Corium

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Amendment #3, Version 4.0, November 14, 2022

A Multicenter, Dose-Optimized, Randomized, Double-Blind, Efficacy and Safety Study with Azstarys® in Children 4 to 12 Years of Age with Attention-Deficit/Hyperactivity Disorder

Protocol No: KP415.P01

Original Protocol (Version 1.0) dated: December 20, 2021
Amendment #1 (Version 2.0) dated: March 23, 2022
Amendment #2 (Version 3.0) dated: June 27, 2022
Amendment #3 (Version 4.0) dated: November 14, 2022

A Multicenter, Dose-Optimized, Randomized, Double-Blind, Efficacy and Safety Study with Azstarys® in Children 4 to 12 Years of Age with Attention-Deficit/Hyperactivity Disorder

Sponsor Approval / Signature Page

Protocol Number	KP415.P01
Protocol Version Date	Amendment #3 November 14, 2022
Version	4.0
Investigational Product	Azstarys®
IND Number	130463
Study Phase	Phase 4
Sponsor	Corium, Inc. 4558 50th St SE Grand Rapids, MI 49512 Phone: 616-656-4563

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Date

A Multicenter, Dose-Optimized, Randomized, Double-Blind, Efficacy and Safety Study with Azstarys® in Children 4 to 12 Years of Age with Attention-Deficit/Hyperactivity Disorder

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct this study as outlined in the protocol, Master Clinical Services Agreement, Statement of Work, and any change orders/amendments to these documents.

I understand the study protocol and will conduct the study according to the procedures therein and according to the principles of Good Clinical Practice and all applicable federal and local regulations.

I will ensure that all individuals assisting with the study are adequately trained and informed about the protocol, investigational product(s), procedures and their study related duties and functions.

I agree not to deviate from the protocol without prior agreement from the Sponsor except to eliminate an immediate safety hazard to the study subjects.

I further agree that the Sponsor, Sponsor designees and federal agencies, shall have access to all source documents and records associated with the study for review and monitoring of the investigational trial.

_____
Site Investigator Name (Print)

_____ _____
Signature Site Investigator Date

_____
Name of Investigational Site

_____
Address of Investigational Site

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS-5	ADHD Rating Scale-5
ADHD-RS-IV	ADHD Rating Scale-IV
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions–Improvement
CGI-S	Clinical Global Impressions–Severity
CL/F	The apparent total plasma clearance after an oral dose (L/h)
CL/F/W	CL/F normalized by body weight (W), in L/h/kg
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CSHQ	Children's Sleep Habits Questionnaire
CV	Coefficient of variation
d-MPH	d-methylphenidate (dexmethylphenidate)
DEA	Drug Enforcement Agency
DMDD	Disruptive Mood Dysregulation Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary of Regulatory Activities
MAOI	Monoamine Oxidase Inhibitor
MINI Kid	Mini-International Neuropsychiatric Interview for Children and Adolescents

Abbreviation	Definition
MMRM	Mixed Model for Repeated Measures
MPH	Methylphenidate
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
Q1	25th Percentile (1st Quartile)
Q3	75th Percentile (3rd Quartile)
QT	Time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOE	Schedule of Events
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
T_{max}	Time to achieve the maximum observed plasma concentration
V_z/F	Apparent volume of distribution after an oral dose (F is the oral bioavailability expressed as a fraction)

PROTOCOL SYNOPSIS

TITLE	A Multicenter, Dose-Optimized, Randomized, Double-Blind, Efficacy and Safety Study with Azstarys® in Children 4 to 12 Years of Age with Attention-Deficit/Hyperactivity Disorder
SPONSOR	Corium, Inc.
PROTOCOL NUMBER	KP415.P01
INVESTIGATIONAL PRODUCT	Azstarys® contains dexmethylphenidate (d-MPH) and serdexmethylphenidate (SDX), a prodrug of d-MPH.
NAME OF ACTIVE INGREDIENT	The chemical name of SDX 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.
ROUTE	Oral
NUMBER OF SITES	Approximately 20 sites in the United States of America
STUDY DESIGN	This is a multicenter, dose-optimized, randomized, double-blind, efficacy and safety study with Azstarys® in children 4 to 12 years of age with attention-deficit/hyperactivity disorder (ADHD). The phases of the study are as follows: • **Screening Period (Visit 1)** Subjects will undergo a Screening Period up to 30 days prior to entering the Treatment Period. • **Double-Blind Treatment Period (Visit 2 through Visit 6)** Eligible subjects will be randomized in a blinded fashion to Azstarys® or placebo at the start of the Treatment Period. Randomization will be applied separately in each cohort and stratified by gender. o **Cohort 1:** Subjects 4 and 5 years (<6 years) will start at 13.1 mg/2.6 mg or matching placebo and may be titrated up or down to doses of 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg Azstarys® or matching placebo approximately each week through Visit 5 o **Cohort 2:** Subjects 6 to 12 years (<13 years) will start at 39.2 mg/7.8 mg or matching placebo and may be titrated up or down to doses of 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg Azstarys® or matching placebo approximately each week through Visit 5 • **Roll-over into Study KP415.P02**

	Subjects of Cohort 1 (ages 4 and 5 years) who successfully complete the treatment phase have the option to participate in a 12-month open-label safety study with Azstarys® (Study KP415.P02). At Visit 6 of the current study, all entry criteria to enroll in Study KP415.P02 (see protocol for Study KP415.P02) will be evaluated (Visit 6 for the current study is also Visit 2 of Study KP415.P02). • **Follow-up Phone Call:** Subjects who will not be rolled over into Study KP415.P02 will receive a Follow-up Phone Call, at 5 ±2 days after administration of the last dose of the Treatment Period. Subjects who elect to use another ADHD treatment will be discontinued from study treatment and from the study (Early Termination [ET]). Subjects who discontinue study treatment prior to the end of the Treatment Period (Visit 6) because of adverse events (AEs), overdosage, or use of a prohibited treatment other than an ADHD treatment will be followed (unless consent is withdrawn) with scheduled assessments until the end of the Treatment Period (Visit 6). If, during the remaining time on study, an ADHD treatment is used, the subject will be discontinued from the study (ET).
PRIMARY OBJECTIVE	• To determine the efficacy of Azstarys® compared to placebo in treating children ages 4 to 12 years old with ADHD.
SECONDARY OBJECTIVE	• To determine the safety and tolerability of Azstarys® compared to placebo in treating children 4 to 12 years old with ADHD. The safety objective includes evaluation of changes in body weight and height, and sleep behavior.
SAMPLE SIZE CALCULATION	Based on data from a previous study (efficacy study with Azstarys® in subjects 6- to 12-years of age), the power and proposed sample size in each age cohort was calculated based on a two-sample t-test as follows (with no multiplicity correction for the two age cohorts): • 90% power to detect a 6-point treatment difference with an SD of 10-points using two-sided α=0.05 in Cohort 1 (4- to 5-years-of-age) yields N=60 per treatment group in a 1:1 ratio for active and placebo for a total sample size of 120 younger subjects • 80% power to detect a 6-point treatment difference with an SD of 10-points using two-sided α=0.05 in Cohort 2 (6- to 12-years of age) yields N=45 per treatment group in a 1:1 ratio for active and placebo for a total sample size of 90 older subjects. A lower power was selected for this cohort

	because efficacy in this age group was previously established. Combining the two age cohorts for a total of 105 subjects per treatment group yields 99% overall study power to detect a between-treatment difference of 6 points with a SD of 10 points using two-sided α=0.05 for a total sample size in the study of 210 subjects. A blinded sample size re-estimation will be conducted to recalculate the SD when approximately 50% of subjects in Cohort 1 have completed Visit 6.
NUMBER OF SUBJECTS	In each age cohort, an appropriate number of subjects will enter the Screening Period to randomize approximately the following number of subjects in the Treatment Period. Randomization between Azstarys® and placebo will be applied within each of two age cohorts: • **Cohort 1 (4 and 5 years of age):** 130 subjects (65 per arm) with the intention to complete with approximately 120 subjects. • **Cohort 2 (6 to 12 years of age):** 100 subjects (50 per arm) with the intention to complete with approximately 90 subjects. The additional number of subjects enrolled is based on an approximate 10% early discontinuation rate. Subjects who terminate early in the Treatment Period will not be replaced. In accordance with a male-to female distribution ratio of 3:1 of children diagnosed with ADHD in clinical practice, it is anticipated that approximately 75% males and 25% females will be enrolled.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria** 1. In Cohort 1, subjects must be at least 4 years old and less than 5 years and 10 months at Screening; in Cohort 2, subjects must be at least 6 years old and less than 12 years and 10 months at Screening. 2. Subjects must have a body weight within the 5th and 95th percentile according to the gender-specific weight-for-age percentile charts from the Centers for Disease Control and Prevention (CDC). See calculator at https://www.infantchart.com/child/. 3. Female subjects must agree, if 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. 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 12 years of age 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. Subjects must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical examinations, vital signs, electrocardiograms (ECGs), medical history, and clinical laboratory values (chemistry, hematology, urinalysis) at Screening. If any of the chemistry or hematology tests 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 voluntarily give written permission for him/her to participate in the study. 6. Subjects in Cohort 2 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 Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid). 8. Subject has had ADHD symptoms present for at least 6 months prior to the Screening Visit. 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 Treatment Period, and abstain from taking these to the end of Visit 6 or ET; and wash out non-stimulant ADHD medications from 14 days prior to the start of the Treatment Period, and abstain from taking these to the end of Visit 6 or ET.

	10. Subject must have a score of ≥4 (Moderately 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. 11. Subjects must have age and sex adjusted ratings of ≥90th percentile Total Score on the ADHD-Rating Scale (ADHD-RS) rated over the past 6 months (for 4- and 5-year old children, use Preschool Version of ADHD-RS-IV; for 6-12 years old children, use ADHD-RS-5). 12. Subject functions at an age-appropriate level intellectually, as determined by the Investigator. 13. Subject must have a systolic and diastolic blood pressure below the 95th percentile for age and gender according to the 2017 AAP guidelines (Flynn 2017) based on the average of 3 measurements 2-5 minutes apart. 14. 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. 15. Subject, parent/legal guardian, and caregiver (if applicable) must be able to speak and understand English or Spanish and be able to communicate satisfactorily with the Investigator and study coordinator. **Exclusion Criteria** 1. If female, must not be pregnant or breastfeeding, and if of childbearing potential, must have a negative urine pregnancy test at the start of the Screening Period. In addition, a positive pregnancy test before the last dose of study drug will result in early termination from the study. 2. Subject with any clinically significant chronic medical condition that, in the judgment of the Investigator, may interfere with the subject'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, depression, 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. 6. Subject taking anticonvulsants for seizure control or antidepressants currently or within the past 2 years before Screening are not eligible for study participation. A past history of febrile seizure or drug-induced seizure is allowed. 7. Subject has a current (last month) psychiatric diagnosis other than specific phobia, motor skills disorders, ODD, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders. Subjects allowed to enroll with any of these DSM disorders will require written justification from the Investigator documenting why the conditions will not interfere with participation and to emphasize that ADHD is the primary indication. 8. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the Columbia-Suicide Severity Rating Scale (C-SSRS) assessment at Screening. 9. Subject has any clinically significant unstable medical abnormality, chronic disease (including asthma or diabetes), 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 absorption, distribution, metabolism, or excretion of study drug. In cases in which the impact of the condition

	upon risk to the subject or study results is unclear, the Medical Monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if controlled) must be discussed with the Medical Monitor during Screening. 10. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant. 11. Subject has a history of, or currently has, a malignancy. 12. Subject has uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) ≤0.8 x the lower limit of normal (LLN) or ≥1.25 x the upper limit of normal (ULN) for the reference laboratory at Screening. 13. Subject has greater than trace proteinuria in the urinalysis at Screening. Subjects with greater than trace proteinuria in the urinalysis at Screening but with a urine protein to creatinine ($U_{P/C}$) ratio <0.2 in a first morning void urine sample will not be excluded from enrollment. 14. Subjects has a current or recent (past 12 months) history of drug abuse; or current or recent history of drug abuse in someone living in the subject's home, or are using or planning to use prohibited drugs during the trial as specified in the protocol. 15. Subject has a positive urine drug screen at Screening. Subjects with a positive methylphenidate (MPH) 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. 16. Subject has participated in any other clinical study with an investigational drug/product within 30 days or at least 5 half-lives, whichever is longer, prior to Screening. 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 intolerability to adequate dose and duration of treatment with MPH products. Judgment of adequate dose and duration is at the discretion of the Investigator. 19. Subject has a positive urine MPH screen by dipstick (e.g., NarcoCheck®) at Visit 2.

<table>
<tr><td></td><td>
20. Subject is planning to initiate psychotherapy during the study (subjects participating in psychotherapy beginning at least 4 weeks before study initiation are permitted to continue).
21. Subject has a history of severe allergies or adverse drug reactions to more than one class of medications.
22. Subject has a history of allergic reaction or a known or suspected sensitivity to MPH or any substance that is contained in the study drug.
23. 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.
24. 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.
25. Subject has one or more siblings living in the same household who are enrolled in this or another clinical drug trial.
26. Subject shows evidence of current physical, sexual, or emotional abuse.
27. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

Rescreening
Subjects who require extension of the screening window and remain eligible for the study may be rescreened upon approval by the Medical Monitor. Subjects who screen fail will not be rescreened.
</td></tr>
<tr><td>TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION</td><td>
The Azstarys® capsules contain two active pharmaceutical ingredients: d-methylphenidate (dexmethylphenidate; d-MPH) hydrochloride, and serdexmethylphenidate (SDX; a prodrug of d-MPH). In terms of total d-MPH dose amounts, all capsule strengths contain 30% of d-MPH and 70% of d-MPH in form of the prodrug. 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>d-MPH (mg)</th><th>SDX (d-MPH) [1] (mg)</th><th>Total d-MPH dose [2] (mg)</th><th>Equimolar d-MPH HCl dose (mg)</th></tr>
<tr><td>2.6</td><td>13.1 (6.1)</td><td>8.6</td><td>10</td></tr>
<tr><td>5.2</td><td>26.1 (12.2)</td><td>17.3</td><td>20</td></tr>
<tr><td>7.8</td><td>39.2 (18.3)</td><td>25.9</td><td>30</td></tr>
</table>
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	10.4	52.3 (24.4)	34.6	40

1. This is dose of SDX. The amount of d-MPH equimolar to each SDX dose is listed in parentheses.
2. The total dose of d-MPH expressed in terms of free base.

