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

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Sponsor & Principal Investigator Approval / Signature Page

Protocol Number	KP415.E01
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Investigational Product	KP415
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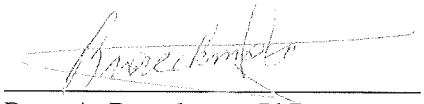
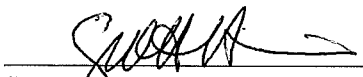
Study Phase	Phase 3
Sponsor	KemPharm, Inc. 1180 Celebration Blvd, Suite 103, Celebration, FL 34747 Phone: 321-939-3416
Academic Research Institution (ARO)	Duke Clinical Research Institution (DCRI) 2400 Pratt Street, Durham, NC 27705 Phone: 919-668-8700
Principal Investigator	Scott H Kollins, PhD Professor, Psychiatry and Behavioral Sciences Director, Duke ADHD Program 2608 Erwin Road Lakeview Pavilion, Durham, NC 27705 Phone: 919-681-0014 Scott.Kollins@duke.edu
Medical Monitor	Linmarie Sikich, MD, MA Associate Professor of Psychiatry & Behavioral Sciences 2608 Erwin Road, Suite 300 Durham, NC 27705 Office: 919-681-1032 linmarie.sikich@duke.edu



Rene A. Braeckman, PhD
Vice President of Clinical Development, KemPharm, Inc.

April 10, 2018
Date



Scott H Kollins, PhD
Principal Investigator, Duke Clinical Research Institution (DCRI)
Professor in Psychiatry and Behavioral Sciences, Duke University

4/19/18
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
ARO	Academic Research Institution
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
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
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
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

LLN	Lower Limit of Normal
LS	Least-square
MedDRA	Medical Dictionary of Regulatory Activities
MAO	Monoamine Oxidase
MAR	Missing at Random
MCID	Minimum Clinically Important Difference
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MMRM	Mixed-Effect Model Repeated Measure model
MPH	Methylphenidate
NCE	New Chemical Entity
NMAR	Not Missing at Random
ODD	Oppositional Defiant Disorder
OTC	Over the Counter
PD	Pharmacodynamic
PERMP	Permanent Product Measure of Performance
PERMP-A	Permanent Product Measure of Performance-Attempted
PERMP-C	Permanent Product Measure of Performance-Correct
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q1	25th Percentile (1st Quartile)
Q3	75th Percentile (3rd 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 Fridericias's formula
RS	Randomized Safety
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale
SKAMP-A	SKAMP-Attention
SKAMP-C	SKAMP-Combined
SKAMP-D	SKAMP-Deportment
SOE	Schedule of Events
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SW	Shapiro-Wilk
$T_{1/2}$	Apparent plasma terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WREMB-R	Weekly Rating of Evening and Morning Behavior - Revised
T_{max}	Time to achieve the maximum observed plasma concentration

PROTOCOL SYNOPSIS

TITLE	A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled, Parallel Efficacy Laboratory Classroom Study with KP415 in Children with Attention-Deficit/Hyperactivity Disorder
SPONSOR	KemPharm, Inc.
PROTOCOL NUMBER	KP415.E01
INVESTIGATIONAL PRODUCT	KP415 (a prodrug of d-methylphenidate, 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	5 sites in the United States of America
STUDY DESIGN	The study is a multicenter, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy laboratory classroom study with KP415 in children with Attention-Deficit/Hyperactivity Disorder (ADHD). The study will consist of a Screening Period, an Open-Label Dose Optimization Phase, a Double-Blind Treatment Phase and a Follow-Up Visit, as follows: • **Screening Period:** Subjects will undergo a screening period up to 49 days prior to entering into the Open-Label Dose Optimization Phase. • **Open-Label Dose Optimization Phase:** During the Dose Optimization Phase, subjects will be titrated to doses of 20, 30 or 40 mg KP415 based on tolerability and best individual dose-response in the opinion of the Investigator. • **Double-Blind Treatment Phase:** Eligible subjects will be randomized to receive single daily doses of KP415 or Placebo for 7 days according to a randomization schedule. The dose of KP415 given in the Treatment Phase will be the same as the optimized dose of KP415 at the end of the Dose Optimization Phase. All subjects will receive their assigned treatment daily for 7 days. The dose will be the same at each day of the Treatment Period. Efficacy and safety assessments will be performed after the last

	dose of the Treatment Period. • **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.
PRIMARY OBJECTIVE	To determine the efficacy of KP415 compared to placebo in treating children 6-12 years old with ADHD in a laboratory classroom setting.
SECONDARY OBJECTIVES	• To determine the onset and duration of the clinical effect of KP415 in treating ADHD in children 6-12 years old in a laboratory classroom setting. • To determine the safety and tolerability of KP415 compared to placebo in treating children 6-12 years old with ADHD in a laboratory classroom setting.
NUMBER OF SUBJECTS	An appropriate number of subjects will enter the Screening Period to enroll approximately 176 subjects in the Open-Label Dose Optimization Phase, and to randomize approximately 140 subjects in the Double-Blind Treatment Phase, with the intention to complete with approximately 126 subjects. Subjects who terminate early in the Treatment Phase will not be replaced.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria (at Screening, 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 (Day 0). 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). 8. Subject must have a score of at least 3 (mildly ill) on the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale. 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 (Day 0), and abstain from taking these to the end of the Follow-Up Visit or Early Termination; and wash out non-stimulant ADHD medications from 21 days prior to the start of the Dose Optimization Phase (Day 0), 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 (DuPaul et al. 2016) of at least 28 at Visit 2 (Day 0). For subjects requiring washout of ADHD medications, this criterion refers to a score following washout. 11. Subjects need to be able to perform at least the basic level of problems on the PERMP, based on a calibration assessment (Placement PERMP) performed at Visit 2 (Day 0). 12. 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 (for example, Conners 3-P and WREMB-R), the caregiver will need to agree to the applicable procedures and visits. 13. 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. 14. Subject must be able to swallow size 3 capsules as demonstrated by easily swallowing a size 3 capsule at Screening. **Exclusion Criteria (at Screening, except when noted otherwise)** 1. If female, must not be pregnant or breastfeeding, and if of childbearing potential, must have a negative serum pregnancy test at Screening. 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 14.8. 2. 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. 3. 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. 4. 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. 5. 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. 6. 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. Participants with school phobia or separation anxiety will not be eligible. 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. 7. Subject has any history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at Screening or at any time before the last dose of study drug.

	8. 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. 9. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant. Screening site ECGs will be centrally over-read, and eligibility will be determined by the Investigator based on the results of the over-read report. 10. Subject has a history of, or currently has a malignancy, except for non-melanomatous skin cancer. 11. 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. 12. Subjects with a history of substance abuse or treatment (including alcohol) within 1 year prior to Screening. 13. 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.

	14. Subject has a positive urine methylphenidate screen at the start of the Dose Optimization Phase (Day 0, Visit 2). 15. Subject who has initiated Cognitive Behavioral Therapy (CBT) for the treatment of ADHD less than 1 month prior to Screening (subjects on stable CBT will be allowed), has initiated behavioral therapy (including school based interventions) less than 1 month prior to Screening, or is receiving behavioral therapy and in the opinion of the Investigator will not be able to follow a stable routine for the duration of the study. Unavoidable changes in school-based interventions that occur during study participation will not be exclusionary, but should be documented by the Investigator, to the extent possible. 16. Subject has participated in a classroom study within 6 months prior to the start of Screening, or 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. 17. 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. 18. Subjects with demonstrated lack of response or intolerance to adequate dose and duration of treatment with methylphenidate products. Judgment of adequate dose and duration is at the discretion of the Investigator. 19. Subjects are using or planning to use prohibited drugs during the trial as specified in the protocol. 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 has any food allergies or dietary restrictions that are determined by the Investigator as too severe to be easily accommodated for during the study. 23. Subject was home-schooled within 12 months prior to Screening. 24. 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. 25. 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. 26. Subject's parent/legal guardian is an investigational site staff member or a relative of an investigational site staff member. 27. Subjects with a family member living in the same household participating in another ADHD clinical trial during the period of Screening through the Follow-Up Visit will be excluded. Subjects with a family member living in the same household participating in the current clinical trial during the administration of study drug (Visits 2 to 6) will be excluded. Different subjects from the same family are allowed in this trial if they are in different cohorts, and there is no overlap in time from Visit 2 to Visit 6. 28. 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)** Subjects will need to meet the following additional eligibility criteria at the end of the Dose Optimization Phase in order to enter into the Double-Blind Treatment Phase: 1. A reduction of ≥30% reduction of ADHD-RS-5 from baseline (Day 0) during the Open-Label Dose Optimization Phase. 2. A CGI-I score of 1 or 2 points (“Very Much Improved” or “Much Improved”) at the end of the Open-Label Dose Optimization Phase. 3. Acceptable tolerability of the optimized KP415 dose experienced during the Dose Optimization Phase. These assessments will be made based on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5). **Rescreening** Subjects who are screened outside the screening window may be rescreened for participation in a later cohort. 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 in another cohort of the study (and will

<table>
<tr><td></td><td>not be rescreened).</td></tr>
<tr><td>TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION</td><td>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.
<table>
<tr><th>Total d-MPH dose [1] (mg)</th><th>d-MPH [2] (mg)</th><th>KP415 Prodrug [3] (mg)</th></tr>
<tr><td>20</td><td>6</td><td>28 (14)</td></tr>
<tr><td>30</td><td>9</td><td>42 (21)</td></tr>
<tr><td>40</td><td>12</td><td>56 (28)</td></tr>
</table>
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.

In the Open-Label Dose Optimization Phase, 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. At Visits 4 and 5, study drug will be administered at the school site by study staff on the morning of the abbreviated laboratory classroom days. Two days before Visit 5, subjects must not take study drug (this is important for obtaining a baseline of the SKAMP/PERMP scores). On the other days of the Dose Optimization Phase, the medication will be taken in the morning at home. The dose taken at the school site at Visit 5 will be the last dose of unblinded study drug.

In the Double-Blind Treatment Phase, the following treatments will be administered:
- Treatment A: one KP415 capsule (test product) once daily for 7 days.
- Treatment B: one matching placebo capsule once daily for 7 days.

