Corium

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Corium Protocol No. KP415.P02

Amendment #1, Version 2.0, November 16, 2022

A Multicenter, Dose-Optimized, Open-Label, Safety/Tolerability and Pharmacokinetic Study with Azstarys® in Children 4 and 5 Years of Age with Attention-Deficit/Hyperactivity Disorder

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Sponsor Approval / Signature Page

Protocol Number	KP415.P02
Protocol Version Date	November 16, 2022
Version	Amendment 1.0, Version 2.0
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 x226

A Multicenter, Dose-Optimized, Open-Label, Safety/Tolerability and Pharmacokinetics Study with Azstarys® in Children 4 and 5 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-IV	ADHD-Rating Scale-IV
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impressions–Severity
CGI-I	Clinical Global Impressions–Improvement
CL/F	F is the oral bioavailability expressed as a fraction
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
ER	Extended Release
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 Conference on Harmonization
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
LLN	Lower Limit of Normal
MAO	Monoamine Oxidase
MedDRA	Medical Dictionary of Regulatory Activities
MINI Kid	Mini-International Neuropsychiatric Interview for Children and Adolescents
MPH	Methylphenidate

Abbreviation	Definition
NHLBI	National Institutes of Health's National Heart, Lung, and Blood Institute
ODD	Oppositional Defiant Disorder
PK	Pharmacokinetic
PKAP	Pharmacokinetic Analysis Plan
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
QTcB	QT interval corrected for heart rate with Bazett's formula
QTcF	QT interval corrected for heart rate with Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDX	Serdexmethylphenidate, a prodrug of d-MPH
SOE	Schedule of Events
NRI	Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
$T_{1/2}$	Apparent plasma terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
T_{max}	Time to achieve the maximum observed plasma concentration
$U_{P/C}$	Urine protein to creatinine (ratio)
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, Open-Label, Safety/Tolerability and Pharmacokinetic Study with Azstarys® in Children 4 and 5 Years of Age with Attention-Deficit/Hyperactivity Disorder
SPONSOR	Corium, Inc.
PROTOCOL NUMBER	KP415.P02
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	The is a multicenter, dose-optimized, open-label, safety/ tolerability and pharmacokinetic (PK) study with Azstarys® in children 4 and 5 years of age with attention-deficit/hyperactivity disorder (ADHD). The phases of the study are as follows: • **Screening Period (New Subjects only):** New Subjects will undergo a Screening Period up to 30 days prior to entering the Dose Optimization Phase. • **Dose Optimization Phase (All Subjects):** During the 3-week Dose Optimization Phase, subjects will start at 13.1 mg/2.6 mg, and may be titrated to doses of 26.1 mg/5.2 mg or 39.2 mg/7.8 mg Azstarys® capsules based on individual tolerability and best dose-response in the opinion of the Investigator. NOTE: Subjects rolled over from Study KP415.P01 will start the current study at Visit 2. They will not undergo the procedures of the Screening Period since they were screened and enrolled in Study KP415.P01. Eligibility of Roll-over Subjects in the current study will be evaluated at Visit 6 in Study KP415.P01. • **Treatment Phase (All Subjects):** Eligible subjects will receive single daily doses of Azstarys® for approximately 360 ±20 days (approximately 12 months). The starting dose of Azstarys® in the Treatment Phase will be the same as the optimized dose of Azstarys® at the end of the Dose Optimization Phase, either 13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day, although, at the Investigator' discretion, based on individual tolerability and dose response, the daily dose may be changed at any

	time to any of the allowed dose levels (13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day). Safety (including vital signs, weight, height, and sleep behavior) and efficacy, assessments will be performed. After approximately all subjects remaining in the study complete approximately 180 days (Visit 11) of the Treatment Phase, an interim analysis will be conducted to evaluate safety parameters. • **Follow-up Phone Call (All Subjects):** Subjects will receive a Follow-up Phone Call, at 5-9 days after administration of the last dose of the Treatment Phase, to evaluate safety parameters. **Roll-over Subjects:** For subjects rolled over from Study KP415.P01, the study will consist of the Dose Optimization Phase, the Treatment Phase, and a Follow-up Phone Call. These subjects will be enrolled in the Dose Optimization Phase of the current study immediately after the last dose of study drug in Study KP415.P01. Some of the assessments in Roll-over Subjects after the last dose of study drug in Study KP415.P01 (Visit 6) will also be part of Study KP415.P02, Visit 2. No assessment will be duplicated at this visit common to both studies.
STUDY EARLY STOPPING RULES	The study will be stopped for any of the following reasons: An interim analysis of the safety data (including weight, height,) will be conducted after approximately all subjects remaining in the study have completed approximately180 days (Visit 11) in the Treatment Phase. After completion of the interim analysis, the study may be stopped early for any of the following stopping rules: a. A clinically significant growth reduction in >40% of subjects. A clinically significant growth reduction is defined by meeting both criteria as follows: 1. A decrease in weight or height z-score versus baseline crossing two percentile lines on a growth chart showing the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. This criterion is based on the recommendation for monitoring stimulant-treated subjects in the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD (Pliszka 2007). 2. For those subjects crossing two percentile lines in weight or height z-score (#1 above), subjects with a decrease in height or weight z-score below the 50th percentile on the growth chart. This criterion excludes overweight subjects at baseline who progress towards a normal weight during treatment as they are not subjected to a safety risk.

	b. An increase in systolic blood pressure >20 mmHg above the 95th percentile for age and gender according to the 2017 AAP guidelines (Flynn 2017) after 180 days of treatment (Visit 11) in >25% of subjects. c. Subjects experienced adverse events (AEs), laboratory parameters, electrocardiograms, or suicidal ideation, considering type, incidence and severity, such that further treatment is not in the best interest of the study participants. The interim safety evaluation for stopping the study early will be judged by the Principal Investigator in collaboration with the Medical Monitor and Sponsor. Treatment in the current study will continue as planned while the interim analysis is conducted. If the decision is made to stop the study, all subjects remaining in the study will undergo the EOT Visit (with safety evaluations including fasting safety labs and ECGs) and a Follow-up Phone Call.
PRIMARY OBJECTIVE	To determine the safety and tolerability of treating children 4- and 5-years-of-age with ADHD with Azstarys® for up 12 months. The safety objective includes changes in weight and height, and sleep behavior.
SECONDARY OBJECTIVES	To determine efficacy with respect to the 12-month maintenance of ADHD symptom control through investigator ratings on the ADHD-RS-IV.
PHARMACOKINETIC OBJECTIVE	To assess the population PK of Azstarys® in children 4 and 5 years old with ADHD.
NUMBER OF SUBJECTS	Approximately 100 subjects will be enrolled in the study. An appropriate number of New Subjects will enter the Screening Period in addition to the Roll-over Subjects to ensure approximately 100 subjects are enrolled in the study. Assuming a dropout rate of up to 50% over 12 months, approximately 50 subjects are expected to complete the 12-month Treatment Phase. Subjects who fail Screening and subjects who terminate early during the Dose Optimization Phase may be replaced. Subjects who terminate early in the Treatment Phase will not be replaced.
SUBJECT SELECTION CRITERIA	Subjects will be either recruited *de novo* (“New Subjects”) for this study, or will be rolled over from Study KP415.P01. **Inclusion Criteria for New Subjects:** 1. New Subjects must be at least 4 years old and less than 5 years and 10 months old 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. Subject 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, ECGs, medical history, and clinical laboratory values (chemistry, hematology, and 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. 4. At least one parent/legal guardian of the subject must voluntarily give written permission for him/her to participate in the study. 5. Subject must meet Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) per clinical evaluation and confirmed by the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid). 6. Subject must have had ADHD symptoms present for at least 6 months prior to the Screening Visit. 7. Subject must be able and willing to wash out current stimulant ADHD medications, including herbal medications from 5 days prior to the start of the Dose Optimization Phase, and abstain from taking these to the end of the Treatment Phase or Early Termination (ET); and wash out non-stimulant ADHD medications from 14 days prior to the start of the Dose Optimization Phase, and abstain from taking these to the end of the Treatment Phase or ET. 8. 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. 9. Subject functions at an age-appropriate level intellectually, as determined by the Investigator. 10. Subject must have age and sex adjusted ratings of ≥90th percentile Total Score on the ADHD-RS-IV (Preschool Version) rated over the past 6 months. 11. 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. 12. Subject's parent/legal guardian and caregiver (if applicable) must understand and be willing and able to comply with all study procedures and visit schedule. If the subject is cared for by a caregiver for relevant parts of a school day, and if, in the opinion of the Investigator, this caregiver is more suitable for certain

	assessments, the caregiver will need to agree to the applicable procedures and visits. 13. Subject's 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. **Inclusion Criteria for Subjects Rolled Over from Study KP415.P01:** The following inclusion criteria will be evaluated no later than Visit 6 in Study KP415.P01 which is the same as Visit 2 (the first study visit for Roll-over Subjects in the present study): 1. Subjects must have completed the Treatment Period of Study KP415.P01. 2. Roll-over Subjects from Study KP415.P01 must have been at least 4 years old and less than 6 years at the time of taking the first dose of Azstarys® in Study KP415.P01. 3. At least one parent/legal guardian of the subject must voluntarily give written permission for the subject to participate in the Study KP415.P02. 4. Subject's parent/legal guardian and caregiver (if applicable) must understand and be willing and able to comply with all study procedures and visit schedule. If the subject is cared for by a caregiver for relevant parts of a school day, and, in the opinion of the Investigator, this caregiver is more suitable for certain assessments, the caregiver will need to agree to the applicable procedures and visits. 5. Subject's 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 for New Subjects:** 1. 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. 2. 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.

	3. 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. 4. Subject has evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS related disorders that might occur in childhood (e.g., Duchenne Muscular dystrophy, myasthenia gravis, or other neurologic or serious neuromuscular disorders), or history of persistent neurological symptoms attributable to serious head injury. 5. Subject taking anticonvulsants for seizure control 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. 6. 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. 7. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening. 8. 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. 9. Subject has a history or presence of abnormal ECGs, which in the Investigator's opinion is clinically significant. 10. Subject has a history of, or currently has a malignancy. 11. 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. 12. Subject has greater than trace proteinuria on 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. 13. Subject has a current or recent (past 12 months) history of drug abuse in someone living in the subjects' home. 14. Subject has a positive urine screen for drugs of abuse at Screening. If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen may test positive for MPH for treatment of their ADHD. All ADHD medications must be washed out per New Subject Inclusion Criterion #7. 15. 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, except for participation in Study KP415.P01. 16. Subject has taken ADHD medications from more than one class within 30 days prior to Screening. Subjects on a stable dose of one ADHD medication with occasional use of ADHD medications from another class are eligible at the discretion of the Investigator. 17. Subject has demonstrated lack of response or intolerability to adequate dose and duration of treatment with methylphenidate products. Judgment of adequate dose and duration is at the discretion of the Investigator. 18. Subject is using or planning to use prohibited drugs during the trial as specified in the protocol. 19. 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). 20. Subject has a history of severe allergies or adverse drug reactions to more than one class of medications. 21. Subject has a history of allergic reaction or a known or suspected sensitivity to MPH or any substance that is contained in the study drug. 22. Subject, parent/legal guardian and caregiver (if applicable, at the Investigator's discretion) has commitments during the study that would interfere with attending study visits.

	23. Subject or subject's family anticipates a move outside the geographic range of the investigative site during the study or plans extended travel inconsistent with the recommended visit interval during study duration. 24. Subject has one or more siblings living in the same household who are enrolled in this or another clinical drug trial. 25. Subject shows evidence of current physical, sexual, or emotional abuse. 26. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study. **Exclusion Criteria for Roll-over Subjects:** 1. Subject developed, since starting Study KP415.P01, 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. 2. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based C-SSRS assessments in Study KP415.P01. 3. Subject had an abnormal ECG in Study KP415.P01, which, in the Investigator's opinion, is clinically significant. 4. Subject has a recent (during Study KP415.P01) history of drug abuse in someone living in the subject's home. 5. Subject is using or planning to use prohibited drugs (as specified in the protocol) during the trial. 6. Subject, parent/legal guardian and caregiver (if applicable, at the Investigator's discretion) has commitments during the study that would interfere with attending study visits. 7. Subject or subject's family anticipates a move outside the geographic range of the investigative site during the study or plans extended travel inconsistent with the recommended visit interval during study duration. 8. Subject has one or more siblings living in the same household who are enrolled in this or another clinical drug trial. 9. Subject shows evidence of current physical, sexual, or emotional abuse. 10. Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study. **Eligibility Criteria (end of Dose Optimization Phase) for All Subjects:** All subjects will need to meet the following additional eligibility criteria at the end of the Dose Optimization Phase in order to enter into the Treatment Phase:

<table>
<tr><td></td><td>
1. A reduction of ≥30% in ADHD-RS-IV from baseline during the Dose Optimization Phase. The baseline is the ADHD-RD-IV score before the first dose of study drug (for Roll-over Subjects, from Study KP415.P01).
2. A CGI-I score of 1 or 2 points (“Very Much Improved” or “Much Improved”) at the end of the Dose Optimization Phase. The improvement will be judged from a baseline before the first dose of study drug (for Roll-over Subjects, from Study KP415.P01).
3. Acceptable tolerability of the optimized Azstarys® dose experienced during the Dose Optimization Phase.
Rescreening:
New Subjects who require extension of the screening window and remain eligible for the study may be rescreened upon written approval by the Medical Monitor. Items to be rescreened will be determined on a case-by-case basis. Subjects who fail screening will not be rescreened. New Subjects who received any dose of study drug and are terminated early or are not eligible to continue in the Treatment Phase, are not eligible to participate later in the study and will not be rescreened.
</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>
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 unblinded (open label) active drug in all phases of the study wherein study drug is administered, as follows:
</td></tr>
</table>