Azstarys® is a Schedule II product under the Controlled Substances Act. Therefore, study sites are required to have the appropriate permit from the Drug Enforcement Agency (DEA) to receive, store, ship and dispense Azstarys® according to all local, state, and federal regulations for Schedule II controlled substances.

All subjects will receive study drug, as follows:

- At Visit 2, subjects will be randomized in a blinded fashion to either Azstarys® or placebo. Randomization will be applied to each cohort separately and will be stratified by gender

During the Treatment Period, daily treatments of double-blind study drug will be administered.

- **Cohort 1:** Subjects 4 and 5 years (<6 years): will start at 13.1 mg/2.6 mg Azstarys® or matching placebo and may be titrated up or down to doses of 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg Azstarys® or matching placebo at Visits 3, 4, and/or 5
- **Cohort 2:** Subjects 6-12 years (<13 years): will start with at 39.2 mg/7.8 mg Azstarys® or matching placebo and may be titrated up or down to doses of 26.1 mg/5.2 mg 39.2 mg/7.8 mg, 52.3 mg/10.4 mg Azstarys® or matching placebo at Visits 3, 4, and/or 5

The daily dose may be changed at Visits 3, 4 and 5 based on a combination of individual tolerability and effect assessed by the Investigator. If a lack of tolerability should occur between visits, the dose may be lowered at any time.

The optimized daily dose will be determined at Visit 5 and will be kept the same for the remainder of the Treatment Period, with the following exception: if a lack of tolerability should occur, the dose may be lowered at any time.

Study drug will be taken orally in the morning within 20 minutes after consuming breakfast. Study drug will be swallowed whole (without crushing, cutting, chewing, opening, or dissolving) or may be taken by sprinkling the contents of the capsule over a small amount of applesauce.

On each day at home (no scheduled visits to the study site) during the Treatment Period, the assigned study drug will be taken under the supervision of the subject's parent or caregiver.

	On days with scheduled visits to the study site, subjects will take the assigned study drug either at home under the supervision of the subject's parent or caregiver before coming to the study site for their scheduled visit, or, if their visit occurs in the morning, subjects may take the assigned study drug at the study site under the supervision of site staff.
ADHD SEVERITY/ EFFICACY EVALUATION CRITERIA	The following scales will be used to assess the changes in ADHD severity: • ADHD-Rating Scale (ADHD-RS): The Preschool Version of ADHD-RS-IV (McGoey 2007) will be used for 4- and 5-year-old subjects (Cohort 1), and ADHD-RS-5 will be used in 6- to 12-year-old subjects (Cohort 2). The ADHD-RS is an 18-item scale (DuPaul 1998, DuPaul 2016) based on Diagnostic and Statistical Manual of Mental Disorders (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 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 inattention. Scores will be obtained during a clinician-directed interview with the parent/guardian/ caregiver at each visit. • Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid; Sheehan 2010). Will be used to confirm the diagnosis of ADHD and identify comorbid psychiatric conditions. • Clinical Global Impressions–Severity (CGI-S): The CGI-S is a clinician-rated scale that evaluates the severity of psychopathology (ADHD symptoms in the study) on a scale from 1 (not at all ill) to 7 (among the most severely ill) (Busner and Targum 2007). • Clinical Global Impressions–Improvement (CGI-I): The CGI-I is a clinician-rated scale that evaluates the improvement of psychopathology (ADHD symptoms in the study) on a scale from 1 (very much improved) to 7 (very much worse). During the Treatment Period, the ADHD-RS, CGI-I and CGI-S scale assessments are the main efficacy response variables (in conjunction with tolerability and safety) to guide dose optimization.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will participate in the study as outpatients for up to 65 days including up to 30 days of Screening, up to 28 days in the Treatment Period, and a Follow-up Phone Call up to 7 days (5 ±2 days) after the administration of the last dose of the Treatment Period.
MEDICATION RESTRICTIONS	Subjects will be prohibited/limited to receive certain medications in the trial, as follows: • Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit. These include: MPH, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, d-MPH, Focalin®, dextroamphetamine, Dexedrine®, Adderall®, Vyvanse®, lisdexamfetamine, and prescription Azstarys®. • Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit. These include: atomoxetine, guanfacine, clonidine. • The following medications are prohibited from 14 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit: o Monoamine oxidase inhibitors (MAOIs). o Norepinephrine reuptake inhibitors (NRIs) and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, and viloxazine. 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 Sedative hypnotics/sleep enhancers (with the exception of melatonin, which is allowed if subjects have taken it for more than 30 days before Screening) • Tricyclic antidepressants as well as Bupropion are prohibited from 30 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit. • Cough and cold medications containing stimulants and/or sedating antihistamines are prohibited from 30 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit.

	All other concomitant medications will be allowed if necessary. **Note:** Subjects who are rolled over into Study KP415.P02 after the end of the Treatment Period in the current study will need to continue to abstain from prohibited medications as explained in the protocol for Study KP415.P02.
SAFETY ASSESSMENTS	• The occurrence of treatment emergent adverse events (TEAEs) will be assessed following the first dose of study drug and ending with the Follow-up Phone Call or ET Visit. • Physical examinations will be performed at Screening, before the first dose of study drug (Visit 2), and at the end of the Treatment Period (Visit 6) or at ET. • Clinical laboratory tests will be performed at Screening and at the end of the Treatment Period (Visit 6) or at ET. Urinalysis will also be performed at Screening, before the first dose of study drug and at the end of the Treatment Period or at ET. • ECG parameters will be collected at Screening and at the end of the Treatment Period (Visit 6) or at ET. • Vital signs, height and body weight will be collected at each visit. Blood pressure data will be analyzed using the 2017 AAP guidelines based on the average of 3 blood pressure measurements 2-5 minutes apart. • Height will be measured at Screening, Visit 2, and at the End of the Treatment Period. • A C-SSRS will be performed at each study visit. • Ratings from the modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be collected at Screening, and at each visit of the Treatment Period, or at ET.
EFFICACY ASSESSMENTS	During the Treatment Period (Visits 2-6): • ADHD-RS-IV (Preschool Version, Cohort 1) or ADHD-RS-5 (Cohort 2) will be assessed at each visit. • CGI-S will be assessed at each visit (Visits 2-6) • CGI-I will be assessed at Visits 3, 4, 5, and 6.
ANALYSIS POPULATIONS	• **Safety Population:** Overall and for each cohort separately, all randomized subjects who received at least one dose of study medication and who have at least one post-dose safety assessment. Safety endpoints will be analyzed using the Safety Population. Demographics and baseline characteristics will be summarized for the Safety Population. • **Intent-to-Treat (ITT) Population:** Overall and for each cohort separately, all subjects who received at least one

	dose of study medication and have at least one post-randomization ADHD-RS Total Score. Demographics and baseline characteristics will be summarized for the ITT Population. All efficacy analyses will be conducted in the ITT Population. • **Per-Protocol (PP) Population**: Overall and for each cohort separately, all randomized subjects who received at least one dose of study medication and have the baseline and at least one post-randomization ADHD-RS Total Score, and who did not miss more than 2 days of therapy and did not use prohibited medications deemed to impact efficacy. The primary efficacy analyses will be conducted in the PP Population as sensitivity analyses.
STATISTICAL METHODS	Descriptive statistics will be presented for baseline, all post baseline measurements, and changes from baseline to all post-baseline measurements, where applicable, for continuous efficacy endpoints by treatment group, overall and separately for each age cohort. For the primary endpoint of change from baseline in ADHD Rating Scale (ADHD-RS) total score, a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fitted using all data as observed. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), baseline ADHD-RS total score, visit and visit-by-treatment interaction as well as a random effect for the subject. The primary efficacy analysis will be based on comparisons of Azstarys® and placebo at Visit 6. From the MMRM model, the Visit 6 difference between least square (LS) means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value. The above analyses will be repeated for each age cohort separately. The primary estimand for this study is the difference in LS means of Azstarys® and placebo with respect to change from baseline in ADHD-RS total score at Visit 6, based on the primary endpoint MMRM model fitted to the Intent-to-Treat population. There will be no adjustments made for the use of prohibited therapies or other intercurrent events. The p-value associated with the primary estimand will be used to test the primary hypothesis of this study, that mean change from baseline to Visit 6 ADHD-RS total score for Azstarys® is different from that of placebo. If Azstarys® is shown to be statistically superior to placebo, then the superiority of Azstarys® to placebo will be tested for each cohort separately. As a sensitivity analysis of the primary endpoint, change from baseline in ADHD-RS total scores, the above analyses will be

	repeated in their entirety using multiple imputation methods to impute the missing data. If the primary analysis renders a significant treatment difference, a tipping point analysis will be performed in order to examine the sensitivity of inferences to departures from the missing at random (MAR) assumption. The imputed values for Azstarys® subjects' visits post discontinuation will be made worse by a delta defined as k times the treatment difference between Azstarys® and placebo obtained from the MI MAR analysis, where k is a shift parameter that is incremented in order to identify the point at which the primary analysis result becomes non-significant (the tipping point). Consideration will then be given to how plausible the imputed values are at the tipping point. If not plausible, then the conclusion for the primary analysis under the MAR assumption is supported. The secondary efficacy endpoints, change from baseline to post-baseline timepoints in ADHD-RS for hyperactivity/impulsivity and the ADHD-RS for inattention as well as change from baseline CGI-S will be analyzed using the same methods as the primary efficacy endpoint. For each endpoint, MMRM ANCOVA models will be fitted using all data as observed. The model will include fixed effects for treatment, age cohort, gender, baseline, visit, and visit-by-treatment interaction as well as a random effect for the subject. From the MMRM models, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value. The analyses will be repeated for each age cohort separately. For the CGI-I, an MMRM ANOVA model will be fitted using all data as observed. The model will include fixed effects for treatment, age cohort, gender, visit and visit-by-treatment interaction as well as a random effect for the subject. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value. The analyses will be repeated for each age cohort separately. Visit 6 CGI-I will also be compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) chi square test within each age cohort stratified by gender. An overall CMH test will also be conducted stratified by gender and age (4 strata). **Type I Error Control for Efficacy** For the primary endpoint, the hypothesis of superiority of Azstarys® to placebo will be tested at a two-sided alpha of 0.05 for the two age cohorts combined. If significant, the same hypothesis will be tested for each age cohort at a two-sided 0.05 level of significance.

	If the primary endpoint comparison is significant for Cohort 1, the superiority of Azstarys® to placebo with respect to the secondary efficacy endpoints, ADHD-RS for hyperactivity/impulsivity and ADHD-RS for inattention, will be tested for Cohort 1 only using a fixed sequence testing procedure in that order. **Safety Analysis** Descriptive statistics will be presented for baseline, all post-baseline measurements, and changes from baseline to all post-baseline measurements, where applicable, for continuous safety endpoints by treatment group, overall and separately for each age cohort. Laboratory shift tables from baseline to each post-baseline time-point will be presented. The incidence of clinically notable vital signs will be summarized. Physical examination findings will be presented in subject listings. Adverse events will be mapped to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting TEAEs will be summarized by MedDRA system organ class and preferred term, by severity, and by relationship to study treatment. The number and percentage of subjects with SAEs and TEAEs leading to treatment discontinuation will also be summarized by MedDRA system organ class and preferred term. Descriptive statistics will be presented by visit for body weight (in kg), change and percent change from baseline in body weight, height (in cm), change and percent change from baseline in height, weight and height z-scores, and weight and height percentiles by treatment group, separately for each age cohort. In addition, descriptive statistics will be tabulated by sex and optimized dose. An MMRM ANCOVA model will be fitted to change from baseline CSHQ total Sleep score. The model will include fixed effects for treatment, age cohort, gender, baseline CSHQ, visit, and visit-by-treatment interaction as well as a random effect for the subject. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI. The MMRM analysis of the change from baseline CSHQ scores will also be conducted separately for each age cohort. An MMRM ANCOVA model will be fitted to change from baseline C-SSRS score. The model will include fixed effects for treatment, age cohort, gender, baseline C-SSRS, visit and visit-by-treatment interaction as well as a random effect for the subject. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with

	the corresponding 95% CI. The MMRM analysis of the change from baseline C-SSRS scores will also be conducted separately for each age cohort. **Interim Analysis** An interim analysis will be conducted for potential sample size increase in subjects 4 and 5 years of age (Cohort 1). When approximately 50% of the Cohort 1 subjects complete their Visit 6 assessments, a blinded sample size re-estimation will be conducted. Subjects will not be identified by treatment group. The within-group standard deviation (σ) will be estimated for change from baseline to Visit 6 ADHD-RS total score using the blinded methodology of Gould and Shih. The blinded analyses will be conducted by a firewalled independent statistician. An exact sample size will not be disclosed to the sponsor. Instead, ranges of sample size will be pre-specified in the interim analysis plan and the upper limit of the applicable range will be recommended instead of the exact sample size. Since the study will remain blinded for the sample size re-assessment, no alpha penalty for the final analysis will be incurred.
STUDY PROCEDURES	The study procedures are outlined in the Schedule of Events SOE) (Section 1).