The daily dose of KP415 in the Treatment Phase will be same</td></tr>
</table>

	as the optimal dose of KP415 at the end of the Dose Optimization Phase, either 20, 30 or 40 mg KP415, or matching placebo. Blinded study medications of each treatment will be administered from Sunday (the day after Visit 5) to Saturday (Visit 6). On Saturday (Visit 6), the blinded doses of study drug will be administered at the school site by study staff on the morning of the laboratory classroom day. On the other days of the Treatment Phase, the medication will be taken in the morning at home. All study drugs will be given orally with 240 mL water. Additional water may be given if needed for both treatments.
LABORATORY CLASSROOM SESSIONS	At Visit 4 and Visit 5, each subject will complete abbreviated practice laboratory classroom sessions with 4 SKAMP/PERMP assessments designed to mirror the pre-dose to 2-hour post-dose period of the full-length laboratory classroom session of Visit 6. The pre-dose assessment (after 2 days of no drug) at Visit 5 will be recorded as the baseline for the SKAMP and PERMP. At Visit 6, subjects will complete a full-length laboratory classroom session that is designed to model a typical school day plus after-school activity totaling up to 13 hours after the 7th and last dose of KP415 or Placebo in the Double-Blind Treatment Phase.
ADHD SEVERITY/EFFICACY EVALUATION CRITERIA	The following scales will be used during the Open-Label Dose Optimization Phase to globally assess the changes in ADHD severity from week to week: • ADHD-Rating Scale-5 (ADHD-RS-5) The ADHD-RS-5 is an 18-item scale 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 scored from 1 (very much improved) to 7 (very much worse). The following scale will be used to assess the effect ofKP415 during the Open-Label Dose Optimization Phase and the efficacy of KP415 versus placebo during the Double-Blind Treatment Phase: • Conners 3rd Edition-Parent (Conners 3-P). The Conners 3-P (short form) is a 43-item parent/guardian/caregiver report that provides evaluation of inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, and peer relationships. The parent/guardian/caregiver will assess changes in ADHD symptoms via the Conners 3-P questionnaire at baseline (Visit 2, Day 0) and at each visit during the Dose-Optimization and the Treatment Phase. • Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) Scale: The 11-item WREMB-R questionnaire is a parent-rated questionnaire that was developed to assess behaviors for their severity during the morning hours (3 items) and evening hours (8 items) (Carlson 2007). The possible score for each item ranges from 0 (no difficulty) to 3 (a lot of difficulty). The Investigator or designee will obtain the scores for the WREMB-R questionnaire by interviewing the parent/guardian/caregiver at Visits 2, 5 and 6. The assessment at Visit 2 is the baseline assessment (after washout of ADHD medications, if applicable); the assessments at Visits 5 and 6 are evaluations at the end of the Dose Optimization and Treatment Phase, respectively. The following scales will be used to assess the efficacy of KP415 versus placebo during the Double-Blind Treatment Phase: • Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale will be performed at Visit 4, Visit 5, and Visit 6. The SKAMP scale is a validated rating of classroom behaviors. It is comprised of 13 items (grouped under the subcategories of attention, deportment, quality of work, and compliance), on which subjects are rated according to a 7-point scale (0 = normal to 6 = maximal impairment) by trained study personnel

	(Swanson 1999). The SKAMP-Combined (SKAMP-C) score is obtained by summing the rating values for each of the 13 items. The SKAMP-Deportment (SKAMP-D) score is a measure of behavior and comprises of 4 items. The SKAMP-Attention (SKAMP-A) score is a measure of attention and comprises 4 items. Higher SKAMP scores signify greater impairment. The SKAMP-C score will be used in the primary efficacy endpoint. • Permanent Product Measure of Performance (PERMP) Rating Scale will be performed at Visit 4, Visit 5 and Visit 6. A Placement PERMP will be performed at Visit 2 (Day 0) to assure that subjects can complete at least the basic level of math problems and to determine the appropriate level of math to be assigned during the practice laboratory classroom day at Visit 4. Based on the practice laboratory classroom day at Visit 4, the final level of math for each subject will be determined for use in the remainder of the study (Visits 5 and 6). The PERMP is an individually calibrated five-page mathematics worksheet consisting of 400 problems. Subjects will be instructed by site staff to work at their seats and complete as many problems as possible in 10 minutes. Performance will be evaluated using two scores: The number of problems attempted (PERMP-A) and the number of problems correct (PERMP-C).
SAFETY EVALUATION CRITERIA	Adverse events, vital signs, physical examination, ECGs, clinical laboratory measurements, and C-SSRS scores will be evaluated for safety.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will participate in the study as outpatients for up to 85 days, including up to 49 days of Screening; a 21-day (±3 days) Dose Optimization Phase, a 7-day Treatment Phase, and a Follow-Up Visit (3 ±2 days after the administration of the last dose of the Treatment Phase).
MEDICATION RESTRICTIONS	Subject's meeting all eligibility requirements will be prohibited/limited to receive certain medications in the trial: • 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 (Day 0) 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 21 days prior to the start of the Dose Optimization Phase (Day 0) 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 21 days prior to the start of the Dose Optimization Phase (Day 0) 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 Dose Optimization Phase (Day 0) 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 (Day 0) and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to the start of the Day 0 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.
EFFICACY ENDPOINTS	The primary efficacy evaluation is based on SKAMP and PERMP scores at pre-dose, and at 0.5. 1, 2, 4, 8, 10, 12, and 13 hours post-dose during the full laboratory classroom day at Visit 6. The baseline SKAMP score is measured at pre-dose at Visit 5. **Primary Efficacy Variable:** • Average of the change from baseline (measured at Visit 5) of the-SKAMP-C scores collected across the

	laboratory classroom day at Visit 6. **Secondary Efficacy Variables:** • Change from baseline (measured at Visit 5) of the SKAMP-C scores measured at each time point on the laboratory classroom day at Visit 6. The serial measures at different times post-dosing will be used to determine onset and duration of the clinical effect of KP415. • Change from baseline of the scores measured at each time point and the average of the scores collected across the laboratory classroom day at Visit 6, for the following endpoints: o SKAMP-D and SKAMP-A scores o PERMP scores o PERMP-A and PERMP-C scores • WREMB-R scores (total score, and morning and evening subscore) at Baseline (Visit 2), Visit 5 and Visit 6.
SAFETY ENDPOINTS	The occurrence of Treatment-Emergent Adverse Events (TEAEs) will be assessed starting following the first dose of open-label drug (KP415), and ending with the Follow-Up Visit or Early Termination Visit. Additional safety evaluations will include physical examinations, vital signs, as well as height and weight, ECG parameters, clinical laboratory tests, and a follow-up C-SSRS administered at each study visit. AEs during the Open-Label Dose Optimization Phase and the Double-Blind Treatment Phase will be will be reported and analyzed separately.
ANALYSIS POPULATIONS	**Intent-to-Treat (ITT) Population:** All randomized subjects who receive at least one dose of double-blind study medication and have at least one SKAMP-C assessments at Visit 6. **Per-Protocol (PP) Population:** ITT subjects who received the morning dose of double-blind study medication at the laboratory test session, who have all 8 post-dose SKAMP-C assessments at Visit 6, who did not miss more than 2 days of therapy during the Double-Blind Treatment Phase, and did not use prohibited medications during the Double-Blind Treatment Phase. **Overall Safety Population:** All subjects who entered the Open-Label Dose Optimization phase and received at least one dose of open-label study medication and had at least one post-dose safety assessment.
STATISTICAL ANALYSES – TREATMENT PHASE	**Efficacy:** Primary and secondary efficacy analyses will be performed on the ITT and PP populations. Descriptive statistics for the all SKAMP and PERMP scores and subscale

	scores will be calculated for each time point on the laboratory classroom days, and for the average of the scores collected across the laboratory classroom day. The difference between treatments (KP415 vs. placebo) will be evaluated for each variable using repeated measures analyses. The treatment comparison will be conducted as a two-sided test at the 5% level of significance. Standard errors and 95% confidence intervals (CIs) will be calculated. Onset of clinical effect is defined as the earliest post-dose time point at which the difference between KP415 and Placebo is statistically significant ($p<0.05$). The duration of the treatment effect is defined as the length of the time interval, such that statistical significance was reached at each time point of this interval. Subgroup analyses will include efficacy and safety endpoints by study site, dose, age, and gender. **Safety:** The frequencies of adverse events (AEs), the results of laboratory assessments, physical examinations, vital signs, ECGs, and suicidal ideation (assessed using the C-SSRS) will be summarized descriptively (by treatment, if applicable) in the Overall Safety Population.
STUDY PROCEDURES	The study procedures are outlined in the Schedule of Events (**Section 1**).

1. SCHEDULE OF EVENTS

ASSESSMENTS	SCREENING PHASE	OPEN-LABEL DOSE OPTIMIZATION PHASE [27]							TREATMENT PHASE		ET [29] (EOS)	FOLLOW-UP (EOS)
Study Day	-49 to -1	0	1-6 (±3 Days)	7 (±3 Days)	8-13 (±3 Days)	14 (±3 Days)	15-20 (±3 Days)	21 (±3 Days)	22-27 (±3 Days)	28 [28] (±3 Days)	-	29-33 (±2 Days)
Visit Number	1	2		3		4		5		6	-	7
Parental Permission/Written or Verbal Assent	X											
ADHD Diagnosis and Confirmation [1]	X											
Placement PERMP [2]		X										
Capsule Swallowing Test [3]	X											
Inclusion/Exclusion	X	X		X		X		X				
Demographics	X											
Medical History [4]	X	X		X		X		X				X
Physical Examination [5]	X										X	X
Body Weight, Height, BMI [6]	X										X	X
Vital Signs [7]	X	X		X		X		X		X	X	X
12-Lead ECG [8]	X										X	X
Chemistry/ Hematology/Urinalysis	X										X	X
Urine Alcohol/Drugs of Abuse Screen [9]	X											
Urine MPH Screen [10]	X	X						X				
Pregnancy Test [11]	X	X						X			X	X
C-SSRS [12]	X	X		X		X		X		X	X	X
Washout ADHD Meds [13]	X											
Open-Label KP415 Dosing [14]			X	X	X	X	X	X				
Randomization [15]								X				
Double-Blind Study Drug Administration [16]									X	X		
Drug Accountability & Compliance Assessment				X		X		X		X		
Laboratory Classroom Sessions [17]						X		X		X		
ADHD-RS-5 [18]		X		X		X		X				
CGI-S [19]	X	X		X		X		X				
CGI-I [20]		X		X		X		X				
Conners 3-P [21]		X		X		X		X		X		

ASSESSMENTS	SCREEING PHASE	OPEN-LABEL DOSE OPTIMIZATION PHASE [27]							TREATMENT PHASE		ET [29] (EOS)	FOLLOW-UP (EOS)
Study Day	-49 to -1	0	1-6 (±3 Days)	7 (±3 Days)	8-13 (±3 Days)	14 (±3 Days)	15-20 (±3 Days)	21 (±3 Days)	22-27 (±3 Days)	28 [28] (±3 Days)	-	29-33 (±2 Days)
Visit Number	1	2		3		4		5		6	-	7
WREMB-R Questionnaire [22]		X						X		X		
2-day washout of open-label KP415 [23]							X					
SKAMP and PERMP [24]						X		X		X		
Adverse Events [25]			X	X	X	X	X	X	X	X	X	X
Concomitant Medications [26]	X	X		X		X		X		X	X	X

EOS = End of Study; ET = Early Termination; 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. A Placement Permanent Product Measure of Performance (PERMP) will be performed at Visit 2 (Day 0) to assure that subjects can complete at least the basic level of math problems and to determine the appropriate level of math to be assigned during the practice laboratory classroom day at Visit 4. Subjects must be able to perform at least the basic level of problems to enroll in the trial.
3. Capsule Swallowing Test: Subjects will take a size 3 capsule with 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.
4. Medical History: A complete medical history including chronic conditions, relevant surgical procedures (with start date), history of alcohol and recreational drug use.
5. Complete physical examination at Screening, and at ET (if possible) or Follow-Up.
6. All physical examinations will include the measurement of body weight. Height and BMI at Screening only.
7. 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. On the full laboratory classroom day (Day 28 ±3 days, Visit 6), vital signs will be collected at any time before dosing.
8. 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). ECGs will be obtained at Screening, and at Early Termination or Follow-Up.
9. 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 1). 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. These medications must be washed out by Day 0.

