exclusion criteria not met
3. Unreported serious adverse events
4. Multiple visits missed or outside permissible windows
5. Materially inadequate record keeping
6. Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
7. Subject repeated non-compliance with study requirements

It is the Investigator’s responsibility to report to the IRB of any Protocol Violation(s) according to the IRBs policy. Copy of the IRB submission will be filed in the site’s regulatory binder and in the Sponsor’s files.

19. DATA MANAGEMENT AND RECORD KEEPING

19.1. Data Management

Data will be recorded at the site on eCRFs. All entries on a eCRF are ultimately the responsibility of the Site Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed and dated. An eCRF must be completed for each participant for whom parental permission was obtained and who has given written or verbal assent. The eCRFs and source documents must be made available to the Sponsor and/or its representatives.

19.2. Record Keeping

The Investigators must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to, protocol, eCRFs, AE reports, subject source data (including records of subjects, subject visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, and monitor visit logs.

The Investigators should maintain the trial documents as required by the applicable regulations, and should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept at the clinical site until written authorization is obtained from the Sponsor.

19.3. Access to Source Data/Documents

The Investigators agree that the Sponsor, their representatives, the IRB, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

20. QUALITY CONTROL AND QUALITY ASSURANCE

By signing the protocol, the Institution and the Sponsor agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted, and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice. (GCP), ICH and other applicable regulations.

21. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In this study, the 2008 version of the Declaration of Helsinki will be adhered to. It can be found on the website of The World Medical Association: http://www.wma.net/en/30publications/10policies/b3/17c.pdf

22. INSURANCE

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Site Investigators and the other collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the

IRB according to regulatory requirements.

23. COMPLETION OF STUDY

The end of the study will be determined by the stopping rules of the study (see **Section 8.6**). The IRB will be notified about the end of the study according to regulatory requirements.

24. STUDY ADMINISTRATIVE INFORMATION

24.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the Investigator by the Sponsor. All substantial protocol amendments will undergo the same review and approval process as the original protocol and may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB according to all relevant regulatory requirements.

A protocol amendment is considered to be a substantial amendment if it is likely to affect the safety, physical, or mental integrity of subjects in the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any Investigational Medicinal Product used in the study.

Any other minor changes to the protocol not considered to be substantial amendments will not need prior approval of the IRB and will be communicated to the Investigator by the Sponsor.

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Appendix A: Instructions for Oral Administration of Study Drug

- **Instructions for taking study drug as a whole capsule**

1. Swallow capsule whole with a cup of water. The capsule needs to be swallowed whole (without crushing, cutting, crushing, chewing, opening, or dissolving). Do not swallow the capsule without water.
2. Take more sips of water as needed, up to approximately 8 ounces (240 mL) of water in total.

- **Instructions for taking study drug with applesauce:**

1. Place approximately 1-2 tablespoons (~15-30 mL) of applesauce into a clean cup.
2. Carefully open the capsule and sprinkle the powder onto the applesauce. Discard the capsule shell in the garbage.
3. Swallow the applesauce with study drug right away. Do not save the applesauce with study drug for later use.
4. To make sure that the entire dose is taken, add more water to the cup, swirl and swallow the water right away.
5. Take more sips of water as needed, up to approximately 7 ounces (210 mL) of water in total.

- **Instructions for taking study drug with water:**

1. Place approximately 1-2 tablespoons (~15-30 mL) of water into a clean cup.
2. Carefully open the capsule and empty the powder into the cup of water. Discard the capsule shell in the garbage.
3. Gently swirl the container of water with study drug.
4. Swallow the water with study drug right away. Do not save the water with study drug for later use.
5. To make sure that the entire dose is taken, add more water to the cup, swirl and swallow the water right away.
6. Take more sips of water as needed, up to approximately 7 ounces (210 mL) of water in total.