1. SCHEDULE OF EVENTS

ASSESSMENTS	SCREENING PERIOD	DOUBLE BLIND TREATMENT PERIOD					EARLY TERMINATION [19]	FOLLOW-UP PHONE CALL
Study Day	-30 to -1	0	7 (±3 days	14 (±3 days)	21 (±3 days)	28 (±3 days)	-	33 (± 2 days)
Visit Number	1	2	3	4	5	6	-	-
Parental Permission (Informed Consent)/Written or Verbal Assent (Cohort 2)	X							
ADHD Diagnosis and Confirmation [1]	X							
Inclusion/Exclusion [2]	X	X						
Demographics	X							
Medical History [3]	X	X						
Physical Examination [4]	X					X	X	
Body Weight & Height [5]	X	X	X	X	X	X	X	
Vital Signs [6]	X	X	X	X	X	X	X	
12-Lead ECG [7]	X					X	X	
Chemistry/Hematology/Urinalysis	X					X	X	
Drugs of Abuse Screen [8]	X							
Urine MPH Screen [9]	X	X						
Urine Pregnancy Test	X	X	X	X	X	X	X	
C-SSRS [10]	X	X	X	X	X	X	X	
Washout ADHD Meds [11]	X	X						
Study Drug Dispensing		X	X	X	X			
Study Drug Dosing [12]			X	X	X	X		
Dose Titration Evaluation			X	X	X			

ASSESSMENTS	SCREENING PERIOD	DOUBLE BLIND TREATMENT PERIOD					EARLY TERMINATION [19]	FOLLOW-UP PHONE CALL
Study Day	-30 to -1	0	7 (±3 days	14 (±3 days)	21 (±3 days)	28 (±3 days)	-	33 (± 2 days)
Visit Number	1	2	3	4	5	6	-	-
Drug Accountability & Compliance Assessment [13]			X	X	X	X	X	
Double-Blind Randomization [14]		X						
ADHD-RS-IV or ADHD-RS-5 [15]	X	X	X	X	X	X	X	
MINI Kid	X							
CGI-S	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	
CSHQ	X	X	X	X	X	X	X	
Adverse Events [16]		X	X	X	X	X	X	X
Concomitant Medications [17]	X	X	X	X	X	X	X	X
Rollover to Study KP415.P02 [18]						X		

ADHD = Attention-Deficit/Hyperactivity Disorder; CGI-S/I = Clinical Global Impressions – Severity/Improvement; CHSQ = Children's Sleep Habits Questionnaire ET = Early Termination; 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 by the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).
2. Study inclusion/exclusion criteria will be evaluated at Screening and Visit 2.
3. Medical History: A complete medical history including chronic conditions, relevant surgical procedures (with start date), and history of drug use.
4. Physical Examination: at Screening and at the end of the Treatment Period or ET (if possible).
5. Height will be recorded in centimeters (cm) using a stadiometer with the subject's shoes removed. Height will be recorded at Screening, Visit 2, and at the end of the Treatment Period. Body weight will be measured in kilograms (kg) using a calibrated scale; subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed. Weight will be recorded at every visit.

6. Vital signs will be collected at each visit. 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. Three (3) blood pressure measurements will be taken 2-5 minutes apart. Only the average of the 3 blood pressure measurements will be entered into the electronic case report form (eCRF).
7. 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.
8. Urine Screen for Drugs of Abuse: Urine samples will be tested for drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone) at the Screening visit. If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation.
9. Urine Screen for Methylphenidate (MPH): Urine samples will be tested for MPH by the clinical laboratory in a sample collected at the Screening Visit. A urine dipstick (e.g., NarcoCheck®) will be used to screen for the presence of MPH in the urine at Visit 2. If a subject's current ADHD medication at Screening contains MPH, the urine screen at Screening may test positive for MPH. All ADHD medications must be washed out by Visit 2 and the MPH urine screen must test negative.
10. Columbia Suicide Severity Rating Scale (C-SSRS): The "Children's Baseline/Screening" version will be assessed at Screening, and the "Children's Since Last Visit" version will be assessed at all other visits. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire will be filled in by the parent/guardian/caregiver. Subjects who have, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study. The follow-up C-SSRS will be obtained via phone.
11. Subjects must wash out ADHD medications prior to Visit 2. Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to Visit 2 to the end of the Treatment Period (Visit 6) or ET Visit. Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Period (Visit 6) or ET Visit. Before or on the day during the Screening Period that the subject 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"). Other prohibited medications and the windows of prohibition are listed in the protocol.
12. Dose Optimization/Treatment Period: Subjects will begin taking study drug at home the morning following Visit 2. The starting dose will be 13.1 mg/2.6 mg day or matching placebo in Cohort 1 and 39.2 mg/7.8 mg or matching placebo in Cohort 2. Dose adjustments, if needed, will be performed at approximately weekly intervals. Actual visit dates may deviate from exactly 7 days apart such that the total duration is 3 weeks (21 ±3 days). The daily doses of study drug used will be 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg Azstarys® or matching placebo. At Visits 3, 4, and 5 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 dose should be increased, decreased, or remain the same for the next week of dosing. If a subject experiences symptoms of intolerance during at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their 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.
13. Drug Accountability & Compliance Assessment: Study drug receipt, dispensing, and return will be recorded by each site's pharmacy staff or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site.
14. Randomization: Subjects will be randomized to Azstarys® or matching placebo within each cohort. Randomization will be stratified by gender.

15. ADHD-Rating Scale (ADHD-RS)-IV or ADHD-RS-5: (Preschool Version of ADHD-RS-IV for Cohort 1; ADHD-RS-5 for Cohort 2): 1 assessment at the indicated visits.
16. Adverse Events: To be assessed and recorded in the eCRF following the first dose of study drug, through either ET or the Follow-up Phone Call. Subject's parent/guardian will be instructed to contact the study site for the reporting of adverse events (AEs) during at-home periods.
17. Concomitant Medications: new and/or changed medications and dose, medical treatments, and/or therapies will be recorded at Screening through either the Follow-up Phone Call or ET.
18. Subjects of Cohort 1 (ages 4 and 5 years), who qualify, have the option to participate in a 12-month open-label safety study with Azstarys® (Study KP415.P02). At Visit 6 of the current study, all entry criteria to enroll in Study KP415.P02 (see protocol for Study KP415.P02) will be evaluated. Visit 6 for the current study is also Visit 2 of Study KP415.P02. Roll-over Subjects will not receive the Follow-up Phone Call in Study KP415.P01.
19. Early Termination: Subjects who meet withdrawal criteria post-dose during the Treatment Period (after at least one dose of study drug is administered) will complete ET procedures. At the discretion of the Investigator, ensuring the safety of the subjects, any Early Termination procedures that were already performed on the same day as part of the procedures of the Treatment Period, do not need to be repeated. Subjects who elect to use another ADHD treatment will be discontinued from study treatment and from the study (ET). Subjects who discontinue study treatment prior to the end of the Treatment Period because of AEs, overdosage, or use of a prohibited treatment other than an ADHD treatment will be followed (unless consent is withdrawn) with scheduled assessments until the end of the Treatment Period (Visit 6). If, during the remaining time on study, an ADHD treatment is used, the subject will be discontinued from the study (ET).
20. Assessment changes due to Coronavirus Disease 2019 (COVID-19): If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, sites will be instructed to collect data for select safety assessments (vital signs, labs, ECG, physical exam) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit. These assessments will be mapped to the nearest scheduled visit. Changes in scheduled visits and corresponding assessments due to COVID-19 restrictions will be captured in the eCRF. Assessments that do not require the subject's presence at the site (e.g., AEs, C-SSRS, ADHD-RS-IV, ADHD-RS-5; CGI-S, CGI-I, CSHQ) will be collected by phone at the scheduled visit times. If needed, alternate measures to dispense study drug to the subject during their COVID-19 isolation period will be implemented (e.g., study drug directly delivered to the subject's residence or dispensed to another family member).

2. BACKGROUND

2.1. Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurobehavioral disorder that occurs in 6% to 8% of children and 4% to 5% of adults worldwide (Wilens 2008). The 3 main symptoms of ADHD include inattention, hyperactivity, and impulsivity. ADHD is theorized to result from a deficiency of neurotransmission of dopamine and norepinephrine either through the insufficient sensitivity of the receptors or amount of dopamine produced. The most common and effective therapeutics for the treatment of ADHD are central nervous system (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 CD®, Concerta®, Daytrana®, Ritalin®, Methylin®, Quillivant XR®, 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.

According to the American Academy of Pediatrics Clinical Practice Guideline for the Evaluation and Treatment of Attention-Deficit/Hyperactivity Disorder, MPH may be considered if behavior therapy is not available or does not provide significant improvement, and there is moderate-to-severe continued disturbance in the 4- through 5-year-old child's functioning (Wolraich 2019). These guidelines go on to state that many young children with ADHD might still require medication to achieve maximum improvement. There are limited clinical studies in this age group with stimulants (MPH and amphetamines) and non-stimulants, although most of the evidence-based data is with MPH medications (Greenhill 2006).

2.2. Azstarys® Product

An extended-duration d-methylphenidate (d-MPH) product has been developed that contains immediate-release (IR) serdexmethylphenidate (SDX), a prodrug of d-MPH, co-formulated with IR d-MPH. SDX is an inactive prodrug until converted to d-MPH in vivo and thus SDX provides a molecular delivery system for d-MPH. The drug product is formulated in a fixed molar dose ratio of 70% SDX Cl:30% d-MPH HCl. Chemically, SDX consists of a single d-MPH molecule covalently attached via a carbamate bond to a methylene oxide linker, which in turn is connected to the nitrogen of the pyridine ring of a nicotinoyl-serine moiety.

The three dosage strengths of the approved formulation, for the treatment of ADHD in subjects ages 6 years and older, are as follows:

- 26.1 mg/5.2 mg Azstarys®
- 39.2 mg/7.8 mg Azstarys®
- 52.3 mg/10.4 mg Azstarys®

To accommodate the lowest dose in children of ages 4 and 5 years, capsules with 13.1 mg/2.6 mg Azstarys® have been developed.

2.3. Dose Justification

The doses used in this study for subjects 6 to 12 years of age (Cohort 2) are the same as used in previous efficacy and safety studies (Study KP415.E01 and Study KP415.S01) and are the same as approved for the treatment of ADHD (Azstarys® Package Insert 2021).

The doses used in this study for subjects 4 and 5 years of age (Cohort 1) are based on [redacted]

Extrapolation of Azstarys® Doses Based on d-MPH Dose Equivalents

[redacted]

Extrapolation of Azstarys® Doses Based on Total Systemic Exposure of d-MPH

[redacted]

Table 1: Predicted Total Systemic Exposure (AUCinf) of d-MPH in Children 4 and 5 Years of Age Utilizing Allometric Scaling of d-MPH Clearance from Observed Data in Children 6 to 12 Years of Age (Study KP415.105)

SDX/d-MPH Dose (mg)		Equimolar d-MPH HCl dose (mg)	Age (years)	Body Weight [a] (kg)	CL/F [b] (L/h)	AUC_{inf} [c] (h*ng/mL)
	Observed in Study KP415.105					
26.1/5.2		20	6-8	29.3	96.9	328
52.3/10.4		40	9-12	39.8	97.4	443
	Predicted for current study from Study KP415.105					
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. For subjects 4-5 years of age, this is the approximate median body weight from the CDC weight-for-age percentile charts.

b. For subjects 4-5 years of age, CL/F was estimated utilizing the allometric scaling equation established with observed CL/F and weight (W) values for subjects 6-17 years of age (Study KP415.105): $CL/F = 179 \times (W/70)^{0.86}$ where the coefficient (179) is CL/F for a weight of 70 kg and the exponent (0.86) is the allometric scaling factor.

c. For subjects 4-5 years of age, AUC_{inf} was calculated as follows: equimolar d-MPH HCl dose divided by predicted CL/F.

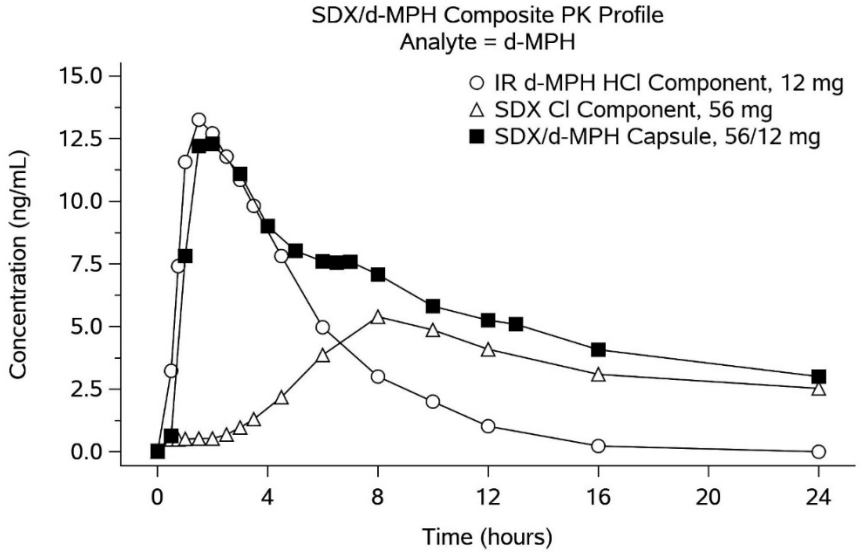
3. CLINICAL PHARMACOLOGY OF AZSTARYS® IN SUBJECTS OF AGE ≥6 YEARS

As part of the clinical development program of Azstarys®, 10 studies were conducted to examine the PK of SDX and SDX-derived d-MPH after oral administration of clinical doses of single-entity SDX Cl or Azstarys®. Of these, 5 studies were conducted after single oral doses of single-entity SDX Cl in healthy adult volunteers, 4 studies were conducted after single or multiple oral doses of Azstarys® in healthy adult volunteers, and 1 study was conducted after a single oral dose of Azstarys® in children (6- to12-years-of-age) and adolescents (13- to 17-years-of-age) with ADHD. Studies were conducted with oral solutions of SDX Cl and Azstarys®, an early capsule formulation of single-entity SDX Cl, or with the final, marketed Azstarys® capsules.

The key findings of the clinical pharmacology program are as follows:

- The PK profile of Azstarys® capsules is a composite of the underlying d-MPH exposure derived from the d-MPH HCl and SDX Cl components (Figure 1). After oral administration, early d-MPH exposure is governed by the d-MPH HCl component and mid- to late-day exposure is governed by gradual, intra-intestinal conversion of inactive SDX to active d-MPH. Similar and predictable d-MPH PK profiles were observed in children (6 to 12 years old), adolescents, and adults, and as a result, the efficacy profiles are also expected to be similar in all 3 age groups.

Figure 1: Plasma Concentration-Time Profiles of d-MPH Predicted for 12 mg immediate-release (IR) d-MPH HCl Component (Based on Dose-Adjusted Focalin Data), 56 mg SDX Cl Component (Dose-Adjusted Data from KP415.108), and 56/12 mg Azstarys® Capsule (Study KP415.107)



PK profile for IR d-MPH HCl, 12 mg component approximated using dose-adjusted data for 2×10 mg Focalin administered orally under fasted condition in Celgene-sponsored study PK-00-001 as reported in the Focalin NDA 21-278 Summary Basis of Approval.
PK profile for SDX Cl, 56 mg component predicted with dose-adjusted data for 60 mg SDX Cl administered orally under fasted condition in study KP415.108 (Treatment A).
PK profile for Azstarys® capsule under fasted conditions, 56/12 mg based on data from study KP415.107 (Treatment B).