10. Urine Screen for Methylphenidate (MPH): Urine samples will be tested for MPH at Screening (Visit 1), at Visit 2, and before administration of study drug at Visit 5. 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 may test positive for MPH. Since all ADHD medications must be washed out by Day 0, they must test negative on Day 0 (Visit 2) for subjects to be eligible to continue in the study.
11. 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, Visit 5 and at Follow-Up or Early Termination. A positive pregnancy test at Screening, or before the last dose of study drug will exclude a subject from further participation in the study.
12. 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 visits of the Dose Optimization Phase (Visits 2, 3, 4 and 5), at Visit 6, and at Follow-Up or Early Termination. Subjects who have any history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at any time before the last dose of study drug, will be excluded from further participation in the study.
13. Subjects must wash out ADHD medications prior to Day 0 (Visit 2). 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 (Day 0) 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 21 days prior to the start of the Dose Optimization Phase (Day 0) 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 12.1** of the protocol.
14. 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 ±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, the Investigator will evaluate the eligibility criteria for continuation into the subsequent Double-Blind Treatment Phase. For subjects eligible for the Treatment Phase, the optimal daily KP415 dose will be used as the daily KP415 dose (or matching placebo) in the Treatment Phase.
15. Randomization: Subjects able to tolerate at least 20 mg/day of KP415 during the Dose Optimization Phase and with an adequate dose-response will be randomized on a 1:1 basis to a treatment of KP415 (Treatment A) or placebo (Treatment B). The appropriate blinded study drug to be taken at home once-a-day in the morning on each of the following 6 days (Days 22-27 ±3 days) will be dispensed to the subjects.
16. Study Drug Administration (Double-Blind Treatment Phase): Subjects on an optimized KP415 dose of 20, 30, and 40 mg at the end of the Dose Optimization Phase will receive 20, 30, and 40 mg,

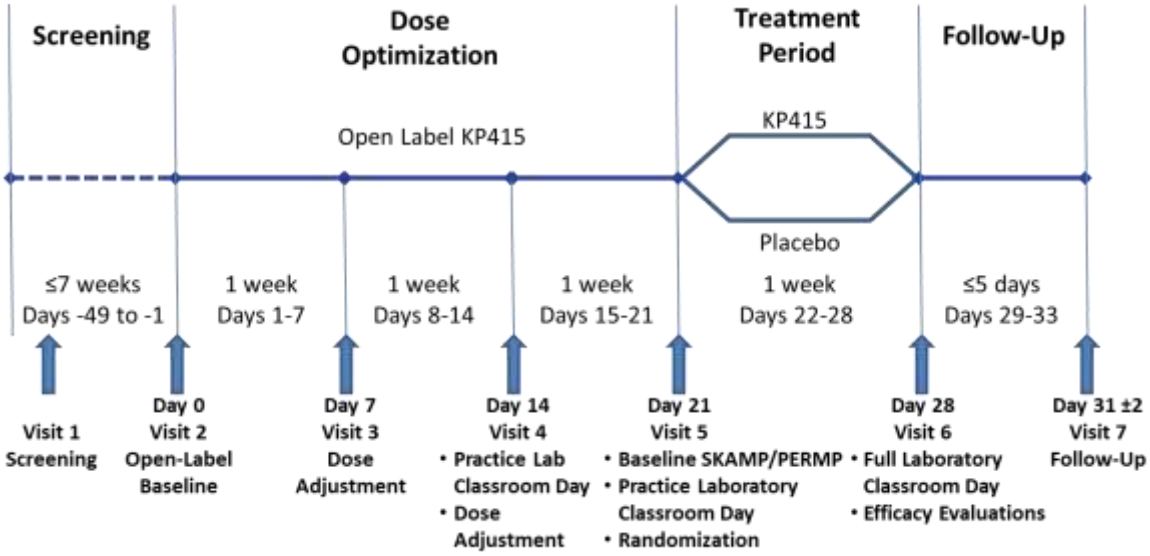
respectively, of KP415 capsules or matching placebo capsules once-per-day for 7 days in the morning. No adjustment of the dose of study drug will be permitted. All study drugs will be given orally. On Days 22-27 ±3 days, subjects will take study drug at home under supervision of their parent or legal guardian. The final dose of study drug will be administered on the 7th day of the Double-Blind Treatment Phase (Day 28 ±3 days; Visit 6) at the laboratory school by study staff. The capsule with study drug will be swallowed with approximately 240 mL of water. Additional water may be given if needed, and the volume of additional water will be recorded.

17. Laboratory Classroom Days: At Visit 4 and Visit 5, each subject will complete abbreviated practice laboratory classroom sessions with 4 SKAMP/PERMP assessments designed to mirror the pre-dose to 2-hour post-dose period of the full-length laboratory classroom session of Visit 6. At Visit 6, subjects will complete a full-length laboratory classroom session that is designed to model a typical school day plus after-school activity totaling up to 13 hours after the 7th and last dose of KP415 or Placebo in the Double-Blind Treatment Phase.
18. ADHD-Rating Scale-5 (ADHD-RS-5) assessment: 1 assessment at the indicated visits.
19. Clinical Global Impressions–Severity (CGI-S) scale assessment: 1 assessment at the indicated visits.
20. Clinical Global Impressions–Improvement (CGI-I) scale assessment: 1 assessment at the indicated visits. CGI-I score of 1 or 2 points ("Very Much Improved" or "Much Improved") at the end of the Open-Label Dose Optimization Phase.
21. Conners 3rd Edition-Parent (Conners 3-P): The parent/guardian/caregiver will assess changes in ADHD symptoms via the Conners 3-P questionnaire at baseline (Visit 2) and at each visit during the Dose-Optimization Phase and the Treatment Phase.
22. Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) Scale: The Investigator or designee will obtain the scores for the WREMB-R questionnaire by interviewing the parent/guardian/caregiver at Visits 2, 5 and 6.
23. Washout of open-label KP415 for 2 days before Visit 5: No study drug will be administered during the 2 days before the baseline SKAMP and PERMP assessment at pre-dose of Visit 5. The 2 days of NO drug (2 skipped doses) entail the doses on the day before Visit 5 and the day before that.
24. Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) and Permanent Product Measure of Performance (PERMP) score assessments:
    - Visit 4 (Day 14 ±3 days): Abbreviated practice laboratory classroom session with SKAMP/PERMP assessments at pre-dose and at 0.5, 1, and 2 hours post-dose. At this visit, the final level of math for each subject will be determined for use in the remainder of the study (Visits 5 and 6).
    - Visit 5 (Day 21 ±3 days): Abbreviated practice laboratory classroom session with SKAMP/PERMP assessments at pre-dose and at 0.5, 1, and 2 hours post-dose. The pre-dose assessment (after 2 days of no drug) will be recorded as the baseline for the SKAMP and PERMP.
    - Visit 6 (Day 28 ±3 days): Full laboratory classroom day with SKAMP/PERMP assessments at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12 and 13 hours post-dose.

    At Visits 4, 5, and 6, subjects will be administered unblinded study drug at the study site.
25. 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.
26. 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.
27. 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).
28. The end of the Treatment Phase is on Day 28 ±3 days (Visit 6), after all post-dosing procedures including all laboratory classroom assessments are completed.
29. 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 or Treatment Phase, do not need to be repeated.

2. STUDY DESIGN SCHEMATIC



Note: The study days listed for Visits 3, 4, and 5 may deviate with ±3 days for individual subjects such that the total duration of the Dose Optimization Phase is 21 days ±3 days (duration ranging from 18 to 24 days). Any deviation of the targeted 21-day Dose Optimization Phase will be carried over into the actual days for the subsequent visits: Visit 6 at Day 28 ±3 days, and Visit 7 at days ranging from Day 29 ±3 days to Day 33 ±3 days.

3. BACKGROUND

3.1. 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 et al. 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.

3.2. Laboratory Classroom Studies

Methylphenidate has been an important treatment option for ADHD for many years, including for the treatment of children with ADHD. Patients with ADHD are titrated to their optimal dose of methylphenidate based on assessments of efficacy and tolerability. Clinical studies with school-age children with ADHD in a laboratory classroom setting (Lawrence et al. 2004; Swanson et al. 2004) are ideally suited for the assessment of stimulant medications and has been previously employed in studies of methylphenidate (Swanson et al. 2003, 2004) and amphetamine medications (McCracken et al. 2003; Swanson et al. 1998). Analog classroom studies facilitate repeated observational measures of attention, deportment, and cognitive performance, and assessment of time course effects in a controlled setting (Swanson et al. 2003; Lawrence et al. 2004). The model enables investigators to collect with carefully controlled methods, documented assessments of drug effect by direct observation over multiple time points throughout the day.

4. KP415: A PRODRUG CONJUGATE

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.

5. OVERVIEW OF CLINICAL STUDIES WITH KP415

The pharmacology, metabolism and toxicology of methylphenidate are well established (Challman 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 2000). Supra-therapeutic doses have shown to cause delirium, hallucinations, bruxism (jaw-grinding), and trismus (jaw clenching) (Morton 2000).

5.1. 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. Since plasma concentrations of the inactive intact KP415 molecule were measured after oral KP415 dosing, circulating levels of prodrug may contribute to the ER profile of KP415-derived d-MPH. No l-MPH levels were detected after KP415 dosing and very low l-MPH levels were measured after Concerta® dosing.