	• In the Dose Optimization Phase, daily treatments of 13.1 mg/2.6 mg, 26.1 mg/5.2 mg and 39.2 mg/7.8 mg open-label capsules will be administered (one capsule/day), for the titration to an optimal daily dose. • In the Treatment Phase, daily treatments of Azstarys® capsules will be administered (one capsule/day), at a daily dose that is the same as the optimal dose at the end of the Dose Optimization Phase, either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg capsules. The Investigator will evaluate the tolerability and dose-response on an ongoing basis during the Treatment Phase, and based on this evaluation, may change the dose. At any time, the daily oral dose will be either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg. 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 approximately 1-2 tablespoons of applesauce. Study drug will be taken orally in the morning at home under the supervision of parent/guardian/caregiver, or, on the visit days, may be taken at the study site under the supervision of study site staff.
ADHD SEVERITY/ EFFICACY EVALUATION CRITERIA	The following scales will be used to assess the changes in ADHD severity: • Preschool Version of ADHD-Rating Scale-IV (ADHD-RS-IV, McGoey 2007). The ADHD-RS-IV is an 18-item scale (DuPaul 1998) 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) (Busner and Targum 2007). During the Dose Optimization Phase, the ADHD-RS-IV, CGI-I and CGI-S scale assessments are the main efficacy response variables (in conjunction with tolerability and safety) to guide dose optimization. During the Treatment Phase, the ADHD-RS-IV and CGI-S scale assessments are the efficacy variables to evaluate the changes in ADHD severity over time and may be used (in conjunction with tolerability and safety) to adjust the dose of study drug.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Roll-over Subjects will participate in the study as outpatients for up to 413 days including approximately 24 (21 ±3 days) days in the Dose Optimization Phase, approximately 380 days (360 ±20 days) in the Treatment Phase, and a Follow-up Phone Call 5-9 days after the administration of the last dose of the Treatment Phase. New Subjects will participate in the study as outpatients for up to 443 days including approximately 30 days of Screening, approximately 24 days (21 ±3 days) in the Dose Optimization Phase, approximately 380 days (360 ±20 days) in the Treatment Phase, and a Follow-up Phone Call 5-9 days after the administration of the last dose of the Treatment Phase.
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 Dose Optimization Phase (Visit 2) to the end of the Treatment Phase or ET Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dextromethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall®, and prescription Azstarys®. • 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 Phase or ET Visit. These include: atomoxetine, guanfacine, clonidine and viloxazine. • The following medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase or ET Visit: o Monoamine oxidase inhibitors (MAOIs), norepinephrine reuptake inhibitors (NRIs) and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine. o Mood stabilizers (e.g., lithium, valproate, quetiapine)

	○ Antipsychotics (e.g., risperidone, olanzapine) ○ Coumarin anticoagulants ○ Anticonvulsants ○ Halogenated anesthetics ○ Phenylbutazone ○ Sedative hypnotics/sleep enhancers (with the exception of melatonin, which is allowed if subjects have taken it for more than 30 days before Screening for New Subjects or before Visit 2 for Roll-over Subjects) • Tricyclic antidepressants and bupropion are prohibited from 30 days prior to the start of the Treatment Phase to the end of the Treatment Phase or ET Visit. • Cough and cold medications containing stimulants should be avoided in the week prior to each scheduled visit. All other concomitant medications will be allowed if necessary. **Note:** Subjects who roll-over from Study KP415.P01 into the current study will need to continue abstaining from all prohibited medications listed above from the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase or ET Visit.
SAFETY ENDPOINTS	• The occurrence of treatment-emergent adverse events (TEAEs) will be assessed starting following the first dose of study drug, and ending with the Follow-up Phone Call or ET Visit. • Physical examinations will be performed at Screening for New Subjects and at Visit 2 for Roll-over Subjects, at Visit 11, and at the end of the Treatment Phase or at ET. • Clinical laboratory tests will be performed at Screening for New Subjects and at Visit 2 for Roll-over Subjects, at Visit 11, and at the end of the Treatment Phase or at ET. • ECG parameters will be collected at Screening for New Subjects and at Visit 2 for Roll-over Subjects, at Visit 11, and at the end of the Treatment Phase or at ET. • Vital signs, height and weight will be collected at each visit. Blood pressure will be analyzed based on the average of 3 blood pressure measurements 2-5 minutes apart. The average of the three measurements will be entered into the eCRF. • Ratings from the C-SSRS will be collected at each study visit to the end of the Treatment Phase. • Ratings from the modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be collected at each visit to assess sleep behavior.
EFFICACY ENDPOINTS	During the Dose Optimization Phase:

	• CGI-S will be assessed at each visit. • ADHD-RS-IV (Preschool version) will be assessed at each visit. • CGI-I will be assessed at Visits 3, 4, and 5 (since CGI-I is an ADHD improvement assessment, it will not be assessed at Screening or at Visit 2). During the Treatment Phase: • ADHD-RS-IV and CGI-S will be assessed at each visit.
ANALYSIS POPULATIONS	• **Treatment-Phase Safety Population:** All enrolled subjects in the Treatment Phase who received at least one dose of study medication in the Treatment Phase and had at least one post-dose safety assessment in the Treatment Phase. All baseline and safety data during the Treatment Phase will be analyzed using this population. • **Efficacy Population:** All enrolled subjects who received at least 30 days of study medication in the Treatment Phase, who had a baseline assessment and at least one post-baseline assessment of efficacy parameters (ADHD-RS-IV, CGI-I) and who had no protocol deviations that could affect the efficacy parameters. All efficacy analyses across the Treatment Phase will be analyzed using this population. • **Dose-Optimization Safety Population:** All enrolled subjects in the Dose Optimization Phase who received at least one dose of study medication in the Dose Optimization Phase and had at least one post-dose safety assessment in the Dose Optimization Phase. All data from the Dose Optimization Phase will be analyzed using this population. • **Pharmacokinetic (PK) Population:** All subjects who received the daily treatment for at least 5 days before the blood samples for PK were collected, without any major protocol deviations potentially affecting PK, and who provided the plasma concentrations for d-methylphenidate required to calculate the population PK parameters of d-MPH. Demographics and baseline characteristics will be summarized for the PK Population overall and by dose received.
STATISTICAL ANALYSES	**Safety Analysis** *Treatment Phase* The safety analyses described below will be performed for the safety data collected during the Treatment Phase based on the Treatment Phase Safety Population (all enrolled subjects in the Treatment Phase who received at least one dose of study medication and had at least one post-dose safety assessment in the Treatment Phase). 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 dose group and overall. 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 MedDRA. The number and percentage of subjects reporting treatment phase TEAEs and abuse-related AEs 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 dose group and overall. An MMRM ANCOVA model will be fitted to change from baseline CSHQ total Sleep score using all data as observed. The model will include fixed effects for optimized dose, baseline CSHQ, visit, and visit-by-dose interaction, as well as a random effect for the subject. From the MMRM model, the difference between LS means of Azstarys® optimized dose levels will be presented along with the corresponding 95% CI for each pairwise comparison. An MMRM ANCOVA model will be fitted to change from baseline C-SSRS score using all data as observed. The model will include fixed effects for optimized dose, baseline C-SSRS, visit and visit-by-dose interaction, as well as a random effect for the subject. From the MMRM model, the difference between LS means of Azstarys® optimized dose levels will be presented along with the corresponding 95% CI for each pairwise comparison. An MMRM ANCOVA model will be fitted to change from baseline for systolic and diastolic blood pressure using all data as observed. The model will include fixed effects for optimized dose, baseline systolic and diastolic blood pressure, visit and visit-by-dose interaction, as well as a random effect for the subject. From the MMRM model, the difference between LS means of Azstarys® optimized dose levels will be presented along with the corresponding 95% CI for each pairwise comparison. *Dose Optimization Phase* The safety analyses described below will be performed for the safety data collected during the Dose Optimization Phase based on the Dose Optimization Phase Safety Population (all enrolled subjects in the Dose Optimization Phase who received at least one dose of study

	medication and had at least one post-dose safety assessment in the Dose Optimization Phase). Descriptive statistics will be presented for baseline, all post baseline measurements, and changes from baseline to all post-baseline measurements during the Dose Optimization Phase, where applicable, for continuous safety endpoints by dose group and overall. 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. The number and percentage of subjects reporting TEAEs and abuse-related AEs during the Dose Optimization Phase 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 during the Dose Optimization Phase will also be summarized by MedDRA system organ class and preferred term. **Efficacy Analysis** *Treatment Phase* The efficacy analyses described below will be performed for the efficacy data collected during the Treatment Phase based on the Efficacy Population (all enrolled subjects who received at least 30 days of study medication in the Treatment Phase, who had a baseline assessment and at least one post-baseline assessment of efficacy parameters and who had no protocol deviations that could affect the efficacy parameters). 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 dose group and overall. An MMRM ANCOVA model will be fitted to change from baseline in ADHD-RS-IV total score using all data as observed. The model will include fixed effects for optimized dose, baseline ADHD-RS total score, visit and visit-by-dose interaction, as well as a random effect for the subject. The primary efficacy analysis will be based on comparisons of Azstarys® optimized dose levels. From the MMRM model, the difference between least square (LS) means of Azstarys® optimized dose levels will be presented along with the corresponding 95% CI for each pairwise comparison. The secondary efficacy endpoints, change from baseline to post-baseline time points in ADHD-RS-IV for hyperactivity/impulsivity, the ADHD-RS-IV for inattention, and change from baseline in CGI-S

	will be analyzed using the same methods as the efficacy endpoint, change from baseline in ADHD-RS-IV Total Score. *Dose Optimization Phase* The ADHS-RS-IV, CGI-S, and CGI-I will be analyzed descriptively for the Dose Optimization Phase. **Interim Analysis** An interim analysis of the safety data will be conducted once all of the subjects remaining in the study complete their Visit 11 assessments, to determine whether the study should be stopped. The interim analysis will primarily focus on the safety assessments, including changes in weight, height, and sleep behavior (CSHQ), during the first 6 months of treatment in the Treatment Phase. The safety data will be analyzed with the same statistical methods as planned for the main analysis after completion of the study to determine if the study early stopping rules have been met.
PHARMACOKINETIC ANALYSIS	A population PK analysis will be performed for d-MPH based on the plasma concentrations of d-MPH measured in 3 samples per subject (sparse sampling approach) during the Treatment Phase. Three (3) blood samples will be drawn as indicated: Sample **1**: • Pre-dose sample: within 30 minutes pre-dose Samples **2** and **3**, taken at <u>two</u> of the following times. A randomization scheme will be used to determine the 2 post-dosing times for the collection of the PK samples in each PK subject: • 15-minute sample: 15-40 minutes post-dose • 2-hour-sample: 1.5– 2.5 hours post-dose • 4-hour sample: 4– 6 hours post-dose Based on the power calculations, a minimum of 40 subjects is required to achieve at least 80% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for d-MPH after Azstarys® administration in this pediatric group. Therefore, complete PK sample sets (pre-dose and 2 post-dose samples) will be collected from at least 40 subjects. In accordance with a male-to female distribution ratio of 3:1 of children diagnosed with ADHD in clinical practice, full PK sample sets will be collected from approximately 30 males and 10 females. Detailed descriptions of the PK analyses will be provided in the pharmacokinetic analysis plan (PKAP).
STUDY PROCEDURES	The study procedures are outlined in the Schedule of Events (Section 1).

1. SCHEDULE OF EVENTS

1.1. Screening and Dose Optimization Phase

ASSESSMENTS[21]	**SCREENING PHASE (NEW SUBJECTS)**[1]	**OPEN-LABEL DOSE OPTIMIZATION PHASE**[20] **(All Subjects)** Days 0-21 ± 3 days (including at-home dosing)			
Study Day	-30 to -1	0		7 (±3 days)	14 (±3 days)
Visit Number	1	2 (New Subjects)	2 (Roll-over Subjects)	3	4
Parental Permission/Written	X		X		
ADHD Diagnosis and Confirmation [2]	X				
Inclusion/Exclusion [3]	X	X	X	X	X
Demographics	X				
Medical History [4]	X	X			
Physical Examination	X		X		
Body Weight and Height [5]	X	X	X	X	X
Vital Signs [6]	X	X	X	X	X
12-Lead ECG [7]	X		X		
Chemistry/Hematology/Urinalysis	X		X		
Urine Drug Screen [8]	X				
C-SSRS [9]	X	X	X	X	X
Washout ADHD Meds [10]	X	X			
Dispensing of unblinded Azstarys® capsules until next visit		X	X	X	X
Azstarys® Dosing [11]				X	X
Drug Accountability & Compliance Assessment [12]				X	X
ADHD-RS-IV [13]	X	X	X	X	X
MINI Kid [14]	X				
CGI-S [15]	X	X	X	X	X
CGI-I [16]			X	X	X
CSHQ [17]	X	X	X	X	X
Adverse Events [18]				X	X
Concomitant Medications [19]	X	X	X	X	X

ECG = electrocardiogram; MPH = methylphenidate; see footnotes for other abbreviations.