- Azstarys® capsules were not bioequivalent to the Reference Listed Drug, Focalin XR (Focalin XR label 2019), with respect to d-MPH exposure. The long-term safety of Azstarys® capsules was established in a clinical trial in patients with ADHD 6- to 12-years-of-age. The efficacy of Azstarys® was evaluated in a laboratory classroom study in children (ages 6 to 12 years) with ADHD. A bridge of the efficacy findings to older age groups is based on PK data with Azstarys® in adolescents and adults, and by relying on the overall efficacy of d-MPH as established by Focalin XR for children, adolescents, and adults.

- Since the systemic exposure of d-MPH after oral administration of a 56/12 mg Azstarys® capsule is not higher than after 40 mg Focalin XR, prior findings of efficacy and safety for Focalin XR (Focalin XR label 2019) can be referenced to support, at least in part, efficacy and safety of Azstarys® capsules.

- Administration of Azstarys® capsule under fed condition (high fat/high calorie meal) and administration of capsule contents sprinkled on applesauce increased peak d-MPH plasma exposure (C_{max}) by 24% and 34%, respectively, and delayed median T_{max} by 1.75 and 2.00 h, respectively, with no significant increase in overall exposure ($AUC_{0\text{-}inf}$). Administration of Azstarys® capsule contents mixed in water under fasted condition was bioequivalent when compared to administration of intact Azstarys® capsule under the fasted condition. Based on these results, Azstarys® capsules can be administered without regard to food. Mixing the capsule contents in water or sprinkling on applesauce are acceptable alternative modes of oral drug administration.

- Following administration of 28/6 mg, 46/9 mg, and 56/12 mg Azstarys® capsules, d-MPH C_{max} and AUC values increased proportionally with an increase in Azstarys® dose over the dose range studied.

- Following multiple doses of 56/12 mg Azstarys® capsules, steady-state of d-MPH was reached after the second dose, with minimal accumulation of d-MPH when comparing Dose 4 to Dose 1. No accumulation of intact SDX was observed with repeat-dosing.

- Following oral administration of 60 mg [^{14}C]-SDX Cl:

    - The mean combined total recoveries of radioactivity in feces and urine over 168 h was 98.9%. The mean total radioactivity recovered in urine and feces were 62.1% and 36.8%, respectively.

    - No SDX-unique metabolites were identified in plasma.

    - Ritalinic acid was the most abundant metabolite in all matrices (i.e., plasma, urine, feces). SDX was only found at trace levels in urine (0.43% of total dose) but was the second most abundant species in the feces, accounting for 10.8% of the total dose. Recovery of d-MPH was generally low in urine and feces, accounting for 2.74% of total dose observed in both excreta.

- Following oral administration, the pharmacologically inactive SDX is largely confined to the intestinal tract until it is converted in the lower intestine to active d-MPH or excreted unchanged in feces. Due to the charged nature of SDX and lack of substrate activity at common transporters, it has poor permeability across cellular membranes, resulting in both minimal systemic absorption and poor tissue penetration. The small fraction of oral SDX that is absorbed (mean oral bioavailability [F]< 3%) remains largely in the intravascular fluid where it remains mostly unmetabolized until excreted unchanged in urine (0.43% of an oral dose of SDX Cl is excreted unchanged).

- The collective nonclinical and clinical safety package have indicated no unique biological effects or toxicities related to SDX as the intact prodrug. Thus, the only role of SDX is to provide a molecular mechanism to gradually and consistently deliver active d-MPH to the patient.

- Following Azstarys® administration (after adjusting for dose), systemic exposure to d-MPH was higher in younger children because CL/F increased with age due to intrinsic body weight differences between younger children and adolescents. As a result, when normalized for body weight, CL/F values of d-MPH were comparable across age groups. Similarly, V_z/F increased with age but when normalized for body weight, V_z/F values of d-MPH were more comparable across age groups. Body weight is thus an appropriate scaling factor between adolescents and children (6 to 12 years old) for exposure of d-MPH after oral Azstarys® dosing.

4. STUDY RATIONALE

The current study will investigate the efficacy and safety of Azstarys® compared to placebo in children with ADHD ages 4 to 12 years.

5. STUDY OBJECTIVES

5.1. Primary Objective

- To determine the efficacy of Azstarys® compared to placebo in treating children ages 4 to 12 years old with ADHD.

5.2. Secondary Objectives

- To determine the safety and tolerability of Azstarys® compared to placebo in treating children 4 to 12 years old with ADHD. The safety objective includes changes in weight and height, and sleep behavior.

6. INVESTIGATIONAL PLAN

6.1. Study Design

This is a multicenter, dose-optimized, randomized, double-blind, efficacy and safety study with Azstarys® in children 4 to 12 years of age with ADHD.

The phases of the study are as follows:

- **Screening Period (Visit 1):**
  Subjects will undergo a Screening Period up to 30 days prior to entering the Treatment Period.
- **Double-Blind Treatment Period (Day after Visit 2 through Visit 6):**
  Eligible subjects will be randomized to Azstarys® or placebo at the start of the Treatment Period. Randomization will be applied to each cohort separately and will be stratified by gender.
    - **Cohort 1**: 4 and 5 years old
    - **Cohort 2**: 6 to 12 years old

During the Treatment Period:

- **Cohort 1:** Subjects 4 and 5 years (<6 years): will start at 13.1 mg/2.6 mg Azstarys® or matching placebo and may be titrated to doses of 26.1 mg/5.2 mg, 39.2 mg/7.8 mg Azstarys® or matching placebo through Visit 5
- **Cohort 2:** Subjects 6 to 12 years (<13 years): will start at 39.2 mg/7.8 mg or matching placebo and may be titrated to doses of 26.1 mg/5.2 mg, 52.3 mg/10.4 mg Azstarys® or matching placebo through Visit 5

- **Roll-over into Study KP415.P02:**
  Subjects of Cohort 1 (ages 4 and 5 years), who qualify, have the option to participate in a 12-month open-label safety study with Azstarys® (Study KP415.P02). At Visit 6 of the current study, all entry criteria to enroll in Study KP415.P02 (see protocol for Study KP415.P02) will be evaluated (Visit 6 for the current study is also Visit 2 of Study KP415.P02).
- **Follow-up Phone Call:**
  Subjects who will not be rolled over into Study KP415.P02 will receive a Follow-up Phone Call, at 5 ±2 days after administration of the last dose of the Treatment Period.

Subjects who elect to use another ADHD treatment will be discontinued from study treatment and from the study (Early Termination [ET]).

Subjects who discontinue study treatment prior to the end of the Treatment Period because of adverse events (AEs), overdosage, or use of a prohibited treatment other than an ADHD treatment will be followed (unless consent is withdrawn) with scheduled assessments until the end of the Treatment Period (Visit 6). If, during the remaining time on study, an ADHD treatment is used, the subject will be discontinued from the study (ET).

6.2. Study Duration

Subjects will participate in the study as out-patients for up to 65 days, including up to 30 days of Screening, up to 28 days in the Treatment Period, and a Follow-up Phone Call up to 7 days (5 ±2 days) after the administration of the last dose of the Treatment Period.

7. SUBJECT SELECTION

7.1. Number of Subjects

In each age cohort, an appropriate number of subjects will enter the Screening Period to enroll approximately the following number of subjects in the Treatment Period:

- **Cohort 1 (4 and 5 years of age):** 130 subjects (65 per arm) with the intention to complete with approximately 120 subjects.
- **Cohort 2 (6 to 12 years of age):** 100 subjects (50 per arm) with the intention to complete with approximately 90 subjects.

The additional number of subjects enrolled is based on an approximate 10% early discontinuation rate. Subjects who terminate early in the Treatment Period will not be replaced.

A blinded sample size re-estimation will be conducted when approximately 50% of subjects in Cohort 1 have completed Visit 6. The sample size may be increased based on that analysis. Details are provided in the Interim Analysis section below (Section 17.6).

In accordance with a male-to female distribution ratio of 3:1 of children diagnosed with ADHD in clinical practice (Barkley 2006; Gaub 1997), it is anticipated that approximately 75% males and 25% females will be enrolled.

7.2. Study Population

Children 4 and 5 years old (Cohort 1) and 6 to 12 years old (Cohort 2) with ADHD who meet the inclusion/exclusion criteria listed below.

7.2.1. Inclusion Criteria

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

1. In Cohort 1, subjects must be at least 4 years old and less than 5 years and 10 months at Screening; in Cohort 2, subjects must be at least 6 years old and less than 12 years and 10 months at Screening.
2. Subjects must have a body weight within the 5th and 95th percentile according to the gender-specific weight-for-age percentile charts from the CDC. See calculator at https://www.infantchart.com/child/.
3. Female subjects must agree, if 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. 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 12 years of age 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. Subjects must be in general good health defined as the absence of any clinically relevant abnormalities as determined by the Investigator based on physical examinations, vital signs, electrocardiograms (ECGs), medical history, and clinical laboratory values (chemistry, hematology, urinalysis) at Screening. If any of the chemistry or hematology tests 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 voluntarily give written permission for him/her to participate in the study.
6. Subjects in Cohort 2 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 Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).

8. Subject has had ADHD symptoms present for at least 6 months prior to the Screening Visit.
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 Treatment Period, and abstain from taking these to the end of Visit 6 or ET; and wash out non-stimulant ADHD medications from 14 days prior to the start of the Treatment Period, and abstain from taking these to the end of Visit 6 or ET.
10. Subject must have a score of ≥4 (Moderately 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.
11. Subjects must have age and sex adjusted ratings of ≥90th percentile Total Score on the ADHD-Rating Scale (ADHD-RS) rated over the past 6 months (for 4- and 5-year-old children, use Preschool Version of ADHD-RS-IV; for 6-12 years old children, use ADHD-RS-5).
12. Subject functions at an age-appropriate level intellectually, as determined by the Investigator.
13. Subject must have a systolic and diastolic blood pressure below the 95th percentile for age and gender according to the 2017 AAP guidelines (Flynn 2017) based on the average of 3 measurements 2-5 minutes apart.
14. 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.
15. Subject, parent/legal guardian, and caregiver (if applicable) must be able to speak and understand English or Spanish and be able to communicate satisfactorily with the Investigator and study coordinator.

7.2.2. Exclusion Criteria

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 urine pregnancy test at the start of the Screening Period. In addition, a positive pregnancy test before the last dose of study drug will result in early termination from the study.
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 CNS such as tumors, inflammation, seizure disorder, depression, 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.
6. Subject taking anticonvulsants for seizure control or antidepressants currently or within the past 2 years before Screening are not eligible for study participation. A past history of febrile seizure or drug-induced seizure is allowed.
7. Subject has a current (last month) psychiatric diagnosis other than specific phobia, motor skills disorders, ODD, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders. Subjects allowed to enroll with any of these DSM disorders will require written justification from the Investigator documenting why the conditions will not interfere with participation and to emphasize that ADHD is the primary indication.
8. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the Columbia-Suicide Severity Rating Scale (C-SSRS) assessment at Screening.
9. Subject has any clinically significant unstable medical abnormality, chronic disease (including asthma or diabetes), 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 absorption, distribution, metabolism, or excretion of study drug. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the medical monitor should be consulted. Any subject with a known cardiovascular disease or condition (even if controlled) must be discussed with the Medical Monitor during Screening.
10. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant.
11. Subject has a history of, or currently has, a malignancy.
12. Subject has uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) $\leq$0.8 x the lower limit of normal (LLN) or $\geq$1.25 x the upper limit of normal (ULN) for the reference laboratory at Screening.
13. Subject has greater than trace proteinuria in the urinalysis at Screening. Subjects with greater than trace proteinuria in the urinalysis at Screening but with a urine protein to creatinine ($U_{P/C}$) ratio <0.2 in a first morning void urine sample will not be excluded from enrollment.

14. Subjects has a current or recent (past 12 months) history of drug abuse; or current or recent history of drug abuse in someone living in the subject's home or are using or planning to use prohibited drugs during the trial as specified in the protocol.
15. Subject has a positive urine drug screen at Screening. Subjects with a positive MPH 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.
16. Subject has participated in any other clinical study with an investigational drug/product within 30 days or at least 5 half-lives, whichever is longer, prior to Screening.
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 intolerability to adequate dose and duration of treatment with MPH products. Judgment of adequate dose and duration is at the discretion of the Investigator.
19. Subject has a positive urine MPH screen by dipstick (e.g., NarcoCheck®) at Visit 2.
20. Subject is planning to initiate psychotherapy during the study (subjects participating in psychotherapy beginning at least 4 weeks before study initiation are permitted to continue).
21. Subject has a history of severe allergies or adverse drug reactions to more than one class of medications.
22. Subject has a history of allergic reaction or a known or suspected sensitivity to MPH or any substance that is contained in the study drug.
23. 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.
24. 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.
25. Subject has one or more siblings living in the same household who are enrolled in this or another clinical drug trial.
26. Subject shows evidence of current physical, sexual, or emotional abuse.
27. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

8. STUDY TREATMENTS

8.1. Study Treatments:

Blinded study drug (Azstarys® or placebo capsules) will be used in the Treatment Period.

8.1.1. Azstarys® Capsules

Azstarys® capsules contain two active pharmaceutical ingredients: d-methylphenidate (dexmethylphenidate; d-MPH) hydrochloride, and serdexmethylphenidate (SDX; a prodrug of d-MPH). In terms of total d-MPH dose amounts, all capsule strengths contain 30% d-MPH and 70% d-MPH in the form of the prodrug. 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.

d-MPH (mg)	SDX (d-MPH) [1] (mg)	Total d-MPH dose [2] (mg)	Equimolar d-MPH HCl dose (mg)
2.6	13.1 (6.1)	8.6	10
5.2	26.1 (12.2)	17.3	20
7.8	39.2 (18.3)	25.9	30
10.4	52.3 (24.4)	34.6	40

1. This is the dose of SDX. The amount of d-MPH equimolar to each SDX dose is listed in parentheses.
2. The total dose of d-MPH expressed in terms of free base.

The inactive ingredients in Azstarys® capsules include: colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, and talc.