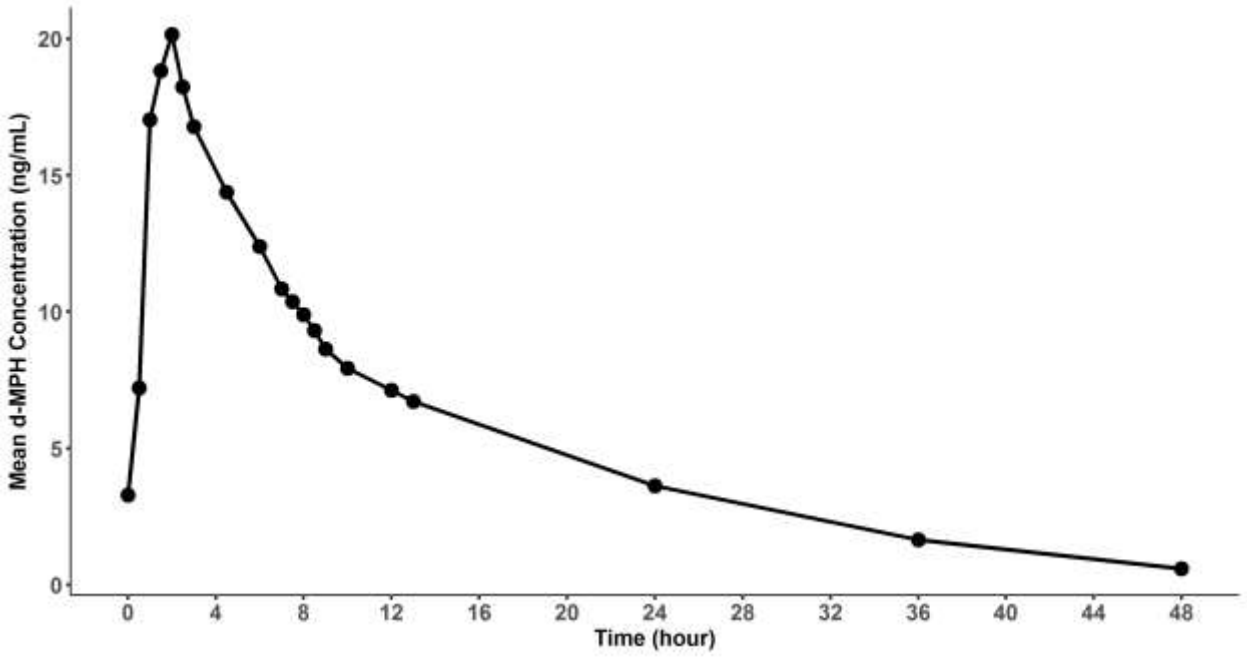
Both treatments were generally well-tolerated. There were no apparent changes in vital signs and ECG parameters between treatments. Safety laboratory values were approximately the same after the treatment phase versus those measured at Screening.

5.2. Study KP415.109

This Phase 1 open-label PK study included a treatment group wherein healthy adult volunteers were dosed 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)



6. STUDY RATIONALE

The current study will investigate the efficacy of KP415 compared to placebo and determine the onset and duration of the clinical effect of KP415 in treating children 6-12 years old with ADHD.

7. STUDY OBJECTIVES

7.1. Primary Objective

To determine the efficacy of KP415 compared to placebo in treating children 6-12 years old with ADHD in a laboratory classroom setting.

7.2. Secondary Objectives

- To determine the onset and duration of the clinical effect of KP415 in treating ADHD in children 6-12 years old in a laboratory classroom setting.
- To determine the safety and tolerability of KP415 compared to placebo in treating children 6-12 years old with ADHD in a laboratory classroom setting.

8. INVESTIGATIONAL PLAN

8.1. Study Design

The study is a multicenter, dose-optimized, double-blind, randomized, placebo-controlled, parallel efficacy laboratory classroom study with KP415 in children with Attention-Deficit/Hyperactivity Disorder (ADHD). The study will consist of a Screening Period, an Open-Label Dose Optimization Phase, a Double-Blind Treatment Phase and a Follow-Up Visit, as follows:

- **Screening Period:** Subjects will undergo a screening period up to 49 days prior to entering into the Open-Label Dose Optimization Phase.
- **Open-Label Dose Optimization Phase:** During the Dose Optimization phase, subjects will be titrated to doses of 20, 30 or 40 mg KP415 based on tolerability and best individual dose-response in the opinion of the Investigator.
- **Double-Blind Treatment Phase:** Eligible subjects will be randomized to receive single daily doses of KP415 or Placebo for 7 days according to a randomization schedule. The dose of KP415 given in the Treatment Phase will be the same as the optimized dose of KP415 at the end of the Dose Optimization Phase. All subjects will receive their assigned treatment daily for 7 days. The dose will be the same at each day of the Treatment Period. Efficacy and safety assessments will be performed after the last dose of the Treatment Period.
- **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

8.2. Study Duration

Subjects will participate in the study as outpatients for up to 85 days, including up to 49 days of Screening; a 21-day (±3 days) Dose Optimization Phase, a 7-day Treatment Phase, and a Follow-Up Visit (3 ±2 days after the administration of the last dose of the Treatment Phase).

9. SUBJECT SELECTION

9.1. Number of Subjects

An appropriate number of subjects will enter the Screening Period to enroll approximately 176 subjects in the Open-Label Dose Optimization Phase, and to randomize approximately 140 subjects in the Double-Blind Treatment Phase, with the intention to complete with approximately 126 subjects. Subjects who terminate early in the Treatment Phase will not be replaced.

9.2. Study Population

Children 6-12 years old with Attention-Deficit/Hyperactivity Disorder who meet the inclusion/exclusion criteria listed below.

9.2.1. Inclusion Criteria (at Screening, 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 (Day 0).

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).

8. Subject must have a score of at least 3 (mildly ill) on the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout (see **Section 12.1**).

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 (Day 0), and abstain from taking these to the end of the Follow-Up Visit or Early Termination; and wash out non-stimulant ADHD medications from 21 days prior to the start of the Dose Optimization Phase (Day 0), 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 (DuPaul et al. 2016) of at least 28 at Visit 2 (Day 0). For subjects requiring washout of ADHD medications, this criterion refers to a score following washout (see **Section 12.1**).

11. Subjects need to be able to perform at least the basic level of problems on the PERMP, based on a calibration assessment (Placement PERMP) performed at Visit 2 (Day 0). Based on the Placement PERMP, the level of math will be determined to be assigned during the practice laboratory classroom day at Visit 4.

12. 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 (for example, Conners 3-P and WREMB-R), the caregiver will need to agree to the applicable procedures and visits.

13. 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.

14. Subject must be able to swallow size 3 capsules as demonstrated by easily swallowing a size 3 capsule at Screening.

9.2.2. Exclusion Criteria (at Screening, 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 serum pregnancy test at Screening. 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 14.8.**

2. 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.

3. 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.

4. 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.

5. 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. 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 is not eligible for study participation.

6. 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. Participants with school phobia or separation anxiety will not be eligible. 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.

7. Subject has any history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at Screening or at any time before the last dose of study drug.

8. 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.

9. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant. Screening site ECGs will be centrally over-read, and eligibility will be determined by the Investigator based on the results of the over-read report.

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

11. 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.

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

13. 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.

14. Subject has a positive urine methylphenidate screen at the start of the Dose Optimization Phase (Day 0, Visit 2).

15. Subject who has initiated Cognitive Behavioral Therapy (CBT) for the treatment of ADHD less than 1 month prior to Screening (subjects on stable CBT will be allowed), has initiated behavioral therapy (including school based interventions) less than 1 month prior to Screening, or is receiving behavioral therapy and in the opinion of the Investigator will not be able to follow a stable routine for the duration of the study. Unavoidable changes in school-based interventions that occur during study participation

will not be exclusionary, but should be documented by the Investigator, to the extent possible.

16. Subject has participated in a classroom study within 6 months prior to the start of Screening, or 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.

17. 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.

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

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

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 has any food allergies or dietary restrictions that are determined by the Investigator as too severe to be easily accommodated for during the study.

23. Subject was home-schooled within 12 months prior to Screening.

24. 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.

25. 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.

26. Subject's parent/legal guardian is an investigational site staff member or a relative of an investigational site staff member or a relative of an investigational site staff member.

27. Subjects with a family member living in the same household participating in another ADHD clinical trial during the period of Screening through the Follow-Up Visit will be

excluded. Subjects with a family member living in the same household participating in the current clinical trial during the administration of study drug (Visits 2 to 6) will be excluded. Different subjects from the same family are allowed in this trial if they are in different cohorts, and there is no overlap in time from Visit 2 to Visit 6.

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

9.2.3. Eligibility Criteria (End of Dose Optimization Phase)

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

1. A reduction of ≥30% reduction of ADHD-RS-5 from baseline (Day 0) during the Open-Label Dose Optimization Phase.

2. A CGI-I score of 1 or 2 points ("Very Much Improved" or "Much Improved") at the end of the Open-Label Dose Optimization Phase.

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

These assessments will be made based on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5)

9.2.4. Rescreening

Subjects who are screened outside the screening window may be rescreened for participation in a later cohort. 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 in another cohort of the study (and will not be rescreened).

10. STUDY TREATMENTS

10.1. KP415 Dose Optimization

In the Open-Label Dose Optimization Phase, 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 based on tolerability and best individual dose-response in the opinion of the Investigator. At Visits 4 and 5, study drug will be administered at the school site by study staff on the morning of the abbreviated laboratory classroom days. Two days before Visit 5, subjects must not take study drug. On the other days of the Dose Optimization Phase, the medication will be taken in the morning at home. The dose taken at the school site at Visit 5 will be the last dose of unblinded study drug.

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, the Investigator will evaluate the eligibility criteria (see **Section 9.2.3**) for continuation into the subsequent Double-Blind Treatment Phase. For subjects eligible for the Treatment Phase, the optimal daily KP415 dose will be used as the daily KP415 dose (or matching placebo) in the Treatment Phase.

10.2. Study Drug Administration in the Double-Blind Treatment Phase

The following treatments will be administered in the Double-Blind Treatment Phase:

- Treatment A: one KP415 capsule (test product) once daily for 7 days.
- Treatment B: one matching placebo capsule once daily for 7 days.

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 or matching placebo.

During the Treatment Phase, blinded study medications of each treatment will be administered from Sunday (the day after Visit 5) to Saturday (Visit 6). On Saturday (Visit 6), the blinded doses of each study drug will be administered at the school site by study staff on the morning of the test laboratory classroom day. On the other days, the medication will be taken in the morning at home. Double-blind study drug will be taken orally with 240 mL water and additional water may be given if needed

10.3. Treatment Assignment/Randomization

Open-Label Dose Optimization Phase: 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.

Double-Blind Treatment Phase: Subjects able to tolerate at least 20 mg/day of KP415 and with

an adequate dose-response during the Dose Optimization Phase (see eligibility criteria in **Section 9.2.3**) will be randomized on Day 21 (Visit 5) of the Treatment Period on a 1:1 basis to a treatment of KP415 (Treatment A) or placebo (Treatment B). Randomization will be stratified by study site.

10.4. Blinding

Open-Label Dose Optimization Phase: the KP415 dose levels during the Dose Optimization Phase including the optimized KP415 dose at the end of the Dose Optimization Phase will not be blinded.

Double-Blind Treatment Phase: the treatment with study drug, either active KP415 or placebo, will be blinded during the Double-Blind Treatment Phase. Neither the subject, the Investigator, or the Sponsor will know the subject's treatment assignment.