1. Screening Visit: For New Subjects only.
2. 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).

3. Study inclusion/exclusion criteria (different for New Subjects and Roll-over Subjects) will be evaluated at Screening (New Subjects) and Visit 2 (all subjects). Inclusion/exclusion criteria to be adhered to throughout the study (e.g., use of prohibited medications, suicidal ideation) will also be evaluated at Visits 3, 4, and 5.
4. Medical History: At Screening, a complete medical history including chronic conditions, relevant surgical procedures (with start date), and history of drug use will be obtained for New Subjects. For Roll-over Subjects, new medical conditions that occurred during their participation in Study KP415.P01 will be recorded at Visit 6 (P01)/Visit 2 (P02) as medical history for this study. At Visit 2, only New Subjects will be reassessed for medical history.
5. 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.
6. Vital sign measurements will be obtained at each visit 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 eCRF.
7. Electrocardiogram (ECG): A 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded.
8. Urine Screen for Drugs of Abuse: Urine samples will be tested for drugs of abuse (amphetamines, methamphetamines, methylphenidate, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone) at the Screening visit for New Subjects. If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for methylphenidate for treatment of their ADHD. All ADHD medications must be washed out per New Subject Inclusion Criterion #7.
9. Columbia Suicide Severity Rating Scale (C-SSRS): The "Children's Baseline/Screening" version will be assessed at Screening, and the "Children's Since Last Visit" version will be assessed at all other visits. Subjects who have, in the opinion of the Investigator, clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening or at any time before the last dose of study drug, will be excluded from further participation in the study.
10. New 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 Phase (Visit 17) or Early Termination (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 Phase (Visit 17) or ET Visit. Before or on the day during the screening period that subjects will need to start the washout of their ADHD medications (for example, 5 days before Visit 2 for stimulants), study site staff will contact the subject's parent/guardian by phone to remind them of the washout ("Washout Phone Call"). Other prohibited medications and the windows of prohibition are listed in the protocol.
11. Dose Optimization: Subjects will begin taking Azstarys® at home the morning following Visit 2. The starting dose will be 13.1 mg/2.6 mg day. Azstarys® dose adjustments, if needed, will be performed at approximately weekly intervals between visits. Actual visit dates may deviate from exactly being spaced 7 days apart such that the total duration of the Dose Optimization Phase is 3 weeks (21 ±3 days). The daily doses of Azstarys® used in the Dose Optimization Phase will be 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg. 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 Azstarys® dose should be increased, decreased, or remain the same for the next week of

dosing. If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their 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.

12. 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.
13. ADHD-Rating Scale-IV (ADHD-RS-IV) assessment: 1 assessment at the indicated visits.
14. Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).
15. Clinical Global Impressions–Severity (CGI-S) scale assessment: 1 assessment at the indicated visits.
16. Clinical Global Impressions–Improvement (CGI-I) scale assessment: 1 assessment at the indicated visits.
17. Children's Sleep Habits Questionnaire (CSHQ) assessment: 1 assessment at the indicated visits.
18. Adverse Events: To be assessed and recorded in the electronic case report form (eCRF) following the first dose of open-label drug, on Day 1, through either the Follow-up Phone Call or ET. Subject's parent/guardian will be instructed to contact the study site for the reporting of AEs during the dosing periods at home.
19. Concomitant Medications: new and/or changed medications and dose, medical treatments and/or therapies will be recorded at Screening through the Follow-up Phone Call or ET.
20. Actual visit dates in the Dose Optimization Phase may deviate from being spaced exactly 7 days apart such that the total duration of the Dose Optimization Phase is 3 weeks (21 ±3 days). Any allowed deviation (up to 3 days in total) of the targeted 21-day Dose Optimization Phase will be carried over into the actual days for the subsequent visits.
21. Assessment changes due to 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, 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).

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

ASSESSMENTS[17]	OPEN-LABEL TREATMENT PHASE (All Subjects)						
Study Day	(Day 21 of Dose Optimization Phase)	30 (±5 days)	60 (±5 days)	90 (±5 days)	120 (±5 days)	150 (±5 days)	180 (±5 days)
Visit Number	5	6	7	8	9	10	11
Inclusion/Exclusion	X						
Physical Examination [1]							X
Body Weight, Height [2]	X	X	X	X	X	X	X
Vital Signs [3]	X	X	X	X	X	X	X
12-Lead ECG [4]							X
C-SSRS [5]	X	X	X	X	X	X	X
Chemistry/Hematology/ Urinalysis							X
Eligibility Criteria for Treatment Phase / Enrollment in Treatment Phase	X						
Dispensing of unblinded Azstarys® capsules until next visit	X	X	X	X	X	X	X
Azstarys® Dosing [6]	X	X	X	X	X	X	X
Drug Accountability & Compliance Assessment [7]	X	X	X	X	X	X	X
ADHD-RS-IV [8]	X	X	X	X	X	X	X
CGI-S [9]	X	X	X	X	X	X	X
CGI-I [10]	X						
CSHQ [11]	X	X	X	X	X	X	X
Adverse Events [12]	X	X	X	X	X	X	X
Concomitant Medications [13]	X	X	X	X	X	X	X
Interim Safety Analysis[14]							X
Dosing Diary dispensing (for PK Subjects)	X	X					
PK Sampling (Randomized)/Dosing Diary collection/review[18]		X	X				

EOS = End of Study; ET = Early Termination; ECG = Electrocardiogram. see footnotes for other abbreviations.
See Section 1.3 for all footnotes.

1.3. Treatment Phase (Second 6 Months), Early Termination and Follow-up Phone Call

ASSESSMENTS[17]	**OPEN-LABEL TREATMENT PHASE (All Subjects)**					**END OF TREATMENT**[15]	**EARLY TERMINATION**[16]	**FOLLOW-UP PHONE CALL** (EOS)
Study Day	210 (±5 days)	240 (±5 days)	270 (±5 days)	300 (±5 days)	330 (±5 days)	360 (±5 days)	-	365 (5-9 days after EOT)
Visit Number	12	13	14	15	16	17	-	18
Physical Examination [1]						X	X	
Body Weight, Height [2]	X	X	X	X	X	X	X	
Vital Signs [3]	X	X	X	X	X	X	X	
12-Lead ECG [4]						X	X	
Chemistry/Hematology/ Urinalysis						X	X	
Dispensing of unblinded Azstarys® capsules for use until the next visit	X	X	X	X	X			
Azstarys® Dosing [6]	X	X	X	X	X	X	X	
Drug Accountability & Compliance Assessment[7]	X	X	X	X	X	X	X	
C-SSRS[5]	X	X	X	X	X	X	X	
ADHD-RS-IV [8]	X	X	X	X	X	X	X	
CGI-S [9]	X	X	X	X	X	X	X	
CSHQ [11]	X	X	X	X	X	X	X	
Adverse Events [12]	X	X	X	X	X	X	X	X
Concomitant Medications [13]	X	X	X	X	X	X	X	X

EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; ECG = Electrocardiogram; see footnotes for other abbreviations.

1. Physical examination at Visit 11, and at Visit 17 (EOT) or ET (if possible).
2. Body weight and height 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.
3. 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 at each visit. Only the average of the 3 blood pressure measurements will be entered into the eCRF.
4. Electrocardiogram (ECG): A 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded.
5. Columbia Suicide Severity Rating Scale (C-SSRS): The "Children's Since Last Visit" version will be assessed at all visits in the Treatment Phase and at ET (if applicable). 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 from Screening to at any time before the last dose of study drug, will be excluded from further participation in the study.

6. Azstarys® Dosing: At Visit 5, the Investigator will evaluate the eligibility criteria based on assessments in the Dose Optimization Phase for continuation into the subsequent Treatment Phase. At Visit 5, All Subjects will be dosed with the last dose of the Dose Optimization Phase. For subjects eligible for the Treatment Phase, the optimal daily dose will be used as the daily dose in the Treatment Phase. Details on doses and dosing methods are found in Section 9.5 and Section 8.3.1.
7. Drug Accountability & Compliance Assessment: All study drug 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.
8. ADHD-Rating Scale-IV (ADHD-RS-IV) assessment: 1 assessment at the indicated visits.
9. Clinical Global Impressions–Severity (CGI-S) scale assessment: 1 assessment at the indicated visits.
10. Clinical Global Impressions–Improvement (CGI-I) scale assessment: 1 assessment at Visit 5.
11. Children's Sleep Habits Questionnaire (CSHQ) assessment: 1 assessment at the indicated visits.
12. Adverse Events: To be assessed and recorded in the eCRF following the first dose of Azstarys®, through either ET or Follow-up Phone Call. Subject's parent/guardian will be instructed to contact the study site for the reporting of AEs while away from the study site.
13. Concomitant Medications: new and/or changed medications and dose, medical treatments and/or therapies will be recorded at Visit 4 through either Follow-up Phone Call or ET. The investigator or designee will also review for prohibited medications (see Section 10).
14. Interim Safety Analysis: An interim analysis of the safety data will be conducted after approximately all subjects remaining in the study have completed approximately 180 days (Visit 11) in the Treatment Phase. After completion of the interim analysis, based on the safety profile of the treatment, the study may be stopped. Treatment in the current study will continue as planned while the interim analysis is conducted. If the decision is made to stop the study, all subjects remaining in the study will undergo the EOT Visit (with safety evaluations including fasting safety labs and ECGs) and a Follow Up Phone Call.
15. End-of-Treatment (EOT): Subjects will receive their last dose of study drug in the study.
16. Early Termination (ET): Subjects who meet withdrawal criteria post-dose during the Treatment Phase (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 ET procedures that were performed on the same day as part of the procedures of the Treatment Phase, do not need to be repeated. Subjects who withdraw early from the study and complete the ET procedures will not have a Follow-up Phone Call. Therefore, the ET Visit is the EOS.
17. Assessment Changes due to COVID-19: If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, then 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, CGI-S, CGI-I, CSHQ) will be collected by phone at the scheduled visit times (remote visit). 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).
18. At visits on which PK samples will be collected (Visit 6 and/or Visit 7), PK Subjects will come to the site in the morning of the scheduled visit and they will receive study drug at the study site after the pre-dose PK sample is collected. The PK Dosing Diary will be reviewed with the parent/caregiver. See Section 14.2 for additional details.

2. BACKGROUND

2.1. Attention-Deficit/Hyperactivity Disorder (ADHD)

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 CNS stimulants, which contain amphetamine or methylphenidate (MPH). Amphetamine-containing products include brand names such as Adderall®, Dexedrine®, Dextrostat®, and Vyvanse®. Methylphenidate containing products include Metadate®, Concerta®, Daytrana®, Ritalin®, Methylin®, 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 (ADHD), 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 serdexmethylphenidate (SDX), a prodrug of d-MPH, co-formulated with immediate-release 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 (Azstarys®) 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.

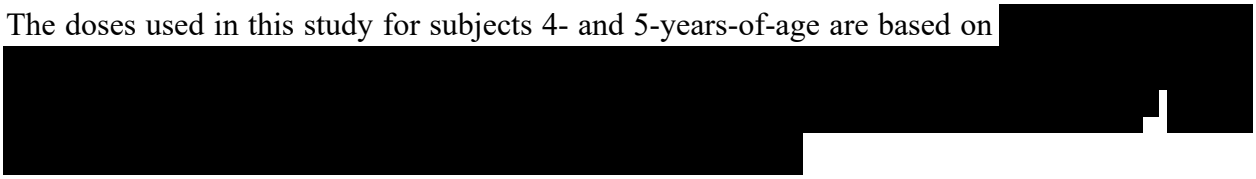
The three dosage strengths of approved formulation, for the treatment of ADHD in subjects ages 6 years and older, are as follows:

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

Doses of the approved 26.1 mg/5.2 mg and 39.2 mg/7.8 mg Azstarys® capsules will be investigated for the treatment of ADHD in subjects ages 4 and 5 years. To accommodate the lowest dose in children of ages 4-5 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 4- and 5-years-of-age are based on



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

3. AZSTARYS® IN SUBJECTS OF AGE ≥6 YEARS

3.1. Clinical Pharmacology of Azstarys®

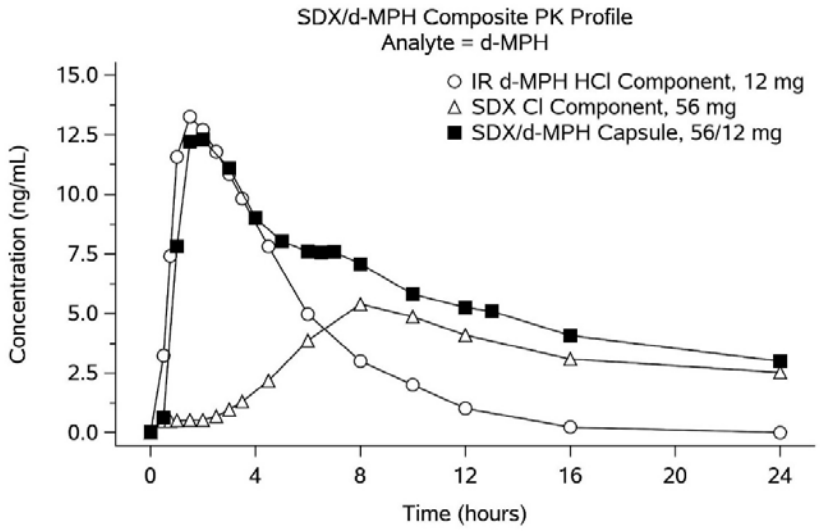
As part of the clinical development program of Azstarys® for the treatment of ADHD in subjects ages 6 years and older, 10 studies were conducted to examine the pharmacokinetics of SDX and SDX-derived d-MPH after oral administration of clinical doses of single-entity SDX Cl or Azstarys®. Of these, 5 studies 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 to 12 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 (6-12 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 Package Insert 2019), with respect to d-MPH exposure. The long-term safety of Azstarys® capsules was established in a clinical trial in patients with ADHD 6-12 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 safety and efficacy for Focalin XR (Focalin XR Package Insert 2019) can be referenced to support, at least in part, safety and efficacy 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 estimated clearance (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, volume of distribution (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 (6-12 years old) for exposure of d-MPH after oral Azstarys® dosing.