Azstarys® is a Schedule II controlled substance. Therefore, study sites are required to have the appropriate permit from the Drug Enforcement Agency (DEA) to receive, store, ship and dispense Azstarys® according to all local, state, and federal regulations for Schedule II controlled substances.

8.1.2. Placebo Capsules

Placebo capsules will visually match the Azstarys® capsules and will contain the following inactive ingredients only: colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, and talc.

8.2. Treatment Assignment

All subjects will receive study drug, as follows:

At Visit 2, subjects will be randomized in a blinded fashion to either Azstarys® or placebo. Randomization will be applied to each cohort separately and will be stratified by gender.

During the Treatment Period, daily treatments of double-blind study drug (one capsule per day) will be administered for titration to an optimal daily dose. Subjects randomized to placebo will receive the dose-associated matching placebo capsules.

- **Cohort 1**: Subjects 4 and 5 years (<6 years): will start at 13.1 mg/2.6 mg Azstarys® or matching placebo and may be titrated to doses of 26.1 mg/5.2 mg, 39.2 mg/7.8 mg Azstarys® or matching placebo at Visits 3, 4, and/or 5.
- **Cohort 2**: Subjects 6-12 years (<13 years): will start with at 39.2 mg/7.8 mg or matching placebo and may be titrated to doses of 26.1 mg/5.2 mg, 52.3 mg/10.4 mg Azstarys® or matching placebo at Visits 3, 4, and/or 5.

The daily dose may be changed at Visits 3, 4 and 5 based on a combination of individual tolerability and effect assessed by the Investigator. If a lack of tolerability should occur between visits, the dose may be lowered at any time.

The optimized daily dose will be determined at Visit 5 and will be kept the same for the remainder of the Treatment Period, with the following exception: if a lack of tolerability should occur, the dose may be lowered at any time.

8.3. Drug Administration

All study drug will be taken orally within 20 minutes after consuming breakfast, at approximately the same time in the morning of each day.

Study drug will be swallowed whole (without crushing, cutting, chewing, opening, or dissolving) or may be taken by sprinkling the contents of the capsule over a small amount of applesauce. See Appendix A for detailed instructions of the oral administration of study drug.

On each day at home (no scheduled visits to the study site) during the Treatment Period, the assigned study drug will be taken under the supervision of the subject's parent or caregiver.

On days with scheduled visits to the study site, subjects will take the assigned study drug either at home under the supervision of the subject's parent or caregiver before coming to the study site for their scheduled visit, or if their visit occurs in the morning, subjects may take the assigned study drug at the study site under the supervision of site staff.

8.4. Blinding

Study drug will be blinded during the Treatment Period. Neither the subject, the Investigator, nor 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 all 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 subject's treatment assignment is essential for the clinical management or welfare of the subject, the Investigator should contact the Medical Monitor (or designee). Prior to unblinding the subject's treatment assignment, the Investigator should assess the relationship of an AE to the administration of the study drug (Yes or No). The Investigator must then contact the Medical Monitor to unblind an individual subject'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 a serious adverse event (SAE) is reported, the Medical Monitor (or designee) may unblind the treatment assignment for an individual subject for expedited regulatory reporting requirements.

8.5. Compliance

Study drug receipt, dispensing, and return will be recorded by each site's pharmacy staff or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by the clinical site. Drug accountability and compliance will be evaluated at each visit in the Treatment Period and will be based on the number of dispensed and returned capsules for each subject. Subjects will be asked

to bring their unused medication to the clinical site at each visit.

Acceptable compliance is defined as 80-100% (inclusive). If compliance between subsequent scheduled visits is outside this acceptance range, or cannot be determined (when, for example, the subject did not return unused study drug), the Investigator or designee will counsel the parent/legal guardian. If a subject is noncompliant more than once, the Investigator will discuss the subject's noncompliance with the Medical Monitor, to decide whether the subject should be terminated early from further participation in the study.

9. STUDY PROCEDURES

The study will consist of a Screening Period, a Double-Blind Treatment Period, and a Follow-up Phone Call. 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.

For instructions on procedures to follow if a subject is unable to attend a visit due to Coronavirus Disease 2019 (COVID-19) restrictions, see Section 9.10.2.

9.1. Screening Procedures

Subjects will complete the Screening Visit within 30 days (Day -30 to Visit 2) prior to starting the Treatment Period. Prior to conducting any study-related activities, including screening procedures, written Informed Consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the parent/legal guardian. For subjects 6 to 12 years old, the Informed Assent must be completed.

The following information collection/assessments will be performed at the Screening Visit:

1. Informed Consent and HIPAA authorization by one parent/legal guardian of the subject.
2. Informed Assent by the subject (Cohort 2, 6 years and older).
3. Subject demographics including date of birth, sex, race, and ethnicity.
4. Review of inclusion/exclusion criteria to determine study eligibility.
5. Record (with start date and stop date [if applicable]) medical history, including chronic conditions, relevant surgical procedures, and medications, including treatments and therapies for ADHD.
6. A complete physical examination.
7. Body weight and height.
8. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature). Three (3) blood pressure measurements will be collected 2-5 minutes apart. The average of the three measurements will be entered into the eCRF.
9. Perform the clinician-administered CGI-S scale assessment. Subjects must have a CGI-S score of ≥4 (Moderately Ill) for further study participation. For subjects requiring washout of ADHD medications, this criterion refers to a score following washout.
10. Perform the ADHD-RS-5 for Cohort 2 and the ADHD-RS-IV assessment for Cohort 1 subjects. Scores will be obtained during a clinician-directed interview with the

parent/guardian/caregiver present. The ADHD subtype in each subject (combined subtype, impulsive/hyperactive subtype, etc.) will be recorded.

11. Perform the MINI Kid.
12. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.
13. Perform the C-SSRS assessment, "Children's Baseline/Screening" version. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire will be completed by the parent/guardian/caregiver. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on a history of attempted suicide and the C-SSRS assessment, will be excluded from enrollment in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
14. 12-lead ECG after subject has been in 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.
15. Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained under fasted or non-fasted conditions (fasted/non-fasted state will be recorded). Clinical laboratory measurements may be repeated at the discretion of the Investigator. Subjects with a greater than trace proteinuria will be asked to provide the study site a morning void urine sample (unscheduled urine sample) to rule out orthostatic proteinuria. This urine sample will be sent to the clinical laboratory where urine protein and creatinine will be quantified and the $U_{P/C}$ ratio will be calculated to rule out "false positive" proteinuria. The morning void urine sample will be collected by the parent/guardian/caregiver under direction of the study site, and will be dropped off at the study site.
16. Urine pregnancy test for female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
17. Perform urine screen for drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone). If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation.
18. Urine samples will be tested for MPH in a clinical laboratory. If the urine test is positive for MPH 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 may test positive for MPH. All ADHD medications must be washed out by Visit 2. Subjects with a positive MPH urine screen by dipstick (e.g., NarcoCheck®) at Visit 2 will be excluded from further participation in the study or may be retested at a later date, and may be enrolled if the MPH urine screen retest is negative, as long as the Screening window has not expired.
19. Before or on the day during the Screening Period that the subject 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 current ADHD medication washout ("Washout Phone Call"). Stimulant ADHD medications, including herbal medications, are prohibited from 5 days prior to Visit 2

to the end of the Treatment Period (Visit 6) or ET Visit. Non-Stimulant ADHD medications are prohibited from 14 days prior to the start of the Treatment Period (Visit 2) to the end of the Treatment Period (Visit 6) or ET Visit. Other prohibited medications and the windows of prohibition are listed in the protocol.

After a subject completes the screening procedures and is considered eligible to take part in the clinical study, they will be instructed when to return to the site to begin the Treatment Period (Visit 2).

9.2. Rescreening

Subjects who require extension of the screening window and remain eligible for the study may be rescreened upon written approval of the Medical Monitor. Subjects who screen fail will not be rescreened.

9.3. Start of Treatment Period (Visit 2)

After a subject complete the screening procedures and is considered eligible to take part in the clinical study, they will be instructed when to begin washout of disallowed medications/treatments and when to return to the clinic at Visit 2 to begin the Treatment Period.

1. Review of inclusion/exclusion criteria to determine whether subject continues to meet study eligibility.
2. Update medical history.
3. Review of concomitant medications, treatment and/or therapies, with special attention to whether the subject has washed out of disallowed medications/treatments in the appropriate time frames before Visit 2.
4. Body weight and height.
5. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature). Three (3) blood pressure measurements will be collected 2-5 minutes apart. The average of the three measurements will be entered into the eCRF.
6. Perform the ADHD-RS-5 for Cohort 2 and the ADHD-RS-IV assessment for Cohort 1 subjects. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.
7. Perform the clinician-administered CGI-S scale assessment. Subjects must have a CGI-S score of ≥4 (Moderately Ill) for further study participation.
8. Perform the CSHQ assessment.
9. Perform the C-SSRS assessment, “Children’s Baseline/Screening” version. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire will be completed by the parent/guardian/caregiver. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on a history of attempted suicide and the C-SSRS assessment, will be excluded from 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.

10. Subjects with a positive MPH urine screen by dipstick (e.g., NarcoCheck®) at Visit 2 will be excluded from further participation in the study. Subjects must have washed out ADHD medications from 5 days prior to Visit 2 and must not use ADHD medications, other than study drug, to the end of the Treatment Period (Visit 6).
11. Urine pregnancy test for female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
12. Assessment and review of AEs. Subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
13. Randomize subjects, by cohort, on a 1:1 basis to double-blinded treatment (Azstarys® or placebo) according to the randomization schedule. Randomization will be stratified by gender within each cohort. The assigned treatment group will be maintained during the Treatment Period; although, the dose may change during dose optimization.
14. Provide subject with double-blind study drug for daily oral administration at home until the next visit. See Section 8 for further details on study treatment and administration.

9.4. At Home During the Treatment Period (Non-visit Days)

While at home during the Treatment Period, subjects will receive study drug according to the procedures detailed in Section 8.3 and Appendix A.

9.5. Treatment Period (Visits 3, 4, and 5)

The following procedures will be performed at Visits 3, 4, and 5:

1. Subjects will take the assigned study drug either at home under the supervision of the subject's parent or caregiver before coming to the study site for their scheduled visit, or if their visit occurs in the morning, subjects will take the assigned study drug at the study site under the supervision of site staff.
2. Record the number of returned and administered capsules of study drug for drug accountability and compliance. Unused study drug will remain at the site.
3. Body weight.
4. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature). Three (3) blood pressure measurements will be collected 2 -5 minutes apart. The average of the three measurements will be entered into the eCRF.
5. Perform the ADHD-RS-5 for Cohort 2 and the ADHD-RS-IV assessment for Cohort 1 subjects. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.
6. Perform the clinician-administered CGI-S scale assessment.
7. Perform the Clinical Global Impressions–Improvement (CGI-I) scale assessment.
8. Perform the CSHQ assessment.
9. Perform the C-SSRS assessment, "Children's Baseline/Screening" version. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire

will be completed by the parent/guardian/caregiver. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on a history of attempted suicide and the C-SSRS assessment, will be excluded from 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.

10. Urine pregnancy test for female subjects of childbearing potential. A positive pregnancy test will exclude a subject from further participation in the study.
11. Review of concomitant medications, treatment and/or therapies.
12. Assessment and review of AEs. Subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
13. Study drug dose adjustments. The Investigator will evaluate the subject's therapeutic responses and tolerability to treatment, and decide whether the current dose should be increased, decreased, or remain the same for the next week.
14. Provide subject with double-blind study drug for daily oral administration at home until the next visit. See Section 8 for further details on study treatment and administration. Dose adjustments from the previous visit will be performed if needed based on the Investigator's assessment.

9.6. End of Treatment Period (Visit 6) or Early Termination Visit

At Visit 6, the last day of the Treatment Period, the final dose of double-blind study drug will be administered.

ET procedures are not required for subjects who fail Screening prior to receiving study drug.

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

Subjects who withdraw early from the study and complete the ET procedures will not have a Follow-up Phone Call. Therefore, the ET Visit is the end of study (EOS) for these subjects.

The following procedures will occur during Visit 6 of the study or at the ET Visit, unless otherwise specified.

1. Subjects will take the assigned study drug either at home under the supervision of the subject's parent or caregiver before coming to the study site for their scheduled visit, or if their visit occurs in the morning, subjects may take the assigned study drug at the study site under the supervision of site staff. May not be applicable for the ET Visit.
2. Record the number of returned and administered capsules of blinded study drug for drug accountability and compliance. Unused study drug will remain at the site.
3. Body weight and height.
4. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after subject has been sitting for a minimum of 3 minutes. Three (3) blood pressure measurements will be collected 2-5 minutes apart. The average of the three measurements will be entered into the eCRF.

5. Perform the C-SSRS assessment, "Children's Since Last Visit" version. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire will be filled in by the parent/guardian/caregiver. Subjects with clinically significant suicidal ideation/behavior, in the opinion of the Investigator, based on a history of attempted suicide and the C-SSRS assessment, will be referred for further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
6. Perform the ADHD-RS-5 for Cohort 2 and the ADHD-RS-IV assessment for Cohort 1 subjects. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.
7. Perform the clinician-administered CGI-S scale assessment.
8. Perform the Clinical Global Impressions–Improvement (CGI-I) scale assessment.
9. Perform the CSHQ assessment.
10. A complete physical examination.
11. Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained under fasted or non-fasted conditions (fasted/non-fasted state will be recorded). Clinical laboratory measurements may be repeated at the discretion of the Investigator. Subjects with a greater than trace proteinuria will be asked to provide the study site a morning void urine sample (unscheduled urine sample) to rule out orthostatic proteinuria. This urine sample will be sent to the clinical laboratory where urine protein and creatinine will be quantified and the $U_{P/C}$ ratio will be calculated to rule out "false positive" proteinuria. The morning void urine sample will be collected by the parent/guardian/caregiver under direction of the study site, and will be dropped off at the study site.
12. Urine pregnancy test for female subjects of childbearing potential.
13. 12-lead ECG after subject has been in 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.
14. Review of concomitant medications, treatment and/or therapies.
15. Assessment of AEs.
16. Subjects in Cohort 1, who have completed the Treatment Period and who qualify, have the option to participate in a 12-month open-label safety study with Azstarys® (Study KP415.P02). At Visit 6 of the current study, all entry criteria to enroll in Study KP415.P02 (see protocol for Study KP415.P02) will be evaluated. Visit 6 for the current study is also Visit 2 of Study KP415.P02. Roll-over Subjects will not receive the Follow-up Phone Call of Study KP415.P01. Subjects who terminate early may not roll over to Study KP415.P02.