Upon completion of the study and after the database is locked according to the Sponsor (or designee) operating procedures, the randomization codes will be provided to the statistician to unblind the study.

Emergency unblinding of patients: Under normal circumstances, the blind will not be broken until subjects have completed treatment. The blind for individual subjects can be broken before study unblinding at the request of the Investigator only if a specific emergency treatment would be dictated by knowing the treatment status of a subject. When knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the Investigator should contact the ARO's Medical Monitor (or designee). Prior to unblinding the patient's treatment assignment, the Investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). The Investigator must then contact the ARO's Medical Monitor to unblind an individual patient's treatment assignment. If the blind is broken for any reason, the Investigator must record the date and reason for breaking the blind on the appropriate electronic Case Report Form (eCRF) and source documents. If an SAE is reported, the ARO's Medical Monitor (or designee) may unblind the treatment assignment for an individual subject for expedited regulatory reporting requirements.

10.5. 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.

11. STUDY PROCEDURES

The study will consist of a Screening Visit, an Open-Label Dose Optimization Phase, a Double-Blinded Treatment Phase, and a Follow-Up Visit. 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:

11.1. Screening Procedures

Subjects will complete the screening visit (Visit 1) within 49 days of starting the Open-Label 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 capsule orally with 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.

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 a history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator 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. 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. These medications must be washed out by Day 0.

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. Since these medications must be washed out by Day 0, the methylphenidate screen must test negative on Day 0 (Visit 2) for subjects to be eligible to continue in the study.

17. Serum β-human chorionic gonadotropin (β-hCG) pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 14.8.**

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 Open-Label Dose Optimization Phase. In addition, they will be instructed with the date on which to begin wash out of any ADHD and other medications prior to Day 0 (Visit 2). See **Section 12.1** for the medications that are prohibited and their associated time frames, including the days that they are prohibited before Day 0 (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: Subjects who are screened outside the screening window may be rescreened for participation in a later cohort. 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 in another cohort of the study (and will not be rescreened).

11.2. Open-Label Dose Optimization Phase (Visit 2-5)

Subjects who meet the inclusion/exclusion criteria during Screening, will enter into the Open-Label Dose Optimization Phase (Visit 2-5). The subjects will undergo the following procedures during these visits.

11.2.1. Visit 2 (Day 0)

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. A Placement Permanent Product Measure of Performance (PERMP) will be performed to assure that subjects can complete at least the basic level of math problems and to determine the appropriate level of math to be assigned during the practice laboratory classroom day at Visit 4. Subjects must be able to perform at least the basic level of problems to enroll in the trial.

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 Columbia Suicide Severity Rating Scale (C-SSRS), "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, 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-Rating Scale-5 (ADHD-RS-5) score (DuPaul et al. 2016) 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.

7. Perform the clinician-administered Clinical Global Impressions–Severity (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.

8. Perform the Clinical Global Impressions–Improvement (CGI-I) scale assessment.

9. Perform the Conners 3-P baseline assessment. The parent/guardian/caregiver will assess the subject's ADHD symptoms using the Conners 3-P questionnaire based on the subject's functioning on the days before Visit 2 (and since washout of ADHD medications, if applicable).

10. Perform the Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) assessment. The Investigator or designee will fill in the WREMB-R questionnaire based on an interview with the parent/guardian/caregiver. The scoring will be based on the subject's morning and evening functioning on the days before Visit 2 (and after washout of ADHD medications, if applicable).

11. Urine samples will be tested for methylphenidate. If the urine test is positive methylphenidate on Day 0, the subject will be excluded from study participation.

12. Urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test at Screening will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 14.8.**

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

14. 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.

15. Provide subject with the starting dose of 30 mg KP415 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).

11.2.2. 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.

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 Columbia Suicide Severity Rating Scale (C-SSRS), "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, 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-Rating Scale-5 (ADHD-RS-5) score (DuPaul et al. 2016) assessment.

7. Perform the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale assessment.

8. Perform the Clinical Global Impressions–Improvement (CGI-I) scale assessment.

9. Perform the Conners 3-P Assessment. The parent/guardian/caregiver will assess the subject's changes in ADHD symptoms using the Conners 3-P questionnaire.

10. 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.

11. 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.

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

11.2.3. Visit 4 (Day 14 ±3 days)

If possible, study site staff will contact the parent/guardian 1 day before Visit 4 to remind them that subjects must come to Visit 4 without taking the study drug since it will be administered by study staff at Visit 4.

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 Columbia Suicide Severity Rating Scale (C-SSRS), "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator 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-Rating Scale-5 (ADHD-RS-5) score (DuPaul et al. 2016) assessment. This assessment may be obtained by phone within 48 hours before the visit.

7. Perform the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale assessment. This assessment may be obtained by phone within 48 hours before the visit.

8. Perform the Clinical Global Impressions–Improvement (CGI-I) scale assessment. This assessment may be obtained by phone within 48 hours before the visit.

9. Administer the open-label KP415 dose at the laboratory school by study staff. The capsule with study drug will be swallowed with approximately 240 mL of water. Additional water may be given if needed.

10. Each subject will complete an abbreviated practice laboratory classroom session with SKAMP and PERMP assessments at pre-dose and at 0.5, 1, and 2 hours post-dose.

11. Perform the Conners 3-P Assessment. The parent/guardian/caregiver will assess the subject's changes in ADHD symptoms using the Conners 3-P questionnaire. The questionnaire form may be provided to the parent/guardian/caregiver at the previous visit, and be filled in by the parent/guardian/caregiver before coming to this visit.

12. 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.

13. 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.

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

11.2.4. Visit 5 (Day 21 ±3 days)

Two days before Visit 5, subjects must not take any study drug (this is important for obtaining a baseline of the SKAMP/PERMP scores). At Visit 5, subjects will be administered unblinded study drug at the study site (this is the last dose of unblinded study drug). If possible, study site staff will contact the parent/guardian 3 days before Visit 5 to remind them that subjects must abstain of taking study drug on the 2 days before Visit 5, and come to Visit 5 without taking the study drug since it will be administered by study staff at Visit 5.

The following procedures will be performed at Visit 5:

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

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. Urine pregnancy test for all female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study. "Of childbearing potential" is defined in **Section 14.8.**

5. Urine samples will be tested for methylphenidate.

6. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, "Children's Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, 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.

7. Administer the open-label KP415 dose at the laboratory school by study staff. The capsule with study drug will be swallowed with approximately 240 mL of water.

Additional water may be given if needed. This dose will be the last dose of unblinded study drug in the Dose Optimization Phase.

8. Each subject will complete an abbreviated practice laboratory classroom session with SKAMP and PERMP assessments at pre-dose and at 0.5, 1, and 2 hours post-dose. The pre-dose SKAMP and PERMP assessments will be recorded as the baseline for these assessments.

9. Perform the ADHD-Rating Scale-5 (ADHD-RS-5) score (DuPaul et al. 2016) assessment. This assessment may be obtained by phone within 48 hours before the visit. This assessment will be made based on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5).

10. Perform the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale assessment. This assessment may be obtained by phone within 48 hours before the visit. This assessment will be made based on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5).

11. Perform the Clinical Global Impressions–Improvement (CGI-I) scale assessment. This assessment may be obtained by phone within 48 hours before the visit. This assessment will be made based on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5).

12. Perform the Conners 3-P Assessment. At this visit, the parent/guardian/caregiver will assess the subject's changes in ADHD symptoms using the Conners 3-P questionnaire based on the subject's functioning on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5). The questionnaire form may be provided to the parent/guardian/caregiver at the previous visit, and be filled in by the parent/guardian/caregiver before coming to this visit.

13. Perform the Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) assessment. The Investigator or designee will fill in the WREMB-R questionnaire based on an interview with the parent/guardian/caregiver. The scoring will be based on the subject's morning and evening functioning on the days before Visit 5 while still taking study drug (and NOT based on the 2 days of no study drug before Visit 5).

15. The Investigator will evaluate the eligibility criteria (see **Section 9.2.3**) for continuation into the subsequent Double-Blind Treatment Phase. For subjects eligible for the Treatment Phase, the optimal daily KP415 dose will be used as the daily KP415 dose (or matching placebo) in the Treatment Phase.

14. Randomize subjects on a 1:1 basis to a treatment of KP415 (Treatment A) or placebo

(Treatment B). The appropriate blinded study drug to be taken at home once-a-day in the morning on each of the following 6 days (Days 22-27 ±3 days) will be dispensed to the subjects.

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.

11.2.5. Unscheduled Visits

At the discretion of the Investigator, subjects may be asked to come to the clinical site for an unscheduled visit. Unscheduled visits can occur at any time during the Dose Optimization Phase, between Visits 2, 3, 4 and 5. 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 is needed.

- 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 based on the C-SSRS assessment, in the opinion of the Investigator, 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 unblinded KP415 drug:

    a. Perform the CGI-I scale assessment.
    b. Perform the Conners 3-P Assessment. The parent/guardian/caregiver will assess the subject's changes in ADHD symptoms using the Conners 3-P questionnaire.
    c. If needed, perform a KP415 dose adjustments: 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. At any day during the Dose Optimization Phase, the daily dose will be either 20, 30 or 40 mg KP415.

If a subject meets withdrawal criteria during the Unscheduled Visit, the subject will be withdrawn and Early Termination procedures will be completed (see **Section 11.4**). 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 Unscheduled Visit do not need to be repeated.

11.3. Treatment Phase: Days 22-27 & Visit 6 (Day 28)

On Days 22-27 ±3 days, subjects will take double-blind study drug at home under supervision of parent or legal guardian. Subject's parent/guardian will contact the study site for the reporting of AEs during the dosing period at home.

The final dose of double-blind study drug will be administered on the 7th day of the double-blind Treatment Phase (Day 28 ±3 days; Visit 6) at the laboratory school by study staff. On Day 28 ±3 days (Visit 6), each subject will complete a full-length laboratory classroom day with efficacy assessments at pre-dose and post-dose study drug.

The following procedures will occur on Day 28 ± 3 days (Visit 6) of the study:

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

2. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after subject has been sitting for a minimum of 3 minutes, will be collected at any time before dosing.

3. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, "Children's Since Last Visit" version. At Visit 6, if a subject has clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

4. Perform the Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) assessment. The Investigator or designee will fill in the WREMB-R questionnaire based on an interview with the parent/guardian/caregiver. The scoring will be based on the subject's morning and evening functioning on the days before Visit 6 while taking blinded study drug.

5. Each subject will complete a full-length laboratory classroom day with efficacy assessments, as listed below.

6. Perform the Conners 3-P Assessment. At Visit 6, the parent/guardian/caregiver will assess the subject's changes in ADHD symptoms using the Conners 3-P questionnaire.