3.2. Clinical Safety of Azstarys®

As part of the Azstarys® development program for the treatment of ADHD in patients 6 years of age and older, the clinical safety and tolerability was investigated in 12 clinical studies, including 1 pivotal Phase 3 efficacy and safety study in children age 6 to 12 years with ADHD (Study KP415.E01) and 1 long-term Phase 3 safety study in children age 6 to 12 years with ADHD (Study KP415.S01).

The long-term, open-label safety Study KP415.S01 was conducted in pediatric patients 6 to 12 years of age with ADHD who either completed the short-term efficacy study (KP415.E01) or were de novo patients. This study was comprised of a 3-week Dose Optimization Phase for subjects not recently treated with Azstarys® followed by a 12-month Treatment Phase for all subjects, during which they received daily doses of the optimized dose of open label Azstarys®.

Of the 282 subjects enrolled, 257 subjects entered the Treatment Phase; a total of 212 subjects received treatment during the Dose-Optimization Phase; during the Treatment Phase 257 subjects received treatment. In total, 189 subjects completed at least 6 months of treatment in the Treatment Phase, and 155 subjects completed approximately 12 months treatment.

During the Dose Optimization Phase of Study KP415.S0, over half (54.3%) of subjects experienced at least 1 treatment-emergent adverse event (TEAE). The most common (≥5% of subjects) preferred terms of TEAEs overall during this phase were decreased appetite (18.8%), insomnia and irritability (both 6.7%), and initial insomnia (5.3%). One subject (0.5%) experienced a serious TEAE during the Dose-Optimization Phase of aggression (grade 2), which was considered unrelated to study drug. The subject was hospitalized, and study drug was discontinued because of the event; the subject recovered after 6 days. Five subjects (2.4%) had the study drug discontinued during the Dose Optimization Phase because of a TEAE (preferred terms of aggression, irritability, psychotic disorder, nausea, and bruxism).

During the Treatment Phase of Study KP415.S01, 108 subjects (45.4%) experienced a related TEAE. The most common (≥5% of subjects) preferred terms of TEAEs overall were decreased appetite (18.5%), upper respiratory tract infection (9.7%), nasopharyngitis (8.0%), weight decreased (7.6%), irritability (6.7%), insomnia (5.0%), and weight increased (5.0%). Six subjects (2.5%) had study drug discontinued during the Treatment Phase due to a total of 8 TEAEs. They included 5 subjects (4.0%) in the Azstarys® 52.3 mg/10.4 mg group (2 of whom had 2 TEAEs leading to study drug discontinuation), 1 subject (3.8%) in the Azstarys® 26.1 mg/5.2 mg group, and no subject in the Azstarys® 39.2 mg/7.8 mg group. As in the Dose Optimization Phase, psychiatric disorders were the most common system organ class of TEAE leading to study drug discontinuation, reported in 5 subjects (2.1%) overall, with preferred terms of irritability (2 subjects [0.8%]), initial insomnia (2 subjects [0.8%]), depression (1 subject [0.4%]), and suicidal ideation (1 subject [0.4%]). Other TEAEs leading to study drug discontinuation consisted of decreased appetite and leukopenia, reported in 1 subject (0.4%) each. All TEAEs leading to discontinuation of study drug during the Treatment Phase were assessed as related to study drug; none of the events was considered serious.

Sleep-related problems, as assessed by the Children's Sleep Habits Questionnaire (CSHQ) showed a small improvement over 12 months of treatment in Study KP415.S01; the changes were not felt to be clinically meaningful; no overall worsening of sleep problems was observed.

Patterns of shift in clinical laboratory test results with respect to baseline showed no clinically meaningful trends to suggest an effect of Azstarys® on any parameter. Mean values for vital signs and the changes from baseline in Study KP415.S01 showed no trends or clinically meaningful treatment group differences to suggest an effect of Azstarys®, except for modest mean increases in pulse rate at several time points, none exceeding 6 bpm.

The effect of treatment with Azstarys® was also investigated in Study KP415.S01. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]); z- scores normalize for the natural growth of children and adolescents by comparisons to age and sex-matched population standards. A z-score change less than 0.5 SD is considered not clinically significant. In this study, the mean increase in weight from baseline to Month 12 was 3.4 kg among study completers. The mean change in z-score from baseline to Month 12 was -0.20, indicating a lower than expected increase in body weight compared to children of the same age and sex, on average. Most of the weight z-score decline occurred in the first 4 months of treatment. The mean increase in height from baseline to Month 12 was 4.9 cm among completers. Using the same z-score analysis for height, the mean change in z-score from baseline to Month 12 was -0.21, indicating a lower than expected increase in height compared to pediatric patients of the same age and sex, on average.

4. STUDY RATIONALE

Awareness of ADHD in children of preschool age has increased with a reported prevalence ranging from >1% to ~12% (reviewed in Childress 2021). In preschool-aged children, it is generally recommended that behavioral intervention is the initial attempted treatment; stimulants are recommended when there has been insufficient improvement in symptoms with behavioral intervention (Wolraich 2019).

As part of the development program of Azstarys® for the treatment of ADHD in patients 6 years of age and older, the clinical safety and tolerability was investigated in children age 6 to 12 years with ADHD (Section 3.2), but no safety data is currently available in subjects age 4 and 5 years with ADHD treated with Azstarys®.

Therefore, the long-term safety and tolerability of daily dose of Azstarys® in children age 4 and 5 years with ADHD will be investigated in the current study. Since there are concerns that CNS stimulants may have a negative effect on sleep and growth, especially in children of preschool age, the safety assessments in this study will include changes in sleep behavior, body weight, and height. In addition, the 12-month maintenance of ADHD symptom control through investigator ratings on the ADHD-RS-IV will be investigated.

5. STUDY OBJECTIVES

5.1. Primary Objective

To determine the safety and tolerability of treating children 4 and 5 years of age with ADHD with Azstarys® for up 12 months. The safety objective includes changes in weight and height, and sleep behavior.

5.2. Secondary Objectives

To determine efficacy with respect to the 12-month maintenance of ADHD symptom control through investigator ratings on the ADHD-RS-IV.

5.3. Pharmacokinetic Objective

To assess the population PK of Azstarys® in children 4 and 5 years old with ADHD.

6. INVESTIGATIONAL PLAN

6.1. Study Design

The is a multicenter, dose-optimized, open-label, safety/tolerability, and PK study with Azstarys® in children 4 and 5 years of age with ADHD.

The phases of the study are as follows:

- **Screening Period (New Subjects Only):** New Subjects will undergo a Screening Period up to 30 days prior to entering the Dose Optimization Phase.

- **Dose Optimization Phase (All Subjects):** During the 3-week Dose Optimization Phase, subjects will start at 13.1 mg/2.6 mg and may be titrated to doses of 26.1 mg/5.2 mg or 39.2 mg/7.8 mg Azstarys® capsules based on individual tolerability and best dose-response in the opinion of the Investigator.

NOTE: Subjects rolled over from Study KP415.P01 will start the current study at Visit 2 (they will not undergo the procedures of the Screening Period in the current study since they were screened and enrolled in Study KP415.P01). Eligibility of Roll-over Subjects in the current study will be evaluated at Visit 6 in Study KP415.P01. Visit 2 in the current study will be on the same day as Visit 6 in Study KP415.P01.

- **Treatment Phase (All Subjects):** Eligible subjects will receive single daily doses of Azstarys® for 360 ±20 days (approximately 12 months).

    - During the Treatment Phase, the starting dose of Azstarys® in will be the same as the optimized dose of Azstarys® at the end of the Dose Optimization Phase, either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg per day, although, at the Investigator's discretion, based on individual tolerability and dose response, the daily dose may be changed at any time to any of the allowed dose levels (13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day).
    - Safety (including vital signs, weight, height, and sleep behavior) and efficacy assessments will be performed during the study. After approximately all subjects remaining in the study have completed approximately 180 days (Visit 11) of the Treatment Phase, an interim analysis will be conducted to evaluate safety parameters.

- **Follow-up Phone Call (All Subjects):** Subjects will receive a Follow-up Phone Call, at 5-9 days after administration of the last dose of the Treatment Phase, to evaluate safety parameters.

6.1.1. Definition of "Roll-over Subjects" and "New Subjects"

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

- **Roll-over Subjects** are subjects who have successfully completed Study KP415.P01 and continue to meet eligibility criteria for Study KP415.P02.

- **New Subjects** are subjects who did not participate in Study KP415.P01 or were not eligible to enter Study KP415.P02 as Roll-over Subjects but are eligible to enter as New Subjects (re-entry).

Roll-over Subjects and New Subjects will need to meet their respective inclusion/exclusion criteria listed in Section 7.2.

6.2. Study Duration

Roll-over Subjects: Roll-over Subjects will participate in the study as outpatients for up to 413 days, including up to 24 (21 ±3 days) days in the Dose Optimization Phase, up to 380 days (360 ±20 days) in the Treatment Phase, and a Follow-up Phone Call up to 9 days (5-9 days) after the administration of the last dose of the Treatment Phase.

New Subjects: New Subjects will participate in the study as outpatients for up to 443 days including up to 30 days of Screening, up to 24 days (21 ±3 days) in the Dose Optimization Phase, up to 380 days (360 ±20 days) in the Treatment Phase, and a Follow-up Phone Call up to 9 days (5-9 days) after the administration of the last dose of the Treatment Phase.

7. SUBJECT SELECTION

7.1. Number of Subjects

Approximately 100 subjects will be enrolled in the study. An appropriate number of New Subjects will enter the Screening Period in addition to the Roll-over Subjects to ensure approximately 100 subjects are enrolled in the study. Assuming a dropout rate of up to 50% over 12 months, approximately 50 subjects are expected to complete the 12-month Treatment Phase.

Subjects who fail Screening and subjects who terminate early during the Dose Optimization Phase may be replaced. Subjects who terminate early in the Treatment Phase will not be replaced.

7.2. Study Population

Subjects will be either recruited *de novo* (New Subjects) for this study, or will be rolled over (Roll-over Subjects) from Study KP415.P01.

7.2.1. Inclusion Criteria for New Subjects

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

1. New Subjects must be at least 4 years old and less than 5 years and 10 months old 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. Subject 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, ECGs, medical history, and clinical laboratory values (chemistry, hematology and 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.

4. At least one parent/legal guardian of the subject must voluntarily give written permission for the subject to participate in the study.

5. Subject must meet Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) per clinical evaluation and confirmed by the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).

6. Subject must have had ADHD symptoms present for at least 6 months prior to the Screening Visit.

7. Subject must be able and willing to wash out current stimulant ADHD medications, including herbal medications from 5 days prior to the start of the Dose Optimization Phase, and abstain from taking these to the end of the Treatment Phase (Visit 17) or Early Termination (ET); and wash out non-stimulant ADHD medications from 14 days prior to the start of the Dose Optimization Phase, and abstain from taking these to the end of the Treatment Phase (Visit 17) or ET.

8. 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.

9. Subject functions at an age-appropriate level intellectually, as determined by the Investigator.

10. Subject must have age and sex adjusted ratings of ≥90th percentile Total Score on the ADHD-RS-IV (Preschool Version) rated over the past 6 months.

11. 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.

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

13. Subject's 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. Inclusion Criteria for Subjects Rolled Over from Study KP415.P01

The following inclusion criteria will be evaluated no later than Visit 6 in Study KP415.P01, which is the same as Visit 2 (the first study visit for Roll-over Subjects in the present study):

1. Subjects must have completed the Treatment Period of Study KP415.P01.

2. Roll-over Subjects from Study KP415.P01 must be at least 4 years old and less than 6 years at the time of taking the first dose of Azstarys® in Study KP415.P01.

3. At least one parent/legal guardian of the subject must voluntarily give written permission for the subject to participate in the study.

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

5. Subject's 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.

7.2.3. Exclusion Criteria for New Subjects

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

1. 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.

2. 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.

3. 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.

4. Subject has evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS related disorders that might occur in childhood (e.g., Duchenne Muscular dystrophy, myasthenia gravis, or other neurologic or serious neuromuscular disorders), or history of persistent neurological symptoms attributable to serious head injury.

5. Subject taking anticonvulsants for seizure control 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.

6. 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.

7. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based on history of attempted suicide and the C-SSRS assessment at Screening.

8. 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 drug 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.

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

10. Subject has a history of, or currently has a malignancy.

11. 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.

12. Subject has greater than trace proteinuria on the urinalysis at Screening. Subjects with greater than trace proteinuria in the urinalysis at Screening but with a urine protein to creatinine (UP/C) ratio <0.2 in a first morning void urine sample will not be excluded from enrollment.