9.7. Follow-up Phone Call

Subjects who will not be rolled over into Study KP415.P02 will receive a Follow-up Phone Call at 5 ±2 days after administration of the last dose of the Treatment Period for the evaluation of safety parameters.

The following will be completed during the Follow-up Phone Call:

1. Review of concomitant medications, treatment and/or therapies.
2. Assessment of AEs.

The Follow-up Phone Call is the EOS for subjects who receive the call.

9.8. End of Study (EOS)

The EOS is one of the following:

- The Follow-up Phone Call for subjects who complete the Treatment Period and are not rolled over into Study KP415.P02.
- Visit 6 for subjects who complete the Treatment Period and are rolled over into Study KP415.P02.
- The ET Visit for subjects who withdraw early from the study.

9.9. Unscheduled Visits

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

Unscheduled visits can occur at any time during the study. Examples of reasons to conduct an unscheduled visit:

- If a subject experiences an AE during at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, further in-person medical evaluation and review may be performed.
- If a subject experiences symptoms of intolerance during at-home treatment or have complaints about increases in ADHD symptoms, they must contact the clinical site, and, at the discretion of the Investigator, their 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). Three (3) blood pressure measurements will be collected approximately 2-5 minutes apart. The average of the three measurements will be entered into the eCRF.
3. Assessment and review of AEs.
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 AEs):
    a. Physical examination.

b. 12-lead ECG after subject has been in 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.

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

d. Clinical laboratory assessments (under fasted or non-fasted conditions).

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

   a. If needed, perform an assessment of ADHD severity. This may include an ADHD-RS, CGI-S, and/or CGI-I scale assessment.
   b. If needed, perform a dose adjustment: based on the ADHD severity assessment, interview with the parent/guardian/caregiver, and safety data, the Investigator will evaluate the subject's therapeutic response and tolerability to treatment, and decide whether the current dose should be increased, decreased, or remain the same. On any day during the study, the daily dose will be either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg Azstarys® or matching placebo capsules.

If a subject meets any of the withdrawal criteria during the Unscheduled Visit, the subject will be withdrawn, and ET procedures will be completed.

9.10. Visit and Assessment Changes Due to COVID-19

9.10.1. General Guidelines

Due to the COVID-19 public health emergency and in alignment with the Food and Drug Administration (FDA) Guidance for Industry, Investigators, and Institutional Review Boards entitled FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (March 2020; updated August 30, 2021), alternative measures will be implemented for some subjects and/or sites participating in the study. Measures will be implemented on an "as needed" basis, to maintain trial continuity, sustain subjects' access to study drug and ensure the continued safety of subjects and the integrity of the study data. Where it is possible, the study will be conducted in accordance with the protocol. However, for some study subjects and sites, the COVID-19 public health emergency and resulting "stay at home" orders, site closures, and travel limitations may lead to difficulties in meeting protocol-specified procedures, including on-site delivery of investigational product and adhering to protocol-mandated on-site visits and laboratory/diagnostic testing for the study. In these circumstances, alternative measures will be employed and documented as protocol deviations that will be summarized within the CSR. These alternative measures are intended to remain in effect only for the duration of the public health emergency related to COVID-19, and are applied only if an on-site study visit cannot occur. The

measures include the delivery of study drug directly to subject's residence and replacing on-site study visits with remote study visits, which may include:

- Adaptation of efficacy assessments
- Alternative methods for safety assessments

A listing of all subjects affected by the COVID-19 related study disruption by subject number and by investigational site, and a description of how the individual's participation was altered will be generated. Specifically, the listing will include, but is not limited to, the following:

- Subjects who had on-site visits converted into remote visits
- Subjects who had visits and/or assessments not performed/missing along with the reason
- Subjects who had efficacy and safety data collected out of window

All of the above study changes will be captured as protocol deviations. Additionally, these data will be captured in the eCRF.

9.10.2. Study-specific Guidelines

If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, sites will be instructed to collect data for select safety assessments (vital signs, labs, ECG, physical exam) when the subject is next able to safely return to an on-site visit, even if those assessments would not normally be done at that visit. These assessments will be mapped to the nearest scheduled visit. Changes in scheduled visits and corresponding assessments due to COVID-19 restrictions will be captured in the eCRF. Instructions will be included in the eCRF completion guidelines for capturing visits and/or assessments that were missed (not performed), delayed, or performed remotely. The following visit and assessment changes will be included in submission datasets:

- All on-site visits that were converted to remote visits due to COVID-19 restrictions will be flagged. This information will be captured in the eCRF and protocol deviation log.
- Missed visits and assessments are flagged if the "not done" field is indicated and the comment field indicates "COVID-19."

Assessments that do not require the subject's presence at the site (e.g., AEs, C-SSRS, ADHD-RS, CGI-S, CGI-I, CSHQ) will be collected by phone at the scheduled visit times.

If needed, alternate measures to dispense study drug to the subjects during their COVID-19 isolation period will be implemented (e.g., study drug directly delivered to the subject's residence or dispensed to another family member).

10. CONCOMITANT MEDICATIONS AND RESTRICTIONS

Subjects will be instructed not to consume any of the below products; however, allowance for an isolated incidences will be evaluated and approved by the study Investigator based on the potential for interaction with the study drug, and impact on subject safety and the validity of the study results.

10.1. Concurrent Medication Restrictions

Permitted and must be reported at Screening:

- ADHD medications, current at Screening and during the 6 months prior to Screening.

- Melatonin, which is allowed if subjects have taken it for more than 30 days before Screening.

Restricted Medications:

Subjects will be prohibited/limited to receive certain medications in the trial, as follows:

- Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Treatment Period to the end of the Treatment Period or ET Visit. These include: MPH, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, d-MPH, Focalin®, dextroamphetamine, Dexedrine®, Adderall®, Vyvanse ® and prescription Azstarys®.
- Non-stimulant ADHD medications are prohibited from 14 days prior to the start of the Treatment Period to the end of the Treatment Period or ET Visit. These include: Atomoxetine, guanfacine, and clonidine.

The following medications are prohibited from 14 days prior to the start of the Treatment Period to the end of the Treatment Period or ET Visit:

- Monoamine oxidase inhibitors (MAOIs).
- NRIs and SSRIs such as fluoxetine, paroxetine, and viloxazine.
- Mood stabilizers (e.g., lithium, valproate, quetiapine).
- Antipsychotics (e.g., risperidone, olanzapine).
- Coumarin anticoagulants.
- Anticonvulsants.
- Halogenated anesthetics.
- Phenylbutazone
- Sedative hypnotics/sleep enhancers (with the exception of melatonin, which is allowed if subjects have taken it for more than 30 days before Screening).
- Tricyclic antidepressants as well as Bupropion are prohibited from 30 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit.
- Cough and cold medications containing stimulants and/or sedating antihistamines are prohibited from 30 days prior to the start of the Treatment Period to the end of the Treatment Period (Visit 6) or ET Visit.

All other concomitant medications will be allowed if necessary. Concomitant use of prescription or nonprescription medications, including reasons for use, will be reviewed, and recorded on the eCRF from the Screening Period through the Follow-up Phone Call.

Note: Subjects who are rolled over into Study KP415.P02 after the end of the Treatment Period in the current study will need to continue to abstain from prohibited medications as explained in the protocol for Study KP415.P02.

10.2. General Restrictions

Female subjects must agree, if 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.

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 the Follow-up Phone Call.

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 12 years of age (including girls who will become 13 years 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."

11. INVESTIGATIONAL PRODUCT

11.1. Active Pharmaceutical Ingredients

The Azstarys® capsules contain two active pharmaceutical ingredients: d-methylphenidate (dexmethylphenidate; d-MPH) hydrochloride, and serdexmethylphenidate (SDX; a prodrug of d-MPH). In terms of total d-MPH dose amounts, all capsule strengths contain 30% of d-MPH and 70% of d-MPH in form of the prodrug. 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).

d-MPH (mg)	SDX (d-MPH) [1] (mg)	Total d-MPH dose [2] (mg)	Equimolar d-MPH HCl dose (mg)
2.6	13.1 (6.1)	8.6	10
5.2	26.1 (12.2)	17.3	20
7.8	39.2 (18.3)	25.9	30
10.4	52.3 (24.4)	34.6	40

1. This is the dose of SDX. The amount of d-MPH equimolar to each SDX dose is listed in parentheses.
2. The total dose of d-MPH expressed in terms of free base.

Blinded capsules of 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, and 52.3 mg/10.4 mg Azstarys® and matching placebo capsules will be used in the Treatment Period. All study drug will be supplied by the Sponsor (or designee). The Sponsor (or designee) will supply sufficient quantities of Azstarys® 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.

11.2. Packaging and Labeling

The Azstarys® capsules and placebo capsules for the Treatment Period will be packaged and labeled appropriately.

All study medication will be blinded throughout the study. Blinded study medication will be dispensed for each subject based on the randomization scheme. The patient randomization number assigned by the Interactive Response Technology (IRT) or similar system/process will correspond to the number on the bottle(s).

Blinded study medication will be packaged as bottles with 10 capsules. One bottle will contain enough drug supply for one subject, for at least 7 days of dosing in the Treatment Period (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.

11.3. Dispensing Procedures

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

- Visit 2: Subjects will be dispensed a blinded bottle with 10 capsules of either 13.1 mg/2.6 mg or 39.2 mg/7.8 mg Azstarys® (starting dose for Cohort 1 and Cohort 2, respectively), or associated placebo capsules.
- Visit 3: Subjects will return to the clinic after 7 ±3 days for Visit 3 with unused study drug and will be dispensed a bottle with 13.1 mg/2.6 mg or 39.2 mg/7.8 mg Azstarys® (same daily dose as Week 1 for Cohort 1 and Cohort 2, respectively), with 26.1 mg/5.2 mg Azstarys® (dose level increase from Week 1 for Cohort 1 subjects or decrease from Week 1 for Cohort 2 subjects), or with 52.3 mg/10.4 mg Azstarys® (dose level increase from Week 1 for Cohort 2 subjects), or associated placebo capsules.
- Visit 4: Subjects will return to the research clinic after 7 ±3 days for Visit 4 with unused study drug, and will be dispensed a bottle with 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg Azstarys® (same daily dose as Week 2, or a dose level decrease or increase from Week 2), or associated placebo capsules.
- Visit 5: Subjects will return to the research clinic after 7 ±3 days for Visit 5 with unused study drug, and will be dispensed a bottle with 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg Azstarys® (same daily dose as Week 3, or dose level decrease or increase from Week 3), or associated placebo capsules.

At Visits 2, 3, 4 and 5, a bottle will be dispensed to the subject's parent or legal 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 study drug for drug accountability and compliance.

In the event that a subject experiences 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 IRT or similar system/process. All efforts will be made to ensure subjects receive daily doses of double-blind study drug for at least 14 days during the Treatment Period.

The Investigator will not supply study drug to anyone other than those named as sub-investigators on FDA Form 1572, designated site staff, and subject's parent/legal guardian in the study.

11.4. Materials Control

Azstarys® is a Schedule II product under the Controlled Substances Act. Therefore, the study site is required to have the appropriate permit from the DEA to receive, store, ship and dispense the Azstarys® product according to all local, state, and federal regulations for Schedule II substances.

Once received and labeled by the onsite pharmacist or designee for use in the study, the drugs will be considered study drug material. The pharmacist or designee will maintain adequate records of the receipt, dispensing, return or other disposition of the drug, including dates, quantity, serial numbers, expiration dates, as appropriate. Reasons for any departure from the expected regimen will be documented. These documents will be made available to regulatory agency inspectors upon request. The Investigator will not supply study drug to anyone other than those named as sub-investigators on FDA Form 1572, designated site staff, and subject's parent/legal guardian in the study.

11.5. 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 for Schedule II controlled substances. Investigational products must not be frozen. The Investigator will ensure that adequate precautions are taken, including storage of the study drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

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

11.6. Study Drug Accountability

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

12. SAFETY ASSESSMENTS

12.1. Medical History

12.2. Physical Examination

A complete physical examination will be completed for all subjects at Screening and at the End-of-Treatment (Visit 6) or ET. The complete physical examination will include a review of the subject's

general appearance, skin, head and neck, musculoskeletal/extremities, heart, lungs, abdomen and a brief examination of the neurological system.

Body weight and height will be determined at each visit. Height will be recorded in centimeters (cm) using a stadiometer with the subject's shoes removed. Body weight will be measured in kilograms (kg) using a calibrated scale; subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.

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

12.3. Children's Sleep Habits Questionnaire (CSHQ)

The modified, abbreviated CSHQ will be used to assess the sleep behavior during the Treatment Period. The CSHQ is a retrospective, 33-item parent questionnaire to examine sleep behavior in small children (Owens 2020). Items are rated on a 3-point scale of "Usually", "Sometimes" and "Rarely" for occurrences in a number of key sleep domains (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness). Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver at Screening, at each visit during the Treatment Period, or at the ET Visit. The total Sleep Disturbance Score is the sum of the frequency ratings of the 33 items.

CSHQ scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver.

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

Suicidal ideation will be assessed by the C-SSRS, Pediatric Version (Posner 2010). The "Children's Baseline/Screening" version will be assessed at Screening, and the "Children's Since Last Visit" version will be assessed at all other visits. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire will be filled in by the parent/guardian/caregiver.

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

12.5. Vital Signs

Vital sign measurements will be obtained at each visit 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. Blood pressure data will be analyzed using the 2017 AAP guidelines (Flynn 2017) based on the average of 3 blood pressure measurements at least 2-5 minutes apart. The average of the three measurements will be entered into the eCRF

12.6. 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. ECGs will be collected at Screening, Visit 6, and at ET.

The following ECG parameters will be recorded:

- Heart Rate (bpm)
- QT Interval (msec)
- RR Interval (msec)
- ECG Evaluation (performed at the clinical site): one of the following: Normal; Abnormal, not clinically significant; Abnormal, clinically significant. If Abnormal, a specific description of the abnormality in the ECG.