7. Administer the final dose of the double-blind study drug on the 7th day of the Double-Blind Treatment Phase at the laboratory school by study staff. The capsule with study drug will be swallowed with approximately 240 mL of water. Additional water may be given if needed, and the volume of additional water will be recorded.

8. Perform the (SKAMP) Swanson, Kotkin, Agler, M-Flynn, and Pelham score assessments at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12 and 13 hours post-dose on the full classroom day.

9. Perform the Permanent Product Measure of Performance (PERMP) score assessment at pre-dose and at 0.5, 1, 2, 4, 8, 10, 12 and 13 hours post-dose on the full classroom day.

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

11. Assessment and review of Adverse Events.

11.4. Early Termination Visit

Early Termination (ET) from the study is defined as withdrawal during the Dose Optimization Phase or Treatment Phase 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. Complete physical examination.
2. Body weight.
3. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after subject has been sitting for a minimum of 3 minutes.
4. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes.
5. Clinical laboratory tests (chemistry, hematology and urinalysis).
6. Urine pregnancy test for all female subjects of childbearing potential. "Of childbearing potential" is defined in **Section 14.8.**
7. Assessment of the Columbia Suicide Severity Rating Scale (C-SSRS), "Children's Since Last Visit" version. If a subject has clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
8. Review of concomitant medications, treatment and/or therapies.
9. Assessment and review of Adverse Events.

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.

11.5. Follow-Up Visit

Subjects who complete the all phases of the study from the Open-Label Dose Optimization Phase through 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. Complete physical examination.
2. Body weight.

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

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

7. Urine pregnancy test for all female subjects of childbearing potential. "Of childbearing potential" is defined in **Section 14.8.**

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

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

10. Assessment and review of adverse events.

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

11.6. 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.

12. CONCOMITANT MEDICATIONS AND RESTRICTIONS

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

12.1. Medication Restrictions

- 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 (Day 0) 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 21 days prior to the start of the Dose Optimization Phase (Day 0) 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 21 days prior to the start of the Dose Optimization Phase (Day 0) 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
    - Coumarin anticoagulants

- Sedative hypnotics/sleep enhancers (with the exception of melatonin) are prohibited from 14 days prior to the start of the Dose Optimization Phase (Day 0) 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 (Day 0) and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to Day 0 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.

12.2. General Restrictions

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 14.8.**

13. INVESTIGATIONAL PRODUCT

13.1. 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.

13.2. 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.

Unblinded capsules with 20, 30 and 40 mg KP415 will be used in the Open-Label Dose Optimization Phase; capsules of 20, 30 and 40 mg KP415 blinded versus placebo capsules will be used in the Double-Blind Treatment Phase. All study drug will be supplied by the Sponsor (or designee). The Sponsor (or designee) will supply sufficient quantities of KP415 and placebo 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 will be commercially available products obtained by each research site.

13.3. Pharmaceutical Formulation

KP415 and placebo are provided in size 3 capsules consisting of an opaque white hydroxypropyl methylcellulose (HPMC) capsule shell without markings. Besides KP415 drug substance, each capsule of double-blind study drug contains the following inactive ingredients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate. The placebo capsules contain microcrystalline cellulose.

13.4. Packaging and Labeling

The KP415 capsules for the Open-Label Dose Optimization Phase, and the KP415 and placebo capsules for the Double-Blind Treatment Phase will be packaged and labeled appropriately.

13.4.1. Open-Label Dose Optimization Phase

Unblinded KP415 capsules will be packaged as bottles with 10 capsules. One bottle contains enough drug supply for one subject, for at least 7 days of dosing in the Open-Label 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. The number on the bottle will be recorded in the Electronic Data Capture (EDC) system for the study.

13.4.2. Double-Blind Treatment Phase

Blinded study medication will be packaged and numbered as a kit for each subject based on the randomization scheme. The patient randomization number assigned by the interactive web response system or similar system/process will correspond to the number on the kit.

Each kit for the Double-Blind Treatment Phase will consist of 1 bottle with 10 capsules of study drug and 1 bottle with 1 capsule of study drug. The bottle with 10 capsules contains enough drug supply for 6 days of dosing at home in the Double-Blind Treatment Phase (1 capsule/day every morning) and 4 extra capsules to cover the potential loss of capsules or extra dosing days before the next visit. The bottle with 1 capsule contains the capsule that will be administered in the research clinic in the morning of the laboratory classroom day on Day 7 (Visit 6). This is the last and final dose of study drug.

Each bottle with 10 capsules will be dispensed to the subjects at Visit 5 with instructions on how to administer the study drug. The number on the bottle will be recorded in the Electronic Data Capture (EDC) system for the study. The bottle with 1 capsule will be labeled with the same number, and will be kept at the research clinic until administration.

The bottles of study drug will be labeled according to the appropriate FDA regulations.

13.5. Dispensing Procedures

13.5.1. Open-Label Dose Optimization Phase

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

- **Visit 2:** At Visit 2, subjects will be dispensed an unblinded bottle with 10 capsules of 30 mg KP415 (starting dose).
- **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 (same daily dose as Week 1), with 20 mg KP415 (dose level decrease from Week 1), or with 40 mg KP415 (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 (same daily dose as Week 2, or either dose level decrease or increase from Week 2).

At Visits 2, 3 and 4, 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 each visit, site personnel will record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance.

At Visits 4 and 5, subjects will be administered unblinded study drug at the study site. During the 2 days before Visit 5, subjects will not take any study drug.

13.5.2. Double-Blind Treatment Phase

Blinded bottles of drug supply (KP415 capsules or matching placebo) will be dispensed at each visit as follows:

- **Visit 5:** Subjects will return to the research clinic after 7 ±3 days after Visit 4, with unused, unblinded study drug.
    - At Visit 5, subjects will be administered unblinded study drug at the study site (this is the last dose of unblinded study drug). During the 2 days before Visit 5, subjects will not take any study drug (this is important for obtaining a baseline of the SKAMP/PERMP scores).
    - At Visit 5, subjects will be assigned double-blind study drug by the interactive web response system or similar system/process. The assigned study drug will consist of one of the following: 20, 30 or 40 mg KP415 capsules or placebo capsules. The bottle (bottle with 10 capsules) will be dispensed to the study subject's parent or

guardian with instructions when and how to administer study drug while at home, starting on the day after Visit 5 (Day 22). On Days 22-27, subjects will take study drug at home under supervision of parent or legal guardian.

- **Visit 6:** Subject's parent or guardian will be instructed to return for Visit 6 with unused study drug. The final dose of study drug will be administered on the last day of the Double-Blind Treatment Phase (Visit 6) at the laboratory school by study staff. One capsule from the second bottle in the drug supply kit (bottle with 1 capsule) will be used for administration. Special care will be taken to assure that subjects receive the same assigned study drug, during the days at home and at the laboratory classroom day.

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 each visit, site personnel will record the number of returned and administered capsules of unblinded (at Visit 5) and blinded (at Visit 6) 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 after the Investigator or designee contacts the interactive web response system or similar system/process. All efforts will be made to ensure subjects receive daily doses of double-blind study drug for at least 7 days during the Double-Blind Treatment Phase.

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.

13.6. 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 in a safe, secure area with limited, controlled access 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.

13.7. 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.

14. SAFETY AND EFFICACY ASSESSMENTS

14.1. 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.

14.2. Physical Examination

A complete physical examination including body weight (lbs or kg) will be completed for all subjects at Screening, and at Early Termination (if possible) or Follow-Up. 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.

Height will be recorded in inches (in) or centimeters (cm) with the subject's shoes removed. Body weight will be measured in pounds (lbs) or kilograms (kg); subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.

14.3. ADHD Diagnosis and Severity Assessments

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).

The following scales will be used during the Open-Label Dose Optimization Phase to globally assess the changes in ADHD severity from week to week:

- **ADHD-Rating Scale-5 (ADHD-RS-5)**: The ADHD-RS-5 is an 18-item scale 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 scored from 1 (very much improved) to 7 (very much worse).

The following scale will be used to assess the effect of open-label KP415 during the Open-Label Dose Optimization Phase and the efficacy of KP415 versus placebo during the Double-Blind Treatment Phase:

- **Conners 3rd Edition-Parent (Conners 3-P):** The Conners 3-P (short form) is a 43-item parent/guardian/caregiver report that provides evaluation of inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, and peer relationships. The parent/guardian/caregiver will assess changes in ADHD symptoms via the Conners 3-P questionnaire at baseline (Visit 2, Day 0) and at each visit during the Dose-Optimization and the Treatment Phase.

- **Weekly Rating of Evening and Morning Behavior - Revised (WREMB-R) Scale:** The 11-item WREMB-R questionnaire is a parent-rated questionnaire that was developed to assess behaviors for their severity during the morning hours (3 items) and evening hours (8 items) (Carlson 2007). The possible score for each item ranges from 0 (no difficulty) to 3 (a lot of difficulty). The Investigator or designee will obtain the scores for the WREMB-R questionnaire by interviewing the parent/guardian/caregiver at Visits 2, 5 and 6. The assessment at Visit 2 is the baseline assessment (after washout of ADHD medications, if applicable); the assessments at Visits 5 and 6 are evaluations at the end of the Dose Optimization and Treatment Phase, respectively.

The following scales will be used to assess the efficacy of KP415 versus placebo during the Double-Blind Treatment Phase:

- **Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)**: Rating scale will be performed at Visit 4, Visit 5, and Visit 6.

The SKAMP scale is a validated rating of subjective impairment of classroom behaviors. It is comprised of 13 items (grouped under the subcategories of attention, deportment, quality of work, and compliance) on which subjects are rated according to a 7-point scale (0 = normal to 6 = maximal impairment) by trained study personnel (Swanson 1999). The SKAMP-Combined (SKAMP-C) score is obtained by summing the rating values for each of the 13 items. The SKAMP-Deportment (SKAMP-D) score is a measure of behavior and comprises of 4 items. The SKAMP-Attention (SKAMP-A) score is a measure of attention and comprises 4 items. The Higher SKAMP scores signify greater impairment. The SKAMP-C score will be used in the primary efficacy endpoint.

- **Permanent Product Measure of Performance (PERMP)**: Rating scale will be performed at Visit 4, Visit 5, and Visit 6. A Placement PERMP will be performed at Visit 2 (Day 0) to assure that subjects can complete at least the basic level of math problems and to determine the appropriate level of math to be assigned during the practice laboratory classroom day at Visit 4. Based on the practice laboratory classroom day at Visit 4, the final level of math for each subject will be determined for use in the remainder of the study (Visits 5 and 6).

  The PERMP is an individually calibrated five-page mathematics worksheet consisting of 400 problems. Subjects will be instructed by site staff to work at their seats and complete as many problems as possible in 10 minutes. Performance will be evaluated using two scores: The number of problems attempted (PERMP-A) and the number of problems correct (PERMP-C).

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

Suicidal ideation will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, Pediatric Version) (Posner et al. 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 (Visits 2, 3, 4 and 5), at Visit 6, and at Follow-Up or Early Termination.