13. A current or recent (past 12 months) history of drug abuse in someone living in the subjects' home.

14. Subject has a positive urine screen for drugs of abuse at Screening. If the urine test is positive for any of the analytes at Screening, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen may test positive for MPH for treatment of their ADHD. All ADHD medications must be washed out per New Subject Inclusion Criterion #7.

15. 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, except for participation in Study KP415.P01.

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

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

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

19. 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).

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

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

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

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

24. Subject has one or more siblings living in the same household who are enrolled in this or another clinical drug trial.

25. Subject shows evidence of current physical, sexual, or emotional abuse.

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

7.2.4. Exclusion Criteria for Roll-over Subjects

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

1. Subject developed, since starting Study KP415.P01, 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.

1. In the opinion of the Investigator, subject has clinically significant suicidal ideation/behavior, based C-SSRS assessments in Study KP415.P01.

2. Subject had an abnormal ECG in Study KP415.P01, which in the Investigator's opinion is clinically significant.

3. Subject has a recent (during Study KP415.P01) history of drug abuse in someone living in the subject's home.

4. Subject is using or planning to use prohibited drugs (as specified in the protocol) during the trial.

5. 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.

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

7. Subject has one or more siblings living in the same household who are enrolled in this or another clinical drug trial.

8. Subject shows evidence of current physical, sexual, or emotional abuse.

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

7.2.5. Eligibility Criteria (end of Dose Optimization Phase) for All Subjects

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

1. A reduction of ≥30% in ADHD-RS-IV from baseline during the Dose Optimization Phase. The baseline is the ADHD-RD-IV score before the first dose of study drug (for Roll-Over Subjects, from Study KP415.P01).

2. A CGI-I score of 1 or 2 points ("Very Much Improved" or "Much Improved") at the end of the Dose Optimization Phase. The improvement will be judged from a baseline before the first dose of study drug (for Roll-over Subjects, from Study KP415.P01).

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

7.2.6. Rescreening

New Subjects who require extension of the screening window and remain eligible for the study may be rescreened upon written approval by the Medical Monitor. Items to be rescreened will be determined on a case-by-case basis. Subjects who screen fail will not be rescreened. New Subjects who received any dose of study drug and are terminated early or are not eligible to continue in the Treatment Phase, are not eligible to participate later in the study (and will not be rescreened).

8. STUDY TREATMENTS

8.1. 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

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.

Unblinded Azstarys® capsules 13.1 mg/2.6 mg, 26.1/5.2 mg, and 39.2 mg/7.8 mg for oral administration will be used in the Dose Optimization Phase and Treatment Phase of the study.

8.2. Treatment in the Dose Optimization Phase (All Subjects)

In the Dose Optimization Phase, daily treatments of 13.1 mg/2.6 mg, 26.1/5.2 mg, and 39.2 mg/7.8 mg open-label Azstarys® capsules will be administered (one capsule/day in the morning), for the titration to an optimal daily Azstarys® dose based on tolerability and best individual dose-response in the opinion of the Investigator.

Subjects will begin taking open-label Azstarys® at home the morning following Visit 2. The starting dose of Azstarys® (Days 1-7 ±3 days) will be 13.1 mg/2.6 mg per day. Azstarys® dose adjustments, if needed, will be performed at approximately weekly intervals between visits (at Visits 3, 4, and 5). Actual visit dates may deviate from exactly being spaced 7 days apart such that the total duration of the Dose Optimization Phase ranges between 18 and 24 days (21 ±3 days). 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 Azstarys® dose should be increased, decreased, or remain the same for the next week of dosing. If subjects experience symptoms of intolerance during the at-home treatment, they must contact the clinical site, and, at the discretion of the Investigator, their Azstarys® dose may be adjusted before the next scheduled visit. Unscheduled visits between visits are allowed as needed, at the discretion of the Investigator.

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

Treatment Phase, although the dose may be changed at any time by the Investigator based on tolerability and response.

8.3. Treatment in the Treatment Phase

All subjects will be administered one unblinded Azstarys® capsule once daily in the Treatment Phase. The starting dose of Azstarys® in the Treatment Phase will be the same as the optimized dose of Azstarys® at the end of the Dose Optimization Phase, either 13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day, although, at the Investigator' discretion, based on individual tolerability and dose response, the daily dose may be changed at any time to any of the allowed dose levels (13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day).

8.3.1. Method of Oral 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 1-2 tablespoons of applesauce. See Appendix A for detailed instructions of the oral administration of study drug. Any of the methods of administration may be used on any day of the study.

Study drug will be taken orally in the morning at home or, at the visit days, may be taken at the study site:

- On each day at home (on study days with no scheduled visits to the study site) during the Dose Optimization Phase and the Treatment Phase, the assigned study drug will be taken under the supervision of the subject's parent/legal guardian 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/legal guardian 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 study site staff. However, on visits at which PK samples will be collected (Visit 6 and/or Visit 7), subjects from whom PK samples will be collected will need to come to the site on the morning of the scheduled visit, and they will receive study drug at the study site after the pre-dose PK sample is collected. It is important that these subjects are notified not to take any study drug at home on the day of Visit 6 and/or Visit 7. An attempt will be made by study site staff to contact the parent/caregiver before Visit 6 and/or Visit 7 to remind them that subject should come to the visit without taking the study drug because it will be administered by study staff.

8.4. Treatment Assignment

Dose Optimization Phase (All Subjects): All eligible subjects will start on a dose of 13.1 mg/2.6 mg per day open-label Azstarys® and the dose will be titrated to either 13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day based on tolerability and best individual dose-response in the opinion of the Investigator.

Treatment Phase (all subjects): All subjects who completed the Dose Optimization Phase will be enrolled at Visit 5 (start of the Treatment Phase) for treatment with the optimized dose of Azstarys® capsules. During the Treatment Phase, at the Investigator' discretion, based on individual tolerability and dose response, the daily dose may be changed at any time to any of the allowed dose levels (13.1 mg/2.6 mg, 26.1/5.2 mg, or 39.2 mg/7.8 mg per day).

8.5. Blinding

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

8.6. Compliance

Drug accountability and compliance will be evaluated at each visit in the Dose Optimization Phase and the Treatment Phase and will be based on the number of dispensed and returned capsules for each subject. For this purpose, subjects will be asked to bring their unused medication to the clinical site. All study drug will be recorded by each site's pharmacy staff member or Investigator-delegated employee. A record of the study drug accountability will be prepared and kept by each study site.

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.

8.7. Study Early Stopping Rules

The study will be stopped early for any of the following reasons:

An interim analysis of the safety data (including weight, height, and CSHQ) will be conducted after approximately all subjects remaining in the study have completed approximately 180 days (Visit 11) in the Treatment Phase. After completion of the interim analysis, the study may be stopped early for any of the following stopping rules:

a. A clinically significant growth reduction in >40% of subjects. A clinically significant growth reduction is defined by meeting both criteria as follows:

1) A decrease in weight or height z-score versus baseline crossing two percentile lines on a growth chart showing the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. This criterion is based on the recommendation for monitoring stimulant-treated subjects in the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD (Pliszka 2007).

2) For those subjects crossing two percentile lines in weight or height z-score (#1 above), subjects with a decrease in height or weight z-score below the 50th percentile on the growth chart. This criterion excludes overweight subjects at baseline who progress towards a normal weight during treatment as this is not considered a safety risk.

b. An increase in systolic blood pressure >20 mmHg above the 95th percentile for age and gender according to the 2017 AAP guidelines (Flynn 2017) after 180 days of treatment (Visit 11) in >25% of subjects.

c. Subjects experienced AEs, laboratory parameters, electrocardiograms, or suicidal ideation, considering type, incidence and severity, such that further treatment is not in the best interest of the study participants.

The interim safety evaluation for stopping the study early will be judged by the Principal Investigator in collaboration with the Medical Monitor and Sponsor. Treatment in the current study will continue as planned while the interim analysis is conducted. If the decision is made to stop the study, all subjects remaining in the study will undergo the EOT Visit (with safety evaluations including fasting safety labs and ECGs) and a Follow-up Phone Call.

9. STUDY PROCEDURES

For New Subjects, the study will include a Screening Phase, a Dose Optimization Phase, a Treatment Phase, and a Follow-up Phone Call.

Subjects rolled over from Study KP415.P01 will not have a Screening Visit. Roll-over Subjects will enter Study KP415.P02 at the same visit as Visit 6 of Study KP415.P01. This visit will be counted as Visit 2 of Study KP415.P02 (see Section 9.2). Following the enrollment procedures, Roll-over Subjects will proceed with the Dose Optimization Phase (see Section 9.3), Treatment Phase, and Follow-up Phone Call.

For instructions on procedures to follow if a subject is unable to attend a visit due to COVID-19 restrictions, see Section 9.7.

The Schedules of Events (SOE) representing the required testing procedures to be performed are included in Section 1. Following is a list of these procedures and assessments:

9.1. Screening Procedures for New Subjects

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

The following procedures will be performed at the Screening Visit:

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

2. Perform the ADHD-Rating Scale ADHD-RS-IV assessment. 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.

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

4. Perform the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).

5. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.

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

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

8. Record medical history including chronic conditions, relevant surgical procedures (with start date), and medications.

9. Record concomitant medications/therapies, including treatments and therapies for ADHD.

10. A complete physical examination.

11. Body weight and height.

12. 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.

13. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) assessment, "Children's Baseline/Screening" version. 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 electrocardiogram (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. 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, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for MPH. All ADHD medications must be washed out per New Subject Inclusion Criterion #7.

After New Subjects complete the Screening procedures and are considered eligible to take part in the clinical study, they will be instructed to return to the clinical site at Visit 2 to begin the Dose Optimization Phase. In addition, if applicable, they will be given the date on which to begin wash out of any ADHD and other medications prior to Visit 2.

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

Rescreening: New Subjects who require extension of the screening window and remain eligible for the study may be rescreened upon written approval by the Medical Monitor. Items to be rescreened will be determined on a case-by-case basis. Subjects who screen fail will not be rescreened. New Subjects who received any dose of study drug and are terminated early or are not eligible to continue in the Treatment Phase, are not eligible to participate later in the study (and will not be rescreened).

9.2. Start-of-Study/Enrollment for Roll-over Subjects (Visit 6/Visit 2)

Subjects of Cohort 1 (subjects ages 4 and 5 years) in Study KP415.P01 who qualify, have the option to participate in Study KP415.P02 after they have received their last dose of Azstarys® in Study KP415.P01 (at Visit 6 in Study KP415.P01). These subjects are designated "Roll-over Subjects" in the current study.

Subject-specific data (e.g., ADHD diagnosis, demographics and medical history) and endpoint data (for example, pre-dose baselines for safety and efficacy evaluations) for Roll-over Subjects will be carried over from Study KP415.P01 to Study KP415.P02. Values for safety and efficacy needed at the start of the Treatment Phase (for example, sleep scale and ADHD-RS-IV assessments) will be assessed at Visit 6 in Study KP415.P01, and this visit is therefore the same as Visit 2 in the current study.

Roll-over Subjects will complete the enrollment procedures listed below during Visit 6/Visit 2. These enrollment procedures are to obtain HIPAA authorization and Parental Permission for participation in the current study, or are administrative in nature, to assure that demographics and medical history are carried over from Study KP415.P01 and are recorded for the current study.

The following enrollment procedures will be performed prior to conducting any study-related activities of Study KP415.P02. Additional procedures common to all subjects beginning at Visit 2 are listed in Section 9.3.

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

   Note: Parental written consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the parent/legal guardian.

2. Data for subject demographics (date of birth, sex, race, and ethnicity) and subject medical history will be rolled over from the previous study.

3. A complete physical examination.

4. 12-lead electrocardiogram (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.

5. Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained under fasted or non-fasted conditions (fasted/non-fasted state will be recorded).

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

9.3. Dose Optimization Phase (All Subjects)

All subjects who meet the inclusion/exclusion criteria during Screening of Study KP415.P02 or Visit 6 of Study KP415.P01 will enter into the Dose Optimization Phase. New Subjects will have been instructed to return to the clinical site at Visit 2 (first visit of the Dose Optimization Phase). In addition, New Subjects will have been instructed with the date on which to begin washout of ADHD and other medications prior to Visit 2. Visits 3, 4, and 5, approximately 7 days apart, are the subsequent visits in the Dose Optimization Phase. All subjects will undergo the procedures outlined in Section 9.3.2 and Section 9.3.3 during these visits.

See Section 9.4 for instructions during at-home (between visits) periods.

9.3.1. Dose Optimization Phase-Visit 2 (All Subjects)

The following procedures will be performed at Visit 2 of Study KP415.P02 (Visit 6 of Study KP415.P01 for Roll-over Subjects):

1. Review of inclusion/exclusion criteria to determine whether subjects continue to meet study eligibility. Note that the list of inclusion/exclusion criteria to be reviewed are different for Roll-over Subjects as compared to New Subjects because Roll-over Subjects already satisfied inclusion/exclusion criteria in Study KP415.P01.

2. Update medical history for New Subject only.

3. Body weight and height.

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-IV assessment. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.

6. Perform the clinician-administered Clinical Global Impressions–Severity (CGI-S) scale assessment. New Subjects must have a CGI-S score of ≥4 (Moderately Ill) for further study participation. Roll-over Subjects do not need to meet a score requirement.

7. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.

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

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

10. New 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 Phase (Visit 17) 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 Phase (Visit 17) or ET Visit. Before or on the day during the screening period that subjects will need to start the washout of their ADHD medications (for example, 5 days before Visit 2 for stimulants), study site staff will contact the subject's parent/guardian by phone to remind them of the washout ("Washout Phone Call"). Other prohibited medications and the windows of prohibition are listed in the protocol.