12.7. Clinical Laboratory Measurements

Up to 40 mL of blood will be collected for clinical chemistries and hematology from each subject during the study and sent to the clinical laboratory. Clinical laboratory samples will be obtained at the Screening Visit, at the end of the Treatment Period (Visit 6), at ET, and at Unscheduled Visits (if applicable).

Urinalysis will also be performed by the clinical laboratory from samples taken at Screening (Visit 1), at the end of the Treatment Period (Visit 6), at ET, and at Unscheduled Visits (if applicable).

Clinical laboratory measurements may be repeated at the discretion of the Investigator.

The clinical laboratory evaluations will consist of the following:

- Total Hematology with differential: red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin, hematocrit and platelets.
- 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, and thyroid stimulating hormone (TSH). TSH will be measured at Screening only (to evaluate the exclusion criterion for subjects with uncontrolled thyroid disease).
- Urinalysis:
    - Urinalysis will include, but not be limited to, the following: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and urobilinogen
    - Unscheduled urine sample: Subjects with a greater than trace proteinuria on any visit (including Screening) with urinalysis assessments throughout the study will be asked to provide the study site a morning void urine sample to rule out orthostatic proteinuria. This urine sample will be sent to the clinical laboratory, where urine protein and creatinine will be quantified, and the urine protein to

creatinine ($U_{P/C}$) ratio will be calculated to rule out "false positive" proteinuria. A $U_{P/C}$ ratio <0.2 will be considered normal. The morning void urine sample will be collected by the parent/guardian/caregiver under direction of the study site, and will be dropped off at the study site.

- Urine Screen for Drugs of Abuse: Urine samples will be tested for drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone) at the Screening visit. If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation.
- Urine Screen for MPH:
    - At Screening, the urine sample collected for urinalysis will also be tested for MPH in the clinical laboratory. Depending on a subject's current ADHD medication at Screening, the urine screen may test positive for MPH. Subjects must wash out current ADHD medications from 5 days prior to Visit 2 and not use them to the end of the Treatment Period (Visit 6) or ET.
    - At Visit 2, urine samples will be tested for MPH with a urine dipstick (e.g., NarcoCheck®) that provides immediate results. Subjects with a positive screen at check-in to the Treatment Period will be excluded from further study participation.

12.8. Adverse Event Assessments

Adverse events (AEs) shall be monitored continuously from the administration of the first dose of study drug until either the Follow-up Phone Call or ET visits as noted on the SOE. Definitions and details of AE reporting and documentation are listed in Section 18.

13. EFFICACY ASSESSMENTS

13.1. ADHD Diagnosis

ADHD-RS: The Preschool Version of ADHD-RS-IV (McGoey 2007) will be used for 4- and 5-year-old subjects (Cohort 1), and ADHD-RS-5 will be used in 6- to 12-year-old subjects (Cohort 2). Although there is a Version 5 of the ADHD-RS, the validated preschool version is currently Version IV. The ADHD-RS-IV and ADHD-RS-5 are 18-item scales (DuPaul 1998, DuPaul 2016) based on Diagnostic and Statistical Manual of Mental Disorders (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 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 inattention. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver at each visit.

At Screening, the ADHD Presentation (Predominantly Inattentive, Hyperactive-Impulsive, or Combined) will be recorded for each subject.

13.2. Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid)

The MINI Kid (Sheehan 2010) will be used to confirm the diagnosis of ADHD and identify comorbid psychiatric conditions at the Screening Visit only.

13.3. 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). The CGI-S will be performed at Screening and at Visits 2, 3, 4, 5, and 6.

13.4. Clinical Global Impressions–Improvement (CGI-I)

The CGI-I is a clinician-rated scale that evaluates the improvement of psychopathology (ADHD symptoms in the study) on a scale from 1 (very much improved) to 7 (very much worse). The CGI-I will be performed at Visits 3, 4, 5, and 6. Since the CGI-I is an assessment of improvement versus the previous visit, there is no CGI-I assessment at baseline (Visit 2).

14. PHARMACODYNAMICS

This study will not include PK evaluations. Therefore, PD assessments are not applicable.

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 after a missed visit, when there is no response to two attempts by phone and a registered letter to the subject. After these 3 failed attempts, the subject will be considered lost to follow-up.
- Sponsor request for early termination of the study.
- Overdosage, at the discretion of the Investigator (e.g., intentional overdosage, multiple occurrences of overdosage).
- For other reasons (reason will be recorded).

If a subject is withdrawn from treatment due to an AE, 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.

15.2. Withdrawal of Subjects Post-Dose Study Drug

If a subject meets withdrawal criteria post-dose during the Treatment Period, the subject will complete, if possible, all study procedures post-dose study drug before starting ET procedures. The subject will be withdrawn and ET procedures will be completed, prior to the subject's discharge from the clinic, if possible.

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 Treatment Period, do not need to be repeated.

The Sponsor may be contacted if clarification is required on a case-by-case basis.

15.3. Replacement of Subjects

Enrolled subjects who withdraw from the study early will not be replaced.

16. EFFICACY ENDPOINTS

The following endpoints will be used to determine efficacy:

16.1. Primary Efficacy Endpoint

- Change from baseline (Visit 2) through the end of treatment (Visit 6) in the ADHD Rating Score (total score). For Cohort 1, the ADHD-RS-IV will be used; for Cohort 2, the ADHD-RS-5 will be used.

16.2. Secondary Efficacy Endpoints

- Changes from baseline (Visit 2) to all post-baseline visits through the last evaluation (Visit 6 or ET) in the ADHD Rating Score for hyperactivity/impulsivity.

- Changes from baseline (Visit 2) to all post-baseline visits through the last evaluation (Visit 6 or ET) in the ADHD Rating Score for inattention.

- Changes from baseline (Visit 2) to all post-baseline visits through the last evaluation (Visit 6 or ET) in the CGI-S.

- CGI-I from Visit 3 to all post-baseline visits through the last evaluation (Visit 6 or ET).

17. STATISTICAL METHODS AND REPORTING

17.1. Sample Size Calculation

Based on data from a previous study (efficacy study with Azstarys® in subjects 6- to 12-years of

age), the power and proposed sample size in each age cohort was calculated based on a two-sample t-test for the comparison of change from baseline to 28 days post-baseline in ADHD Rating Scale total score as follows (with no multiplicity correction for the two age cohorts):

- 90% power to detect a 6-point treatment difference with an SD of 10-points using two-sided α=0.05 in the Younger Cohort (4- to 5-years of age) yields N=60 per treatment group in a 1:1 ratio for Active and Placebo for a total sample size of 120 younger subjects
- 80% power to detect a 6-point treatment difference with an SD of 10-points using two-sided α=0.05 in the Older Cohort (6- to 12-years of age) yields N=45 per treatment group in a 1:1 ratio for Active and Placebo for a total sample size of 90 older subjects. A lower power was selected for this cohort because efficacy in this age group was previously established.

Combining the two age cohorts for a total of 105 subjects per treatment group yields 99% overall study power to detect a between-treatment difference of 6 points with a SD of 10 points using two-sided α=0.05 for a total sample size in the study of 210 subjects.

A blinded sample size re-estimation will be conducted when approximately 50% of subjects in Cohort 1 have completed Visit 6. The sample size may be increased based on that analysis. Details are presented in the Interim Analysis section below.

Supporting Material for the Assumed Mean Treatment Difference and SD:

The estimation of the point estimate of 6 points and a SD of 10 points is based on the following data:

- No clinical studies with MPH have been published that used a parallel design with active vs placebo throughout the study. Dose titration with active investigational drug followed by randomized withdrawal in part of the population to a placebo arm was typical. Therefore, the mean ADHD-RS-5 (total score) change from baseline (CFB) in the titration phases of the Phase 3 studies conducted with Azstarys® were used (Table 2 and Table 3).
- Point Estimate: Based on the range of CFB seen in E01 (-25.6) and S01 (-28.2) during 4 weeks of treatment, a treatment difference of active vs placebo of 6 is a conservative treatment effect that accounts for a potentially large placebo effect.
- Variability: The SD (10 points) was estimated as approximately the overall mean of the SD values of CFB at each visit across both studies (E01 and S01 studies, Table 2 and Table 3, respectively). Based on the range of coefficients of variation (CVs) seen in E01 (16.7-54.8%) and S01 (18.7-63.0%) during 4 weeks of treatment, a SD of 10 is equivalent to a CV of 10/6 = 167%, and is very conservative.

Table 2: Mean ADHD-RS-5 Total Scores by Visit During the Dose Optimization Phase (ITT Population, KP415.E01)

	N	Mean (SD)	CV (%)	Mean Change from Baseline (SD)	CV (%)
Baseline (Visit 2)	150	41.8 (7.0)	16.7		
Visit 3	150	22.1 (12.4)	54.8	-19.6 (11.7)	59.7
Visit 4	150	18.9 (9.3)	49.2	-22.8 (9.9)	43.4
Visit 5	150	16.2 (7.7)	47.5	-25.6 (8.6)	33.6

Source: Table 22 in Study KP415.E01 CSR

Table 3: Mean ADHD-RS-5 Total Scores by Visit During the Dose Optimization Phase (Efficacy Population, KP415.S01)

	N	Mean (SD)	CV (%)	Mean Change from Baseline (SD)	CV (%)
Baseline (Visit 2)	225	41.5 (7.7)	18.7		
Visit 3	159	24.6 (13.9)	56.6	-18.4 (14.0)	76.1
Visit 4	159	19.4 (12.3)	63.0	-23.5 (12.9)	54.9
Visit 5	159	14.1 (8.3)	59.1	-28.8 (9.3)	32.3

Source: Table 11-1 in Study KP415.S01 CSR

17.2. Analysis Populations

Safety Population is defined overall and for each cohort separately. Safety population includes all randomized subjects who received at least one dose of study medication and who have at least one post-dose safety assessment. Safety endpoints will be analyzed using the Safety Population. Demographics and baseline characteristics will be summarized for the Safety Population.

Intent-to-Treat (ITT) Population is defined overall and for each cohort separately. ITT population includes all subjects who received at least one dose of study medication and have at least one post-randomization ADHD-RS Total Score. Demographics and baseline characteristics will be summarized for the ITT Population. All efficacy analyses will be conducted in the ITT Population.

Per-Protocol (PP) Population is defined overall and for each cohort separately. PP population includes all randomized subjects who received at least one dose of study medication and have the baseline and at least one post-randomization ADHD-RS Total Score, and did not use prohibited medications deemed to impact efficacy. The primary efficacy analyses will be conducted in the PP Population, as sensitivity analyses.

17.3. Statistical Analyses

A Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will include detailed descriptions of all analyses to be conducted on all data collected for this study as well as complete details on the procedures to handle missing data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All clinical study data will be presented in subject data listings. Descriptive statistics will be

presented by treatment group for all endpoints and will include number of subjects (n), mean, standard deviation (SD), median, minimum. and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. Unless otherwise specified, all tests will be 2-tailed at 0.05 level of significance. All CIs will be two-sided 95% CIs.

Within each cohort and overall, the numbers of subjects screened, the number of subjects randomized, and the number of subjects in the safety, ITT, and PP Populations will be displayed overall and by treatment group. For randomized subjects who discontinue from the study, the primary reason for discontinuation will be listed and summarized by treatment group overall and by age cohort.

Demographic and baseline disease characteristic data will be summarized descriptively by treatment group, overall and by age cohort, including sex, age, and race as well as weight, height, BMI, and ADHD subtype. The study medication doses received will be analyzed descriptively and the optimized dose will be analyzed descriptively overall and by age cohort. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Frequencies and percentages of subjects using each concomitant medication will be presented by treatment group, overall and by age cohort.

17.4. Efficacy Analyses

17.4.1. Primary Efficacy Endpoint Analyses

Descriptive statistics will be presented for baseline (Visit 2), all post baseline measurements (Visits 3 to 6), and changes from baseline to all post-baseline measurements of ADHD Rating Scale (ADHD-RS) total score by treatment group, overall and separately for each age cohort.

For the primary endpoint of change from baseline in ADHD Rating Scale (ADHD-RS) total score, a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fitted using all data as observed. The dependent variable will be change from baseline (Visit 2) in ADHD Rating Scale total score for all post-baseline assessments for each subject. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), baseline ADHD-RS total score, visit (Visit 3, 4, 5, and 6), and visit-by-treatment interaction as well as a random effect for the subject. The mixed model will utilize restricted maximum likelihood estimation with the Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. The model will assume an unstructured covariance matrix. If the model does not converge under the unstructured covariance matrix when using the SAS PROC MIXED default Newton-Raphson algorithm, other numerical methods such as the Fisher scoring algorithm will be tried. Details regarding the alternative algorithm(s) will be provided in the study SAP. If the model using the unstructured covariance matrix still fails to converge, alternative covariance structures will be used until convergence is reached based on an ordered list of progressively more specific covariance structures which will be documented in the SAP. If a structured covariance is used, then a robust sandwich estimator will be utilized for estimating the variance of the treatment effect estimate.

The primary efficacy analysis will be based on comparisons of Azstarys® and placebo at Visit 6. From the MMRM model, the Visit 6 difference between least square (LS) means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value.

The above analyses will be repeated for each age cohort separately.

The primary estimand for this study is the difference in LS means of Azstarys® and placebo with respect to change from baseline in ADHD-RS total score at Visit 6, based on the primary endpoint MMRM model fitted to the Intent-to-Treat population. There will be no adjustments made for the use of prohibited therapies or other intercurrent events. The p-value associated with the primary estimand will be used to test the primary hypothesis of this study, that mean change from baseline to Visit 6 ADHD-RS total score for Azstarys® is different from that of placebo. If Azstarys® is shown to be statistically superior to placebo, then the superiority of Azstarys® to placebo will be tested for each cohort separately.