Subjects with a history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at Screening or 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.

14.5. 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. On the full laboratory classroom day (Day 28 ±3 days, Visit 6), vital signs will

be collected at any time before dosing.

14.6. 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, and at Early Termination or Follow-Up. ECG recordings will be evaluated by skilled readers operating from a centralized ECG laboratory. One reader should read all the ECG recordings from a given subject.

14.7. 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 during the Screening Period and at Follow-Up or Early Termination. Clinical Laboratory Measurements may be repeated at the discretion of the Investigator.

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 (to evaluate the exclusion criterion for subjects with 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: At Screening (Visit 1) and Day 0 (Visit 2), 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. The alcohol and drugs of abuse urine screen at Visit 2 is performed to document the results and, if applicable, to record whether subjects have washed out their ADHD medications before Visit 2

- Urine Screen for Methylphenidate: At Screening (Visit 1), on Day 0 (Visit 2), and at Visit 5, before administration of study drug, 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 contains MPH, the urine screen at Screening may test positive for MPH. Since all ADHD medications must be washed out by Day 0, they must test negative on Day 0 (Visit 2) for subjects to be eligible to continue in the study. The MPH urine screen at Visit 5 is performed to document whether subjects have abstained from their unblinded study medication starting 2 days before Visit 5.

14.8. 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 Visit 2 (Day 0), Visit 5 (Day 21), 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”.

14.9. Adverse Event Assessments

Adverse Events will be assessed and recorded from Day 1 through either Follow-Up or Early Termination. While subjects are in the laboratory classroom after administration of study drug (Visit 6), 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 18**.

15. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

15.1. 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.
- Protocol violation requiring discontinuation of study treatment.
- Lost to follow-up.
- Sponsor request for early termination of the study.
- Positive pregnancy test (tested in females of childbearing potential).
- 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 Open-Label Dose Optimization Phase or the Double-Blind 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 Open-Label Dose Optimization Phase or the Double-Blind Treatment Phase do not need to be repeated.

15.2. Replacement of Subjects

Subjects who withdraw from the study during the Double-Blind Treatment Phase will not be replaced. Subjects who withdraw from the study during the Open-Label Dose Optimization Phase may be replaced.

16. EFFICACY ENDPOINTS

The following endpoints will be used to determine efficacy:

16.1. Primary Efficacy Variable:

- Average of the change from baseline (measured at Visit 5) of the SKAMP-C scores collected across the laboratory classroom day at Visit 6.

16.2. Secondary Efficacy Variables:

- Change from baseline (measured at Visit 5) of the SKAMP-C scores measured at each time point on the laboratory classroom day at Visit 6. The serial measures at different times post-dosing will be used to determine onset and duration of the clinical effect of KP415.
- Change from baseline of the scores measured at each time point and the average of the scores collected across the laboratory classroom day at Visit 6, for the following endpoints:
  - SKAMP-D and SKAMP-A scores
  - PERMP scores
  - PERMP-A and PERMP-C scores
- WREMB-R scores (total score, and morning and evening subscore) at Baseline (Visit 2), Visit 5 and Visit 6.

16.3. Safety Endpoints:

The occurrence of Treatment-Emergent Adverse Events (TEAEs) will be assessed starting following the first dose of open-label drug (KP415), and ending with the Follow-Up Visit or Early Termination Visit. Additional safety evaluations will include physical examinations, vital signs, as well as height and weight, ECG Parameters, clinical laboratory tests, and a follow-up C-SSRS administered at each study visit. AEs during the Open-Label Dose Optimization Phase and the Double-Blind Treatment Phase will be will be reported and analyzed separately.

17. STATISTICAL CONSIDERATIONS

This section summarizes the statistical considerations for this protocol. Details will be provided in the Statistical Analysis Plan for Protocol No: KP415.E01 (SAP_KP) prior to the primary endpoint database lock and unblinding of the trial.

17.1. Statistical Hypotheses

17.1.1. Primary Efficacy Endpoint(s):

The primary efficacy endpoint will be the mean change from the baseline measurement at Visit 5 and SKAMP-C scores ($\overline{\Delta SKAMP-C}$) collected across the laboratory classroom day at Visit 6.

17.1.2. Secondary Efficacy Endpoints

The following is a list of the secondary endpoints:

- $\overline{\Delta SKAMP - C}$ scores at each time point on the laboratory classroom day at Visit 6. The serial measures at different times post-dosing will be used to determine onset and duration of the clinical effect of KP415.
- The mean change from baseline at each time point collected across the laboratory classroom day at Visit 6 for the following endpoints:
  - SKAMP-D and SKAMP-A scores
  - PERMP scores
  - PERMP-A and PERMP-C scores
- WREMB-R scores (total score, and morning and evening subscore)

17.2. Sample Size Calculation

Test Treatment does not have Carry-over Effect: The primary hypothesis is that the test drug is superior (change in SKAMP-C from baseline measured at Visit 5 are lower) when compared to placebo. The null and alternative hypotheses are as follows:

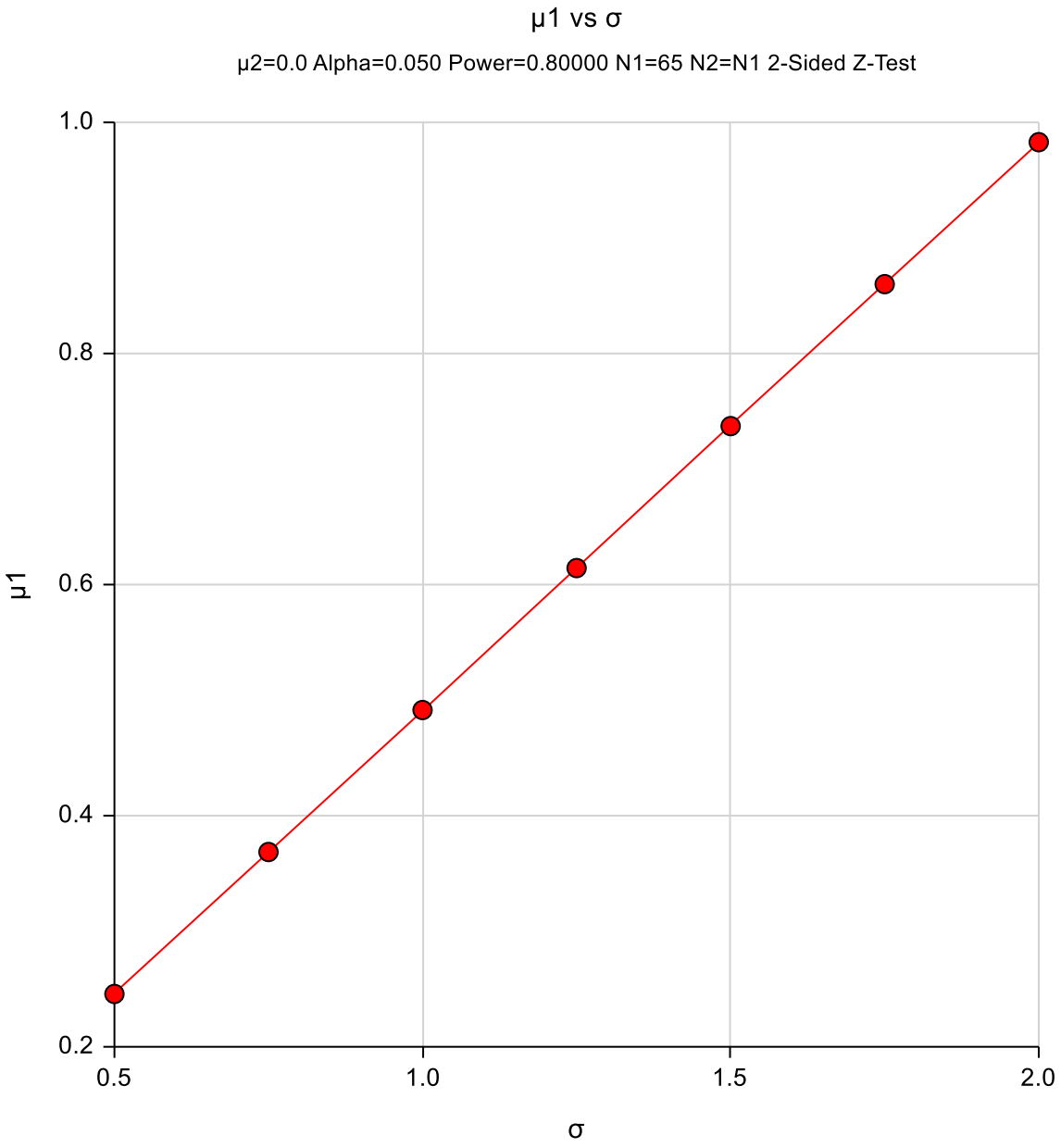
$$H_0: \overline{\Delta SKAMP - C}_{control} - \overline{\Delta SKAMP - C}_{test} = 0$$
$$H_A: \overline{\Delta SKAMP - C}_{control} - \overline{\Delta SKAMP - C}_{test} \neq 0$$

Studies of this type often have a clinically and statistically relevant ($p < 0.05$) interaction effect between treatment and time. Therefore, if the interaction between treatment and time is statistically relevant, then the hypothesis test will be based on the interaction effect. If the interaction is not statistically relevant, then the hypothesis test will be based on just the treatment main effect.

Drug efficacy studies are sized to be able to detect at least the Minimum Clinically Important Difference (MCID). MCID has not been established for the SKAMP-C scores. However, Rai et al. (Rai et. al. 2015) noted "0.5 standard deviations has been suggested to correspond to the MCID in a number of studies". Biederman et al. (Biederman et al. 2007) also noted, in a similar study on lisdexamfetamine dimesylate, "Previous studies of amphetamine products using the SKAMP-D to assess efficacy in children with ADHD have disclosed an effect size of greater than .50." Therefore, the SD is assumed to be 1 and the MCID is assumed to be 0.5.

Therefore, assuming a mean difference between test and control for ΔSKAMP-C of 0.5 units and a standard deviation (SD) of 1.0, 126 subjects would need to complete the study, assuming 80% power when testing a significance level of $\alpha = 0.05$ (2-sided two-sample z-test). Figure 2 shows the change in the detectable effect size with a range and SD's. The figure shows that even if the SD is 50% greater than expected, the minimum detectable effect size changes from -0.5 to -.0.7. Given previous studies of amphetamine products using $\Delta SKAMP - C$ in a classroom setting showed differences of greater than 1 with SD's close to 1 (McCracken et al. 2003; Biederman et al. 2007; Swanson et al. 1998).

Figure 2: Change in Effect Sizes for a Range of Standard Deviations



The samples sizes are based on the Two Sample Z-Test assuming Equal Variance module in PASS Version 15.0.3.