11. Provide subject with open-label Azstarys® for daily oral administration at home until the next visit. This will include capsules of 13.1 mg/2.6 mg Azstarys® as the starting dose to begin the Dose Optimization Phase. Dose adjustments, if needed, will be performed at approximately weekly intervals between visits of the Dose Optimization Phase. Subjects will be instructed to return unused study drug at the next visit.

12. Instruct the subjects how to take study drug: Study drug will be taken orally within 20 minutes after consuming breakfast, at approximately the same time in the morning of each day. See Appendix A for detailed instructions. Any of the methods of administration may be used on any day of the study.

9.3.2. Dose Optimization Phase-Visits 3 and 4 (All Subjects)

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

1. Subjects will take the assigned study drug either at home under the supervision of the subject's parent/legal guardian 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.

The assigned study drug will be taken orally within 20 minutes after consuming breakfast, at approximately the same time in the morning of each day. See Appendix A for detailed instructions of the oral administration of study drug.

2. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance. Remaining/returned capsules of study drug will be retained by study site staff.

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

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-IV assessment. 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 Children's Sleep Habits Questionnaire (CSHQ).

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

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. Azstarys® dosing and 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 of titration.

14. Provide subject with open-label Azstarys® for daily oral administration at home until the next visit. Subjects will be instructed to return unused study drug at the next visit.

9.3.3. End of Dose Optimization Phase-Visit 5 (All Subjects)

On the day of Visit 5, the last day of the Dose Optimization Phase, subjects will be administered the last dose of study drug in the Dose Optimization Phase.

The following procedures will be performed at Visit 5:

1. See dosing/treatment instructions in Section 9.3.2, Item 1.

2. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance. Remaining/returned capsules of study drug will be retained by study site staff.

3. Review of inclusion/exclusion criteria to determine whether subject continues to meet study eligibility.
   In addition, the Investigator will evaluate the eligibility criteria for continuation into the Treatment Phase. The Treatment Phase Eligibility Criteria are as follows:

   1. A reduction of ≥30% in ADHD-RS-IV from baseline during the Dose Optimization Phase. The baseline is the ADHD-RD-IV score before the first dose of study drug (for Roll-over Subjects, from Study KP415.P01).
   2. A CGI-I score of 1 or 2 points ("Very Much Improved" or "Much Improved") at the end of the Dose Optimization Phase. The improvement will be judged from a baseline before the first dose of study drug (for Roll-over Subjects, from Study KP415.P01).
   3. Acceptable tolerability of the optimized Azstarys® dose experienced during the Dose Optimization Phase

   Subjects who, at Visit 5, are found not to be eligible for continuation in the Treatment Phase will also receive a Follow-up Phone Call (Section 9.8) during the interval of 5 to 9 days after Visit 5. These subjects are not considered early terminators.

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-IV assessment. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.

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

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

9. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.

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

11. Review of concomitant medications, treatment and/or therapies, with specific awareness of the use of prohibited medications/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. Establish the optimized daily Azstarys® dose for subjects eligible to continue in the Treatment Phase and provide subjects with study drug for daily oral administration at home until the next visit. The optimized dose for All Subjects is the optimized dose level established at the end of the Dose Optimization Phase. Subjects will be instructed to return unused study drug at the next visit.

14. Dispense dosing diary to subjects who will participate in PK sampling.

9.4. Treatment During At-home Periods (All Subjects)

While at home during the Dose Optimization Phase and Treatment Phase, subjects will take unblinded study drug as follows: On each day at home (between visits), the assigned study drug will be taken orally in the morning within 20 minutes after consuming breakfast under the supervision of the subject's parent or caregiver (see exception below for PK subjects on PK Visits). Study drug should be taken at approximately the same time in the morning of each day. See Appendix A for detailed instructions of the oral administration of study drug.

Treatment and Dosing Diary for PK Subjects on PK Visits:

1. On visits at which PK samples will be collected (Visit 6 and/or Visit 7), subjects from whom PK samples will be collected (PK subjects) will withhold study drug and will need to come to the site on the morning of the scheduled visit. They will receive study drug at the study site under the supervision of study staff after the pre-dose PK sample is collected.

2. **Dosing Diary**: A Dosing Diary will be collected for subjects for whom PK samples will be collected during Visit 6 and/or Visit 7. The Diary will be completed on each day while at home during the 7 days before Visit 6 and/or Visit 7. Approximately 1 week before each PK visit, site staff will contact the subject's parent/caregiver by phone to remind them to complete the dosing diary. The subject's parent or caregiver will complete the daily diary with the dates and times of oral administration of study drug to the subject. The collection of the dosing time, the dose level administered, and the mode of administration (whole capsule or in applesauce) on each study day is important for analysis of the Population PK. A diary template will be provided by study staff at Visits 5 and/or 6.

Subject's parent/guardian will contact the study site for the reporting of AEs during the dosing periods at home. Subjects will need to adhere to all medication restrictions.

9.5. Treatment Phase (All Subjects)

Subjects able to tolerate at least 13.1 mg/2.6 mg per day of Azstarys® and with an adequate dose-response will be enrolled into the Treatment Phase. Subjects will continue to the Treatment Phase immediately after completing the Dose Optimization Phase.

All subjects eligible to participate in the Treatment Phase will receive non-blinded oral capsules of Azstarys® (one capsule). The dose level is an optimized dose of 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg determined at the end of the Dose Optimization Phase. Based on individual tolerability and dose-response during the Treatment Phase, at the discretion of the Investigator, the dose may be changed (increased or decreased, to one of the 3 dose levels of 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg capsules). Subjects will take study drug (one capsule/day, orally) in the morning at home under supervision of their parent or legal guardian. The final dose of study drug will be administered on the last day of the Treatment Phase (Day 360 ±20 days; Visit 17). If the study is stopped early, based on the stopping rules, the last day of the Treatment Phase (Visit 17) may occur earlier than Day 360 for some or all subjects.

Further details on dosing methods are in Section 8.3.1 and Appendix A.

9.5.1. Treatment Phase Visits 6 through Visit 16

The first dose of study drug in the Treatment Phase will be taken at home on the day after Visit 5 and the last dose of study drug in the Treatment Phase will be taken at the study site during Visit 17.

For subjects participating in PK visits (**Visit 6 and/or Visit 7**), approximately 1 week before each PK visit, site staff will contact the subject's parent/caregiver by phone to remind them to complete the dosing diary

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

1. See dosing/treatment instructions in Section 9.3.2, Item 1.

2. For PK subjects at PK visits (**Visit 6 and/or Visit 7**), study staff will collect the diary of the previous week and will review the diary entries for completeness with the subject's parent or caregiver.

3. For PK subjects at PK visits (**Visit 6 and/or Visit 7**), blood samples (3 mL each) for PK assessments will be collected at specified times relative to the time of oral administration of open-label study drug. In total (combined from Visits 6 and 7), **3** PK samples are needed:
   Sample **1**:
   - Pre-dose sample: within 30 minutes pre-dose

   Samples **2** and **3**, taken at two of the following times. A randomization scheme will be used to determine the 2 post-dosing times for the collection of the PK samples in each PK subject:
   - 15-minute sample: 15-40 minutes post-dose
   - 2-hour-sample: 1.5– 2.5 hours post-dose
   - 4-hour sample: 4– 6 hours post-dose

   The 3 blood samples may be collected at either Visit 6 or Visit 7, or may be divided between visits (2 samples at Visit 6 and 1 sample at Visit 7, or vice-versa).

4. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance. Remaining capsules of study drug will need to be returned to study site staff.

5. A complete physical examination. **(Visit 11 only).**

6. 12-lead electrocardiogram (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. **(Visit 11 only).**

7. Clinical laboratory tests (chemistry, hematology, and urinalysis) under fasted or non-fasted conditions (the fasted/non-fasted state will be recorded) **(Visit 11 only).** 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.

8. Body weight and height.

9. 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.

10. Perform the ADHD-RS-IV assessment. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.

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

12. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.

13. Perform the Columbia Suicide Severity Rating Scale (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 based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

14. Review of concomitant medications, treatment and/or therapies, with specific awareness of the use of prohibited medications/therapies.

15. 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.

16. Provide subject with study drug (optimized dose of Azstarys®) for daily oral administration at home until the next visit. Subjects will be instructed to return unused study drug at the next visit.

17. Dispense Dosing Diary (**Visit 6 only**) to subjects who will participate in PK sampling at Visit 7.

For instructions on procedures to follow if a subject is unable to attend a visit due to COVID-19 restrictions, see Section 9.7.

9.5.2. End-of-Treatment Phase (Visit 17) or Early Termination Visit

Visit 17 is the End-of-Treatment (EOT) Visit. This is the last day of the Treatment Phase. The following procedures will be performed at Visit 17 after administration of the last dose of study drug or at the ET Visit.

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 EOS for these subjects.

1. Study drug will be taken orally in the morning at home under the supervision of parent/guardian/caregiver, or may be taken at the study site under the supervision of study site staff. May not be applicable for ET Visit.

2. Record the number of returned and administered capsules of unblinded study drug for drug accountability and compliance. Remaining capsules of study drug will need to be returned to study site staff.

3. A complete physical examination.

4. 12-lead electrocardiogram (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.

5. Clinical laboratory tests (chemistry, hematology, and urinalysis) obtained under fasted or non-fasted conditions (the fasted/non-fasted state will be recorded). Subjects with a greater than trace proteinuria will be asked to provide the study site with 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.

6. Body weight and height.

7. 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.

8. Perform the ADHD-RS-IV assessment. Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver present.

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

10. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.

11. Perform the Columbia Suicide Severity Rating Scale (C-SSRS), "Children's Since Last Visit" version. The C-SSRS questionnaire will be filled in by the parent/guardian/caregiver. For subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

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

13. 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.

9.6. Unscheduled Visits

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

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

- 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 Azstarys® dose may be adjusted before the next scheduled visit.

- If a subject is not able to attend the site for a scheduled visit due to COVID-19 restrictions, see Section 9.7 for procedures.

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 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, each at the discretion of the Investigator:

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).
    e. Perform the Children's Sleep Habits Questionnaire (CSHQ) assessment.
2. If 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-IV and/or CGI-S scale assessment, and/or, during the Dose Optimization Phase, a 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, or 39.2 mg/7.8 mg Azstarys® 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.

9.7. Visit and Assessment Changes Due to COVID-19

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 safety and efficacy data collected out of window

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

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. Assessments that do not require the subject's presence at the site (e.g., AEs, C-SSRS, ADHD-RS-IV, 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).

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."

9.8. Follow-up Phone Call (End of Study)

Subjects who complete the Treatment Phase will receive a Follow-up Phone Call during the interval of 5 to 9 days after the administration of the last dose of study drug. Subjects who, at Visit 5, are found to be ineligible for continuation in the Treatment Phase will also receive a Follow-up Phone Call during the interval of 5 to 9 days after Visit 5. These subjects are not considered early terminators. The Follow-up Phone Call is the EOS for all subjects except those who terminated early.

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 EOS for these subjects.

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

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

2. Assessment and review of AEs.

9.9. End of Study (EOS)

The End of Study (EOS) is either the Follow-up Phone Call for subjects who complete the Treatment Phase, or the ET Visit for subjects who withdraw early from the study.

10. CONCOMITANT MEDICATIONS AND RESTRICTIONS

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

10.1. Medication Restrictions for Roll-over Subjects

Subjects who roll over at Visit 6 of Study KP415.P01 (i.e., Visit 2 in the current study) will need to continue abstaining from all prohibited medications in this trial, as follows:

- Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dexmethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall®, and prescription Azstarys®.

- Non-stimulant ADHD medications are prohibited from the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit. These include: atomoxetine, guanfacine, and clonidine and viloxazine.

- The following medications are prohibited from the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit:

    - Tricyclic antidepressants, bupropion, norepinephrine reuptake inhibitors (NRIs) and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and paroxetine.
    - Monoamine oxidase inhibitors (MAOIs)
    - Mood stabilizers (e.g., lithium, valproate, quetiapine)
    - Antipsychotics (e.g., risperidone, olanzapine)
    - Coumarin anticoagulants
    - Anticonvulsants
    - Halogenated anesthetics
    - Phenylbutazone

- Cough and cold medications containing stimulants should be avoided in the week prior to each scheduled visit.

- Sedative hypnotics/sleep enhancers (with the exception of melatonin; see below) are prohibited from the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit.

- Melatonin is allowed in the current trial if subjects have taken it during the Treatment Phase of Study KP415.P01. Otherwise, melatonin is prohibited from the start of Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit.

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

10.2. Medication Restrictions for New Subjects

- Stimulant ADHD medications (with the exception of study drug), including herbal medications, are prohibited from 5 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit. These include: methylphenidate, amphetamine, Ritalin®, Ritalin® SR, Metadate® ER, Concerta®, dextromethylphenidate, Focalin®, dextroamphetamine, Dexedrine®, Adderall® and prescription Azstarys®.

- 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 Phase (Visit 17) or ET Visit. These include: atomoxetine, guanfacine, clonidine and viloxazine.

- The following medications are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit:

    - Monoamine oxidase inhibitors (MAOIs) serotonin-norepinephrine reuptake inhibitors (NRIs) and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine
    - Mood stabilizers (e.g., lithium, valproate, quetiapine)
    - Antipsychotics (e.g., risperidone, olanzapine)
    - Coumarin anticoagulants
    - Anticonvulsants
    - Halogenated anesthetics
    - Phenylbutazone
- Tricyclic antidepressants and bupropion are prohibited from 30 days prior to the start of the Treatment Phase to the end of the Treatment Phase (Visit 17) or ET Visit.