To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. Subjects who discontinue treatment due to adverse events, overdosage, and use of prohibited medications will be followed through the end of study unless and until they withdraw consent or start a new ADHD medication (as treatment with a new ADHD medication will confound the effects of the randomized treatment)**.** Despite these measures, it is expected that there would still be some missing primary endpoint data in this study. Missing primary endpoint data will be handled as follows:

As a sensitivity analysis of the primary endpoint, change from baseline in ADHD-RS total scores, the above analyses will be repeated in their entirety using multiple imputation methods to impute the missing data. The following three steps will be followed:

In step 1, missing data will be imputed with multiple imputation (MI) using SAS PROC MI. The SAS PROC MI will be used for imputing the change from baseline in ADHD-RS total score over time. Missing values at intermittent timepoints prior to the permanent discontinuation of study drug will be imputed using the MCMC option. Since classification variables such as treatment group cannot be included in the MCMC statement directly, a BY statement will be included in the PROC MI code to provide separate imputation models for each treatment group. Missing data following permanent discontinuation of study drug will be imputed by treatment group under the assumption of MAR using the regression option from the monotone statement of SAS PROC MI. Baseline and post-baseline scheduled visits will be used in the regression option to impute the missing values. The output from PROC MI will be a data set containing multiple repetitions of the original data set, along with the newly imputed values. A minimum of 30 repetitions will be performed.

In step 2 of the primary analysis, each MI repetition will be analyzed separately to test the equality of the change from baseline in ADHD-RS total score means for Azstarys® and placebo.

In step 3, the results from each separate analysis in step 2 will be pooled using SAS PROC MIANALYZE. The pooled results will contain the estimate for the mean difference between Azstarys® and placebo for the change from baseline in ADHD-RS total score at Visit 6, as well as the corresponding standard error, 95% CI, and p-value.

If the primary analysis renders a significant treatment difference, a tipping point analysis will be performed in order to examine the sensitivity of inferences to departures from the missing at random (MAR) assumption. Details will be provided in the SAP and a summary is provided below:

As missing values following early discontinuations may not be consistent with a MAR assumption, a sensitivity analysis using multiple imputation under a missing not at random (MNAR) assumption will be performed searching for a tipping point that reverses the primary analysis conclusion. The imputed values for Azstarys® subjects' visits post discontinuation will be made worse by a delta defined as k times the treatment difference between Azstarys® and placebo obtained from the MI

MAR analysis, where k is a shift parameter that is incremented in order to identify the point at which the primary analysis result becomes non-significant (the tipping point). Consideration will then be given to how plausible the imputed values are at the tipping point. If not plausible, then the conclusion for the primary analysis under the MAR assumption is supported.

17.4.2. Analyses of Secondary Efficacy Endpoints

Descriptive statistics will be presented for baseline (Visit 2), all post baseline measurements (Visits 3 to 6), and changes from baseline to all post-baseline measurements of ADHD-RS for hyperactivity/impulsivity and ADHD-RS for inattention by treatment group, overall and separately for each age cohort.

The secondary efficacy endpoints, change from baseline to post-baseline timepoints in ADHD-RS for hyperactivity/impulsivity and the ADHD-RS for inattention will be analyzed using the same methods as the primary efficacy endpoint, change from baseline in ADHD-RS Total Score.

Descriptive statistics will be presented for baseline (Visit 2), all post baseline measurements (Visits 3 to 6), and changes from baseline to all post-baseline measurements of CGI-S by treatment group, overall and separately for each age cohort. A MMRM ANCOVA model will be fitted using all data as observed. The dependent variable will be change from baseline in CGI-S post-baseline assessments for each subject. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), baseline CGI-S, visit (Visit 3, 4, 5, and 6), and visit-by-treatment interaction as well as a random effect for the subject. The mixed model will be fitted in the same manner as described above for the primary endpoint analysis. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value.

Descriptive statistics will be presented for all post baseline measurements of CGI-I by treatment group, overall and for each age cohort separately. A MMRM ANOVA model will be fitted using all data as observed. The dependent variable will be CGI-I post-baseline assessments for each subject. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), visit (Visit 3, 4, 5, and 6), and visit-by-treatment interaction as well as a random effect for the subject. The mixed model will be fitted in the same manner as described above for the primary endpoint analysis. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value.

Visit 6 CGI-I will also be compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) chi square test within each age cohort stratified by gender. An overall CMH test will also be conducted stratified by gender and age (4 strata).

17.4.3. Type I Error Control for Efficacy

For the primary endpoint, the hypothesis of superiority of Azstarys® to placebo will be tested at a two-sided alpha of 0.05 for the two age cohorts combined. If significant, the same hypothesis will be tested for each age cohort at a two-sided 0.05 level of significance.

If the primary endpoint comparison is significant for Cohort 1, the superiority of Azstarys® to placebo with respect to the secondary efficacy endpoints, ADHD-RS for hyperactivity/impulsivity and ADHD-RS for inattention, will be tested for Cohort 1 only using a fixed sequence testing procedure in that order.

17.5. Safety Analysis

Unless otherwise specified, all safety analyses will be performed on the safety population, by treatment group, overall and separately for the two age cohorts.

Continuous laboratory data will be examined for trends using descriptive statistics of actual values and changes from baseline over time. Shift tables from baseline to each post-baseline time-point will be presented. Vital signs and ECG parameters will be summarized using descriptive statistics of actual values and changes from baseline over time. The incidence of clinically notable vital signs will be summarized. Physical examination findings will be presented in subject listings.

Adverse events will be mapped to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent adverse events (TEAEs) are AEs that begin in the time period following the first administration of study medication through 5 days after the last dose of study medication or existing AEs that worsen in the time period following the first dose of study medication through 5 days after the last dose of study medication. The number and percentage of subjects reporting TEAEs will be summarized by MedDRA system organ class and preferred term, by severity, and by relationship to study treatment. Drug-related AEs will be considered those at least possibly related to study medication based on the Investigator's assessment. The number and percentage of subjects with SAEs, and the number and percentage of subjects with AEs leading to treatment discontinuation will also be summarized by MedDRA system organ class and preferred term.

Descriptive statistics will be presented by visit for body weight (in kg), change and percent change from baseline in body weight, height (in cm), change and percent change from baseline in height, weight and height z-scores, and weight and height percentiles by treatment group, separately for each age cohort. The descriptive statistics will include n, mean, standard deviation (SD), median, 1st and 3rd quartile (Q1, Q3), and range (minimum and maximum). In addition, descriptive statistics will be tabulated by sex and optimized dose.

The CSHQ total Sleep Disturbance Score and the change and percent change from baseline CSHQ score will be analyzed descriptively by treatment overall and by age cohort. A MMRM ANCOVA model will be fitted using all data as observed. The dependent variable will be change from baseline to all post-baseline assessments of the CSHQ score for each subject. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), baseline CSHQ, visit (Visit 3, 4, 5, and 6), and visit-by-treatment interaction as well as a random effect for the subject. The mixed model will be fitted in the same manner as described above for the primary endpoint analysis. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI. The MMRM analysis of the change from baseline CSHQ scores will also be conducted separately for each age cohort.

Descriptive statistics by treatment group will be displayed for baseline, observed values, and changes from baseline in C-SSRS for all post-baseline assessments, overall and by age cohort. A MMRM ANCOVA model will be fitted using all data as observed. The dependent variable will be change from baseline to all post-baseline assessments of the C-SSRS score for each subject. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), baseline C-SSRS, visit (Visit 3, 4, 5, and 6), and visit-by-treatment interaction as well as a random effect for the subject. The mixed model will be fitted in the same manner as described above for the primary endpoint analysis. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95%

CI. The MMRM analysis of the change from baseline C-SSRS scores will also be conducted separately for each age cohort.

17.6. Interim Analysis

An interim analysis will be conducted for potential sample size increase in subjects 4 and 5 years of age (Cohort 1). When approximately 50% of the Cohort 1 subjects complete their Visit 6 assessments, a blinded sample size re-estimation will be conducted. Subjects will not be identified by treatment group. The within-group standard deviation (σ) will be estimated for change from baseline to Visit 6 ADHD-RS total score using the blinded methodology of Gould and Shih. The adjusted variance estimate will be used, which was recommended by Friede and Kieser and is similar to the estimate proposed by Zucker. Friede and Kieser and Waksman showed this estimate to be superior to the one obtained from the EM algorithm which was also proposed by Gould and Shih.

The blinded analyses will be conducted by a firewalled independent statistician. An exact sample size based on the abovementioned methodology will not be disclosed to the Sponsor. Instead, ranges of sample size will be pre-specified in the interim analysis plan and the upper limit of the applicable range will be recommended instead of the exact sample size. Since the study will remain blinded for the sample size re-assessment, no alpha penalty for the final analysis will be incurred.

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 AEs 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 Phone Call or the ET 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. AEs 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. Adverse Event Grading

The severity of each AE will be graded by the investigator using the following categories:

Mild	Does not interfere with subject's usual function (awareness of symptoms or signs, but easily tolerated [no specific medical intervention required]).
Moderate	Interferes to some extent with subject's usual function (enough discomfort to interfere with usual activity [minimal intervention; local intervention; noninvasive intervention]).
Severe	Interferes significantly with subject's usual function (incapacity to work or to do usual activities [significant symptoms requiring hospitalization or invasive intervention]).

If there is a change in severity of an AE, only the maximum severity of the AE should be recorded.

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study product stopped
- Study product temporarily interrupted
- Concomitant medication
- Other, specify

18.1.4. Adverse Event Relationship to Study Drug

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

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

18.2. Serious Adverse Events

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE
- 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.

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/qualified designee will complete a SAE/Overdosage report with required information regarding the SAE in accordance with the Safety Management Plan and submit the completed form to the Pharmacovigilance service provider. The event will also be entered into the appropriate AE module of the eCRF as soon as possible. Preliminary reports of SAEs must be followed by detailed descriptions later on, such as including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Serious adverse events considered probably or possibly related to study drug shall also be classified by the Sponsor as being "expected" or "unexpected." An unexpected event is one that is not listed in the Investigator's Brochure or Azstarys® Prescribing Information document.

All serious event reporting by Sponsor will adhere to 21 Code of Federal Regulations (CFR) 312.32 for Investigational New Drug (ND) substances (7-day or 15-day alerts) and 21 CFR 314.80 for marketed drugs (15-day alerts). Unexpected fatal or life-threatening SAEs considered probably or possibly related to the study drug by the Sponsor will be reported to the FDA by the Sponsor with an IND Safety report within 7 days of the receipt of the initial information. The Institutional Review Board (IRB) will be notified of the 7- and 15-day 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 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.

Serious adverse event assessment, treatment, and follow up shall be performed up to at least 30 days after last dose for events considered definitely, probably, or possibly related to study drug, and continue 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 (by cohort), i.e., > 39.2 mg/7.8 mg Azstarys® for Cohort 1 or > 52.3 mg/10.4 mg Azstarys® for Cohort 2. If the overdosage has an associated AE or SAE, the site is to report and document the event as listed in this protocol.

Signs and symptoms of acute MPH overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension,

tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis (Azstarys® Package Insert 2021).

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

19. 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 SAEs
4. Multiple visits missed or outside permissible windows
5. Materially inadequate record keeping
6. Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
7. Subject repeated non-compliance with study requirements

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

20. DATA MANAGEMENT AND RECORD KEEPING

20.1. Data Management

Data will be recorded at the site on eCRFs using EDC. All entries on an eCRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. An eCRF must be completed for each participant who has given informed consent. The eCRFs and source documents must be made available to Sponsor and/or its representatives.

20.2. Record Keeping

The Investigator 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, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae.

The Investigator and affiliated Institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated Institution should take measures to prevent

accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

20.3. Access to Source Data/Documents

The Investigator and research Institution 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.

21. QUALITY CONTROL AND QUALITY ASSURANCE

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

22. 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: https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf.

23. PUBLICATION POLICY

Confidentiality, presentation, and publication of manuscripts containing the study data, and patent applications related to unpublished study-related information and unpublished information given to the Investigator by the Sponsor and/or its representatives shall be handled as set forth in a mutual written agreement between the Sponsor and the Institution. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

24. FINANCING AND INSURANCE

24.1. Finances

Prior to starting the study, the Principal Investigator and/or Institution will sign an agreement with the Sponsor related to conducting the clinical trial. This agreement will include the financial information agreed upon by the parties.

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

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

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

27. REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA, American Psychiatric Association, 2013.

Azstarys® Package Insert, Corium, 2021.

Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment (3rd edition). The Guilford Press, 2006.

Busner J, Targum SD. The Clinical Global Impressions Scale: Applying a research tool in clinical practice. Psychiatry 4:28–37, 2007.

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV (for Children and Adolescents): Checklists, Norms, and Clinical Interpretation. New York: Guildford, 1998.

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-5 for Children and Adolescents: Checklists, Norms, and Clinical Interpretation. New York: Guildford, 2016.

Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents [published correction appears in Pediatrics. 2017 Nov 30] [published correction appears in Pediatrics. 2018 Sep;142(3):]. Pediatrics. 2017;140(3):e20171904. doi:10.1542/peds.2017-1904.

Focalin XR® [Package Insert].Novartis Pharmaceuticals Corporation. 2021.

Food and Drug Administration (FDA) Guidance for Industry, Investigators, and Institutional Review Boards entitled FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. March 2020; updated August 30, 2021.

Gaub M, Carlson CL. Gender differences in ADHD: a meta-analysis and critical review. J Am Acad Child Adolesc Psychiatry. 1997, 36(8):1036-1045.

Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293. Erratum in: J Am Acad Child Adolesc Psychiatry. 2007;46(1):141.

McGoey KE, DuPaul GJ, Haley E, Shelton T. Parent and teacher ratings of attention-deficit/hyperactivity disorder in preschool: The ADHD rating scale-IV preschool version. J Psychopathol Behav Assess 29:269–276, 2007.

Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep 23:1043–1051, 2000.

Posner K, Brent D, Lucas C, et al. Columbia-Suicide Severity Rating Scale (C-SSRS) Pediatric Baseline Version. New York, NY: The Research Foundation for Mental Hygiene, Inc., 20102010.

Sheehan DV et al. Reliability and validity of the Mini International Neuropsychiatric Interview for children and adolescents (MINI Kid). J Clin Psychiatry 2010;71(3):313-326.

Wilens T, Adler LA, Adams J, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. J Am Acad Child Adolesc Psychiatry 47:21-31,2008.

Wilens TE, Biederman J. The stimulants. Psychiatr Clin N Amer. 15:191-222,1992.

Wolraich ML, Hagan JF, Allan C, et al; Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactive Disorder. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4):e20192528. Pediatrics. 2020;145(3):e20193997. doi:10.1542/peds.2019-3997.

Appendix A: Instructions for Oral Administration of Study Drug

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

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

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

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