Assuming an approximate 10% dropout during the Double-Blind Treatment Phase, 140 subjects are planned to be randomized in the Double-Blind Treatment Phase. Assuming an approximate 20% dropout during the Open-Label Dose Optimization Phase, 176 subjects are planned to be enrolled in the Open-Label Dose Optimization Phase.

17.3. Populations for Analysis

There are three populations in this study:

Intent-to-Treat (ITT) Population: All randomized subjects who receive at least one dose of double-blind study medication and have at least one post-dose SKAMP-C assessments at Visit 6.

Per-Protocol (PP) Population: ITT subjects who received the morning dose of double-blind study medication at the laboratory test session, who have all 8 post-dose SKAMP-C assessments at Visit 6, who did not miss more than 2 days of therapy during the Double-Blind Treatment Phase, and did not use prohibited medications during the Double-Blind Treatment Period.

Overall Safety Population: All subjects who entered the Open-Label Dose Optimization phase and received at least one dose of open-label study medication and had at least one post-dose safety assessment. This will include subjects who were randomized as well as those subjects who were never randomized. This population will be used for safety analyses.

17.4. Statistical Analyses

17.4.1. General Approach

Analysis Populations: All baseline analyses will be performed using the ITT, PP and Overall Safety populations. All efficacy analyses will be performed using both the ITT and PP populations. All safety analyses will use the Overall Safety Population.

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

- Continuous data: n, mean, standard deviation, median and interquartile range, minimum and maximum
- Categorical: n/N, percentage of total per arm and 95% confidence interval per category
- Binary: n/N, percentage per arm and 95% confidence interval

Missing Data: The following applies to the primary and secondary efficacy endpoint and safety analyses. If there is < 5% of patients with outcome data points missing, then no additional sensitivity analyses will be performed. If there are ≥ 5% of patients with missing outcome data, then the missingness will be assessed. If the outcome data is considered to missing at random (MAR), no additional steps will be taken to handle the missing data (see SAP for details). If the outcome data is Not Missing at Random (NMAR), a sensitivity analysis using a pattern-mixture model (see SAP for details) will be performed.

If there is < 5% of patients with covariate data values missing, then no additional sensitivity analyses will be performed. If there are ≥ 5% of patients with missing covariate data values, then the missingness will be assessed. If the covariate data is considered to be MAR, a sensitivity analyses

using multiple imputation methods (see SAP for details) will be performed. If the covariate data is NMAR, alternative imputation methods such as pattern mixture model will be assessed (see SAP for details).

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan. Any retrospective or exploratory analyses not defined by the protocol or the statistical analysis plan will be explained in the clinical study report.

17.4.2. Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint treatment effect is the SKAMP-C scores over the day during Visit 6. Though the SKAMP questionnaire uses the Likert scale, the SKAMP-C, which aggregates the scores from all the domains, will be treated as a continuous measure.

The estimate of the difference between test and control will be based on a repeated measures analysis using a Mixed-Effect Model Repeated Measure (MMRM) model where:

- Time, treatment and the interaction of time and treatment are the fixed effects. Site will be included as a fixed effect. If site effect is not statistically significant, it will be removed from the model.
- Subject is the random effect.

Prior to conducting any analyses, we will be looking at the distribution of data. The outcome data will be assessed for normality using Shapiro-Wilk (SW) test. If there is evidence of a lack of normality, several normalizing transformations will be considered. See SAP for details. Point estimates for each treatment group and treatment mean group differences (KP415 – Placebo) will be presented with standard errors and 95% confidence intervals An unstructured (co)variance structure shared across treatment groups will be specified to model the within-subject errors. If the p-value for interaction between treatment and baseline covariate is not < 0.05, then that covariate will be dropped from the model and the analysis will be re-run. Model fit will be assessed using graphical and quantitative methods. See SAP for details.

Studies of this type often have a clinically and statistically relevant ($p < 0.05$) interaction effect between treatment and time. Therefore, if the interaction between treatment and time are statistically relevant, then the hypothesis test will be based on the interaction effect. If the interaction is not statistically relevant, then the hypothesis test will be based on just the treatment main effect.

17.4.3. Analysis of the Secondary Endpoints

The secondary endpoint analyses described in this section will be performed if the primary endpoint

hypothesis test is significant. If the primary endpoint hypothesis test is not significant, only the descriptive statistics will be provided.

SKAMP-C measured at each time point at Visit 6: The same MMRM model developed for the primary efficacy endpoint will be used to estimate the least square means and their corresponding 95% confidence interval for each time and treatment combination. Differences in least square means between the treatment arms and unadjusted p-values will be reported for each time point.

Onset of clinical effect is defined as the earliest post-dose time point at which the difference between KP415 and Placebo is statistically significant ($p<0.05$) between KP415 and placebo as measured by the SKAMP-C Score. The duration of the treatment effect is defined as the length of the time interval, such that statistical significance was reached at each time point of this interval.

All other secondary endpoints: The remaining secondary endpoints will be treated as continuous data. The overall interaction effect of treatment and time or the treatment effect if the interaction is significant and the individual time point estimates will be determined using the same model analysis methods and output described for the SKAMP-C endpoint.

17.4.4. Sensitivity Analyses

As a sensitivity analysis, the interaction of treatment and unbalanced baseline covariates identified in the baseline characteristic analysis will be included in the primary and secondary models. If the p-value for interaction between treatment and baseline covariate is not significant ($p \geq 0.01$), then that covariate will be dropped from the model and the analysis will be re-run.

17.4.5. Safety Analysis

All analyses of safety will be conducted on the Overall Safety Population. The safety assessment will be based on adverse events, physical exams, vital signs, ECG parameters, clinical laboratory tests and C-SSRS scores.

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, and by treatment. 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 treatment.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline

for each of the parameters using descriptive statistics by treatment group. Those subjects with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings. See **Section 18** for more information on safety data.

17.4.6. Baseline Descriptive Statistics

The key baseline characteristics (see the Statistical Analysis Plan (SAP) for list of baseline characteristics) will summarized descriptively per treatment arm and the two arms will be compared statistically. For continuous variables, the data will be assessed as to whether they are normally distributed using the Shapiro-Wilk test (SW). If this is no evidence of lack of normality (SW $p>0.05$), then the two arms will be compared using the t-test with unequal variances. If SW indicates that there is evidence that the variable is not normally distributed (SW $p < 0.05$), then the non-parametric Wilcoxon rank sum test will be used to compare the two arms. For binary and categorical variables, the chi-square test will be used for the comparison between the two arms.

As a sensitivity analysis, if there is evidence of a difference in baseline characteristics ($p <0.01$), and the difference is considered clinically relevant by the Principal Investigator of the study, the primary and secondary efficacy endpoint analyses will include these variables as covariates.

17.4.7. Planned Interim Analyses

There are no planned interim analyses.

17.4.8. Sub-Group Analyses

The subgroup analyses described in this section will be performed if the primary endpoint is significant. If the primary endpoint is not significant, then only the descriptive statistics will be provided.

The primary efficacy endpoint model and analysis methods along with the safety endpoints and analyses will be used to analyze any subgroups such as site, dose, age and gender. Please see the SAP for the list of subgroup and further details about the analyses.

17.4.9. Tabulation of Individual Participant Data

A listing of date and type of each subject's TEAE will be provided.

17.4.10. Exploratory Analyses

Changes in ADHD severity will be compared from week to week in the ITT and PP Population based on ADHD-RS-5, CGI-S, CGI-I, and Conners 3-P. Please see the SAP for further details about the analyses.

18. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

18.1. Adverse Events

18.1.1. 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).

18.1.2. 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.

18.1.3. 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.

18.1.4. 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.

18.2. 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.

18.2.1. 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 or designee will enter the SAE into the electronic database. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to the appropriate sponsor contact. If the EDC system is temporarily unavailable, the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to the appropriate sponsor contact. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

If EDC is not functional, a paper SAE form will be utilized and provided to the following contact:

DCRI Safety Surveillance
DCRISafetysurveillance@duke.edu
Fax: 919-668-7138
Telephone: 919-668-8624

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 ARO. The ARO will notify the Sponsor by the end of the next business day after SAE notification receipt from the site.

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 event reporting by Sponsor will adhere to 21 CFR 312.32 for IND drugs (7-day or 15-day alerts) and 21 CFR 314.80 for marketed drugs (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.

18.3. 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.

18.4. 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. Notifications of known incidences of subjects taking more than one capsule of study drug per day (irrespective of the dose size) will be provided by each study site to the ARO. The ARO will notify the sponsor before the end of the next business day after ARO's notification receipt from the site. If there is an associated AE or SAE, the site is to report the event on the electronic case report form within 24 hours.

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).

19. PREGNANCY

Females with a positive pregnancy test will terminate the study early. The initial report of a pregnancy during the study will be provided by the site to the ARO. The ARO will notify the

Sponsor before the end of the next business day after ARO's notification by the site, and ARO will report to the IRB within a time frame after the incident identification as required by the IRB.

All pregnancies will be followed to at least the completion/termination of the pregnancy. The Investigator will document the subject visits accordingly and record the information in the clinical site's source documents. If the pregnancy continues to delivery, the outcome (health of the infant), in addition to the maternal health status, must be included in the report.

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.

20. 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. Improper breaking of the blind
5. Multiple visits missed or outside permissible windows
6. Materially inadequate record keeping
7. Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
8. Subject repeated non-compliance with study requirements

It is the Site Investigator's responsibility to report to the IRB any Protocol Violation(s) according to the IRB's policy. A copy of the IRB submission will be filed in the site's regulatory binder and in the Sponsor's files at the ARO.

21. DATA MANAGEMENT AND RECORD KEEPING

21.1. 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.

21.2. Record Keeping

The Site Investigators and Academic Research Organization (ARO) 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 Site Investigators, their affiliated Institutions and the ARO 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 in the clinical site's and ARO's archives until written authorization is obtained from the Sponsor.

21.3. Access to Source Data/Documents

The Site Investigators and ARO 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.

22. QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor and/or Sponsor's representatives will perform quality control and quality assurance checks of this clinical trial that it sponsors. Before the enrollment of any patient in this study, personnel of the ARO will review with the Site Investigators and site personnel the appropriate documents and processes to conduct the trial including the protocol, Investigator's Brochure, eCRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by CRAs from the ARO, or—as needed--other ARO personnel and/or other Sponsor personnel and/or representatives. During these visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, ARO personnel will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to Site Investigators.

The ARO and Sponsor agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol and accepted standards of Good Clinical Practice (GCP) per the International Council for Harmonisation (ICH E6(R2)).

23. 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

24. INSURANCE

24.1. Insurance Compensation

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.

25. COMPLETION OF STUDY

The end of the study will be at the time of the last subject, last visit. The IRB will be notified about the end of the study according to regulatory requirements.

26. STUDY ADMINISTRATIVE INFORMATION

26.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the Site Investigators by the ARO. 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 Site Investigators by the ARO.

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