- Sedative hypnotics/sleep enhancers (with the exception of melatonin; see below) are prohibited from 14 days prior to the start of the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit.

- Melatonin is allowed if new subjects have taken it for more than 30 days before Screening and are on a stable dose. Otherwise, melatonin is prohibited from 5 days prior to the Dose Optimization Phase (Visit 2) to the end of the Treatment Phase (Visit 17) or ET Visit.

- Cough and cold medications containing stimulants should be avoided in the week prior to each scheduled visit.

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

11. INVESTIGATIONAL PRODUCT

11.1. Active Pharmaceutical Ingredients

The Azstarys® capsules contain two active pharmaceutical ingredients: d-methylphenidate (dexmethylphenidate; d-MPH) hydrochloride, and 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

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.

Unblinded capsules with 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, and 39.2 mg/7.8 mg Azstarys® will be used in the study. All study drug will be supplied by the Sponsor (or designee). The Sponsor (or designee) will supply sufficient quantities of Azstarys® 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 at the site and, subsequently, in the final study report.

11.2. Packaging and Labeling

The Azstarys® capsules will be packaged and labeled according to the appropriate FDA regulations.

11.2.1. Dose Optimization Phase

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

11.2.2. Treatment Phase

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

11.3. Dispensing and Drug Return Procedures

11.3.1. General Dispensing and Drug Return Procedures

Unblinded bottles of drug supply (Azstarys® capsules) will be dispensed at the indicated visits of the study with enough capsules for treatment until the next visit.

At each visit, a bottle will be dispensed to the subject's parent or guardian with instructions on when and how to administer study drug while at home, under supervision of parent or legal guardian.

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

Subjects will be instructed to report lost study drug to the study site as soon as possible after the loss. Lost drug supply may be replaced with the appropriate new bottle.

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

11.3.2. Dispensing in Dose Optimization Phase (Visits 2, 3, and 4)

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

- **Visit 2:** Subjects will be dispensed a bottle with 10 capsules of 13.1 mg/2.6 mg Azstarys® product (starting dose for Dose Optimization).

- **Visit 3:** Subjects will return to the clinical site after 7 ±3 days for Visit 3 with unused study drug, and will be dispensed a bottle of 10 capsules containing 13.1 mg/2.6 mg capsules (same daily dose as Week 1), 26.1 mg/5.2 mg Azstarys® capsules (dose level increase from Week 1), or 39.2 mg/7.8 mg Azstarys® capsules (dose level increase from Week 1).

- **Visit 4:** Subjects will return to the clinical site after 7 ±3 days for Visit 4 with unused study drug, and will be dispensed a bottle of 10 capsules containing 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg Azstarys®, as appropriate for dose level increase or decrease from the previous visit.

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

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

- **Visit 5:** Subjects will be dispensed an unblinded bottle with 35 capsules of the optimized dose of Azstarys® (either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg capsules). The optimized dose will be determined at the end of the Dose Optimization Phase (Visit 5).

- **Visit 6 to Visit 16:** Subjects will return to the clinical site with unused study drug, and, at Visits 7 through 16, will be dispensed a new bottle with 35 capsules of either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg Azstarys® product. Because the Investigator may increase or decrease the dose of Azstarys® during the Treatment Phase, based on individual tolerability and dose response, the capsule strengths dispensed at each visit from Visit 7 to Visit 16 may be different from the previous visit.

11.3.4. Dispensing at Unscheduled Visits

At unscheduled visits, if needed, the Investigator may decide to change the daily Azstarys® dose. In this case, a new bottle with capsules of either 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, or 39.2 mg/7.8 mg Azstarys® product will be dispensed to the subject, and unused study drug previously dispensed will need to be returned. The same dispensing and drug return procedures will be followed as for scheduled visits.

11.4. Materials Control

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.

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 subjects 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 at the study site in a safe, secure area with limited, controlled access for Schedule II substances in accordance with all local, state, and federal regulations. Investigational products must not be frozen. The Investigator will ensure that adequate precautions are taken, including storage of the study drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

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

11.6. Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject throughout the study will be maintained on an ongoing basis by a member of the study site staff. The number of bottles and/or capsules of study drug dispensed and returned 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

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

For Roll-over Subjects, new medical conditions that occurred during their participation in Study KP415.P01 will be recorded at Visit 6 (P01)/Visit 2 (P02) as medical history for this study. At Visit 2, only New Subjects will be reassessed for medical history.

12.2. Physical Examination

A complete physical examination will be completed at Screening (New Subjects only), after approximately 6 months of treatment in the Treatment Phase (Visit 11), after the last dose of study drug in the Treatment Phase (Visit 17), or at ET (if possible).

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.

12.3. Vital Signs

Vital sign measurements will be obtained after the subject has been seated for 3 minutes. Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. Three (3) blood pressure measurements will be collected 2-5 minutes apart, and the average of the 3 blood pressure measurements will be recorded in the eCRF. At the discretion of the Investigator, in order to ensure accuracy, out-of-range vital signs (except blood pressure) may be repeated once, 2-5 minutes after an abnormal finding.

12.4. Body Weight and Height

Body weight and height will be collected 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.

12.5. 12-Lead Electrocardiogram

A 12-lead ECG will be obtained after the subject has been in a supine position for a minimum of 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded.

The 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.

12.6. Children's Sleep Habits Questionnaire (CSHQ)

Ratings from the modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be collected to assess changes in sleep behavior throughout the study. The CSHQ is a retrospective, 33-item parent questionnaire to examine sleep behavior in small children (Owens 2000). 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). 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 during all visits through the end of the Treatment Phase. For New Subjects, the Visit 2 CSHQ score will be used as baseline; for Roll-over Subjects the CSHQ score from Visit 2 in Study KP415.P01 will be used as baseline.

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

Suicidal ideation will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, Pediatric Version) (Posner 2010). The "Children's Baseline/Screening" version will be used at Screening, and the "Children's Since Last Visit" version will be used at all visits through the Treatment Phase or ET. 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.

12.8. Clinical Laboratory Measurements

Clinical laboratory measurements will be collected before the first dose of study drug (at Screening in the current study for New Subjects, and at Screening in Study KP415.P01 for Roll-over Subjects), at Visit 11, and after the last dose of study drug In the Treatment Phase (Visit 17) or at ET. Clinical laboratory measurements may be repeated at the discretion of the Investigator. Approximately 40 mL of blood will be collected for clinical chemistries and hematology from each subject during the study.

At Screening (Visit 1), Visit 11, Visit 17, ET (if applicable), and Unscheduled Visits (if applicable), blood samples for clinical laboratory measurements will be collected under fasted or non-fasted conditions. The fasted/non-fasted status of blood collections for clinical laboratory measurements will be recorded.

Urinalysis will also be performed by the clinical laboratory from samples taken at Screening (Visit 1), Visit 11, Visit 17, ET (if applicable), and 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 TSH. TSH will be measured at Screening only (New Subjects only) to evaluate the exclusion criterion for uncontrolled thyroid disease.

- Urinalysis:

    - Urinalysis will be completed at Screening (Visit 1), Visit 11, EOT (Visit 17), and ET for, but not limited to, bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and urobilinogen.

    - Unscheduled urine sample: Subjects with a greater than trace proteinuria at any visit (including Screening) at which urinalysis assessments are required will be asked to provide the study site with 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 $U_{P/C}$ 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 (New Subjects only):

    - At Screening, urine samples will be tested for drugs of abuse (amphetamines, methamphetamines, methylphenidate, benzodiazepines, barbiturates, cannabinoids, cocaine, opioids including oxycodone). If the urine test is positive for any of the analytes, the subject will be excluded from study participation, with the exception of the following: Depending on a subject's current ADHD medication at Screening, the urine screen at Screening may test positive for MPH

for treatment of their ADHD. All ADHD medications must be washed out per New Subject Inclusion Criterion #7.

12.9. Treatment-Emergent Adverse Event Assessments (TEAEs)

Adverse events will be assessed and recorded from the first day of study drug administration (after administration of the first dose) through either Follow-up Phone Call or ET. During at-home dosing, the subject's parent/guardian will be instructed to contact the study site for the reporting of AEs. In addition, at each study visit, study staff will interview the parent/guardian regarding AEs during the preceding at-home period. In cases in which the occurrence of an AE is unclear or for safety-related medical questions, the Medical Monitor should be consulted.

13. EFFICACY ASSESSMENTS

13.1. ADHD Diagnosis

For New Subjects at Screening, eligible subjects must meet the inclusion criteria for a primary diagnosis of ADHD by Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) per clinical evaluation. Since Roll-over Subjects from Study KP415.P01 will need to have that study completed, their ADHD diagnosis and diagnosis confirmation will be conducted in Study KP415.P01.

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-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 at the Screening Visit only (in New Subjects).

13.3. ADHD Severity Over Time

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

13.4. ADHD-RS-IV

ADHD-Rating Scale (ADHD-RS): The Preschool Version of ADHD-RS-IV (McGoey 2007) will be used (although there is a Version 5 of the ADHD-RS, the validated preschool version is currently Version IV). The ADHD-RS-IV is an 18-item scale (DuPaul 1998) 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 (New Subjects), the ADHD subtype (combined subtype, impulsive/hyperactive subtype, etc.) will be recorded. For Roll-over Subjects, the ADHD subtype from Study KP415.P01 will be used.

13.5. 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 through 17.

13.6. 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) (Busner and Targum 2007). The CGI-I will be performed at Visits 4 and 5. Since the CGI-I is an assessment of improvement versus the previous visit, there is no CGI-I assessment at Screening or Visit 2 for New Subjects.

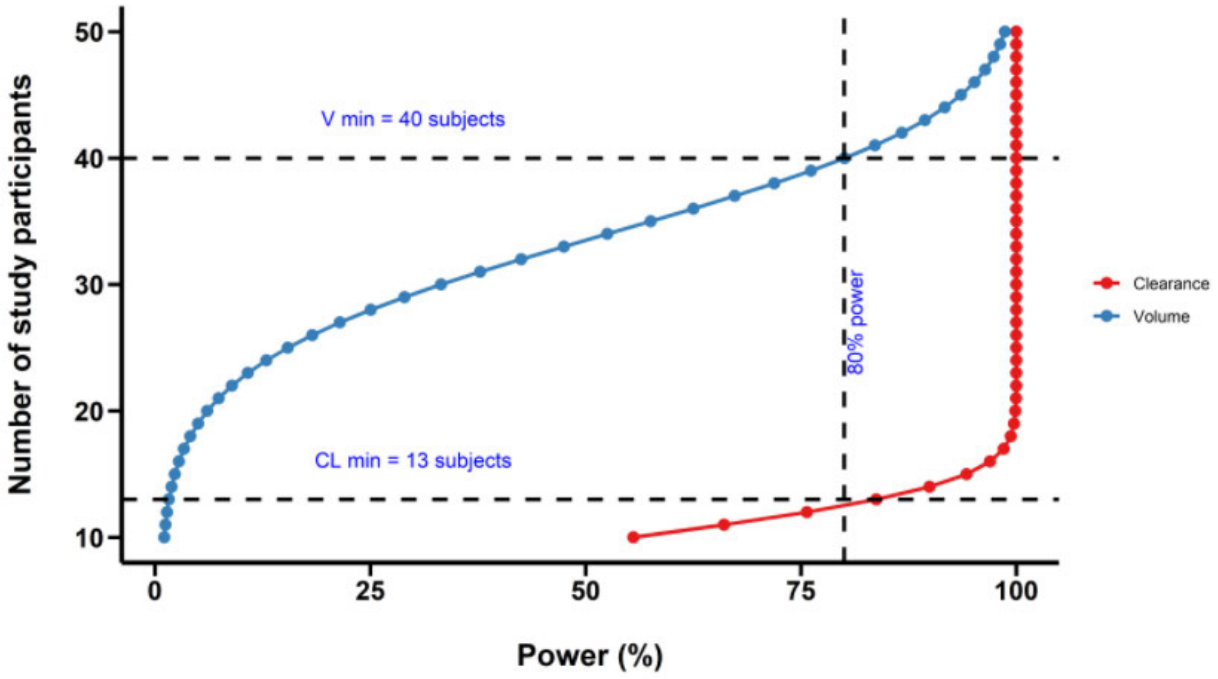
14. PHARMACOKINETIC ASSESSMENTS

Time points for PK samples were selected based on a D-optimal design analysis using concentration-time data following administration of Azstarys in adult and pediatric patients (Studies KP415.104, KP415.105, KP415.107, KP415.110). Briefly, a population PK model, including covariates, was developed from the d-MPH concentration-time data following administration of Azstarys. The population PK model was used in a D-optimal design analysis to compare the impact of number of subjects, number of PK samples, and optimal time of PK sample collection on the precision of estimated clearance (CL/F) and V_z/F. The sampling schedule described below would be expected to permit estimation of CL/F with a percent relative standard error (%RSE) of 10% and estimation of V_z/F with a %RSE of 19%.

14.1. Population PK Sample Size

The sample size for the number of subjects from whom PK samples will be collected for the population PK analysis was determined in accordance with the 2014 draft FDA Guidance for Industry, General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (FDA Guidance 2014). The power to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for d-MPH in this pediatric group with at least 80% power was calculated following the method of Wang et al. (Wang 2012). The power for clearance and volume of distribution for samples sizes from 10 to 50 subjects is shown in Figure 2.

Figure 2: Estimated Power for Clearance and Volume of Distribution of d-MPH for Different Samples Sizes.



Note: Based on an estimated percent relative standard error (%RSE) of 10 for clearance and 19 for volume of distribution of d-MPH after Azstarys® dosing in subjects 4-5 years of age.

Based on the power calculations, a minimum of 40 subjects is required to achieve at least 80% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for d-MPH after Azstarys® administration in this pediatric group. Therefore, complete PK sample sets (pre-dose and 3 post-dose samples) will be collected from at least 40 subjects. In accordance with a male-to female distribution ratio of 3:1 of children diagnosed with ADHD in clinical practice (Barkley 2006; Gaub 1997), full PK sample sets will be collected from approximately 30 males and 10 females.

14.2. Pharmacokinetic Plasma Sample Collection

During Visits 6 and/or 7, a total of three (3) blood samples (3 mL each) for PK analyses will be collected at specified times relative to the time of oral administration of open-label study drug on the day of PK sample collection.

A total of approximately 9 mL blood per subject will be collected for PK analysis. The blood samples may be drawn from an indwelling intravenous catheter or by needle stick, and the use of a local anesthetic cream may be used to make the experience as painless as possible for the child. All blood samples will be drawn by experienced phlebotomy staff. Three (3) blood samples will be drawn as indicated:

Sample **1**:

- Pre-dose sample: within 30 minutes pre-dose

Samples **2** and **3**, taken at two of the following times. A randomization scheme will be used to determine the 2 post-dosing times for the collection of the PK samples in each PK subject:

- 15-minute sample: 15-40 minutes post-dose
- 2-hour-sample: 1.5– 2.5 hours post-dose
- 4-hour sample: 4– 6 hours post-dose

The 3 blood samples may be collected at either Visit 6 or Visit 7, or may be divided between visits (2 samples at Visit 6 and 1 sample at Visit 7, or vice-versa).

Detailed instructions for the collection, processing, storage and shipment of the plasma PK samples will be included in the Laboratory Manual. All retained samples will be destroyed by the analytical laboratory upon the final PK analysis report.

14.3. Bioanalytical Methodology

Quantitation of SDX, d-MPH, and ritalinic acid in plasma samples will be performed using validated bioanalytical methods.

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.
- AE that, in the opinion of the Investigator, indicates it would be in the best interest of the subject to discontinue study treatment.
- Lack of efficacy.
- Protocol violation requiring discontinuation of study treatment.
- Lost to follow-up: a missed visit and two attempts (phone and registered letter) to the reach the subject without success. After these 3 events, 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).
- 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 Phase, 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. At the discretion of the Investigator, ensuring the safety of the subject, ET procedures that were performed on the same day as part of the procedures of the Treatment Phase 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

Subjects who withdraw from the study during the Screening or Dose Optimization Period may be replaced to ensure that the approximate planned number of subjects complete the study (see Section 7.1).

16. STUDY ENDPOINTS

This study is primarily a safety study in the target patient population after approximately 12 months of daily oral doses of Azstarys® capsules. Therefore, the primary endpoint is safety.

16.1. Safety Endpoints

The safety endpoints of this study include the following for all subjects:

- The occurrence of treatment-emergent adverse events (TEAEs) will be assessed starting following the first dose of study drug, and ending with the Follow-up Phone Call or ET Visit.
- Physical examinations will be performed at Screening for New Subjects and at Visit 2 for Roll-over Subjects, before the first dose of study drug, at Visit 11, and at the end of the Treatment Phase (Visit 17) or at ET.
- Clinical laboratory tests will be performed at Screening for New Subjects and at Visit 2 for Roll-over Subjects, before the first dose of study drug, at Visit 11, and at the end of the Treatment Phase (Visit 17) or at ET.
- Electrocardiogram (ECG) parameters will be collected at Screening for New Subjects and at Visit 2 for Roll-over Subjects, before the first dose of study drug, at Visit 11, and at the end of the Treatment Phase (Visit 17) or at ET.
- Vital signs, height, and weight will be collected at each study visit.
- The Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed at Screening (New Subjects) and during all visits in the Dose Optimization Phase and the Treatment Phase for all subjects.
- The modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) scores will be used to assess the sleep behavior during all visits in the Dose Optimization Phase and the Treatment Phase for all subjects. The baseline will be measured before the first dose of study drug (Visit 2).

16.2. Efficacy Endpoints

During the Dose Optimization Phase (all subjects):

- CGI-S will be assessed at each visit (Visits 1-5).
- ADHD-RS-IV (Preschool version) Total Score will be assessed at each visit (Visits 1-5).
- CGI-I will be assessed at Visits 2, 3, 4, and 5 in Roll-over Subjects and at Visits 3, 4, and 5 in New Subjects).
- The baseline CGI-S and ADHD-RS-IV score will be the last value before the first dose of Azstarys® in the current study for New Subjects and from Study KP415.P01 for Roll-over Subjects.

During the Treatment Phase (all subjects):

- ADHD-RS-IV and CGI-S will be assessed at each visit (Visits 5-17), including change in ADHD-RS-IV hyperactivity/impulsivity and inattention subscales.

17. STATISTICAL ANALYSIS AND REPORTING

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

17.1. Sample Size Calculation

No formal sample size calculations were conducted. It was determined that approximately 50 subjects are adequate to satisfy the primary objective of the study, which is to determine the safety and tolerability of Azstarys® in treating children with ADHD for approximately 12 months. Assuming a dropout rate of up to 50% over 12 months, approximately 100 subjects will be enrolled and approximately 50 subjects are expected to complete the 12-month Treatment Phase.

17.2. Analysis Populations

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

- ***Treatment-Phase Safety Population:*** All enrolled subjects in the Treatment Phase who received at least one dose of study medication in the Treatment Phase and had at least one post-dose safety assessment in the Treatment Phase. All baseline and safety data during the Treatment Phase will be analyzed using this population.

- ***Efficacy Population:*** All enrolled subjects who received at least 30 days of study medication in the Treatment Phase, who had a baseline assessment and at least one post-baseline assessment of efficacy parameters (ADHD-RS-IV, CGI-I) and who had no protocol deviations that could affect the efficacy parameters. All efficacy analyses across the Treatment Phase will be analyzed using this population.

- ***Dose-Optimization Safety Population:*** All enrolled subjects in the Dose Optimization Phase who received at least one dose of study medication in the Dose Optimization Phase and had at least one post-dose safety assessment in the Dose Optimization Phase. All data from the Dose Optimization Phase will be analyzed using this population.

- ***Pharmacokinetic (PK) Population***: All subjects who received the daily treatment for at least 5 days before the blood samples for PK were collected, without any major protocol deviations potentially affecting PK, and who provided the plasma concentrations for d-methylphenidate required to calculate the population PK parameters of d-MPH. Demographics and baseline characteristics will be summarized for the PK Population overall and by dose received.

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 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.

The numbers of subjects screened, the number of subjects enrolled in each Phase, the number of Roll-over Subjects who participated in KP415.P01, the number of subjects remaining in the study by month, and the number of subjects in the Treatment-Phase Safety Population, Efficacy Population, Dose-Optimization Safety Population, and Pharmacokinetic Population will be displayed. For subjects who discontinue from the study, the primary reason for discontinuation will be listed and summarized by treatment phase, dose group and overall.

Demographic and baseline disease characteristic data will be summarized descriptively, including sex, age, and race as well as weight, height, body mass index (BMI), and ADHD subtype. The optimized dose of Azstarys® for each subject as well as the average dose received by each subject during the study will be analyzed descriptively. 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 optimized dose group and overall.

17.3.1. Safety Analysis – Treatment Phase

The safety analyses described below will be performed for the safety data collected during the Treatment Phase based on the Treatment Phase Safety Population.

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) for the Treatment Phase are AEs that begin in the time period following the first administration of study medication in the Treatment Phase 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 in the Treatment Phase 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.

Abuse-related AEs will be analyzed in accordance with the 2017 FDA Guidance for Industry, Assessment of Abuse Potential of Drugs. The number and percentage of subjects with Abuse-related AEs will 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. The descriptive statistics will include n, mean, standard deviation (SD), median, 1st and 3rd quartile (Q1, Q3), and range (minimum and maximum). The number and percentage of subjects with clinically notable weight loss (a weight decrease from baseline >5%) will be presented. 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 optimized dose and overall. An 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 during the Treatment Phase. The model will include fixed effects for optimized dose, baseline CSHQ score, visit (Visits 6 to 17), and visit-by-dose 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 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 analysis will be based on pairwise comparisons of Azstarys® optimized dose levels. From the MMRM model, the difference between least square (LS) means of Azstarys ® optimized dose levels will be presented along with the corresponding 95% CIs for each pairwise comparison.

Blood pressure data will be analyzed using the 2017 AAP guidelines based on the average of 3 blood pressure measurements 2-5 minutes apart at each visit. Descriptive statistics will be presented by visit for observed systolic and diastolic blood pressure (in mmHg) and the

corresponding change and percent change from baseline, as well as blood pressure z-scores, and blood pressure percentiles. MMRM ANCOVA models will be fitted using all data as observed. The dependent variable will be change from baseline to the post-baseline assessments of the systolic and diastolic blood pressure measurements for each subject during the Treatment Phase. The model will include fixed effects for optimized dose, baseline blood pressure, visit (Visits 6 to 17), and visit-by-dose 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 safety endpoint.

The analysis will be based on comparisons of Azstarys® optimized dose levels. From the MMRM model, the difference between least square (LS) means of Azstarys ® optimized dose levels will be presented along with the corresponding 95% CIs for each pairwise comparison.

Descriptive statistics will be displayed for baseline, observed values, and changes from baseline in C-SSRS for all post-baseline assessments. An 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 optimized dose, baseline C-SSRS, visit (Visits 6 to 17), and visit-by-dose 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 safety endpoint.

17.3.2. Safety Analyses – Dose Optimization Phase

The safety analyses described below will be performed for the safety data collected during the Dose Optimization Phase based on the Dose Optimization Phase Safety Population. Baseline for the Dose Optimization Phase is the last observed value prior to the first dose of Azstarys® in the Dose Optimization Phase.

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.

TEAEs for the Dose Optimization Phase are AEs that begin in the time period following the first administration of study medication in the Dose Optimization Phase until the first dose of study medication in the Treatment Phase or existing AEs that worsen in that time period. 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.

17.3.3. Efficacy Analyses – Treatment Phase

The efficacy analyses described below will be performed for the efficacy data collected during the Treatment Phase based on the Efficacy Population. The baseline for efficacy endpoints will be the last value before the first administration of study drug. For Roll-over Subjects, the baseline from Study KP415.P01 will be used.

Descriptive statistics will be presented for baseline, all post baseline measurements, and changes from baseline to all post-baseline measurements of ADHD Rating Scale-IV (ADHD-RS-IV) total score by optimized dose group and overall.

For the primary endpoint of change from baseline in ADHD Rating Scale (ADHD-RS-IV) total score, a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fitted using all data as observed for the Treatment Phase. The dependent variable will be change from baseline in ADHD Rating Scale-IV total score for all post-baseline assessments for each subject. The model will include fixed effects for optimized dose, baseline ADHD-RS-IV total score, visit (Visits 6 to 17), and visit-by-dose 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 safety endpoint analysis.

The primary efficacy analysis will be based on comparisons of Azstarys® optimized dose levels. From the MMRM model, the difference between least square (LS) means of Azstarys® optimized dose levels will be presented along with the corresponding 95% CIs for each pairwise comparison.

Descriptive statistics will be presented for baseline, all post baseline measurements, and changes from baseline to all post-baseline measurements of CGI-S. An MMRM ANCOVA model will be fitted using all data as observed during the Treatment Phase. The dependent variable will be change from baseline in CGI-S post-baseline assessments for each subject. The model will include fixed effects for optimized dose, baseline CGI-S, visit (Visits 6 to 17), and visit-by-dose 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 safety endpoint analysis. From the MMRM model, the pairwise differences between LS means of Azstarys® optimized dose levels will be presented along with the corresponding 95% CI for each pairwise comparison.

Descriptive statistics will be presented for baseline, all post baseline measurements during the Treatment Phase (Visits 6 to 17), and changes from baseline to all post-baseline measurements during the Treatment Phase of ADHD-RS-IV for hyperactivity/impulsivity and ADHD-RS-IV for inattention by optimized dose group, and overall.

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

17.3.4. Efficacy Analyses – Dose Optimization Phase

The ADHS-RS-IV, CGI-S, and CGI-I will be analyzed descriptively for the Dose Optimization Phase and discussed in detail in the SAP.

17.3.5. Pharmacokinetic Analyses

Detailed descriptions of the PK analyses will be provided in the pharmacokinetic analysis plan (PKAP).

17.3.6. Interim Analysis

An interim analysis of the safety data will be conducted once all of the subjects remaining in the study complete their Visit 11 assessments to determine whether the study should be stopped. The interim analysis will primarily focus on the safety assessments (primary endpoints), including changes in weight, height, and sleep behavior (CSHQ), during the first 6 months of treatment in the Treatment Phase. The safety data will be analyzed with the same statistical methods as planned for the main analysis after completion of the study to determine if the study early stopping rules have been met. Details of the analyses will be described in the SAP.

17.3.7. Subgroup Analyses

Subgroup analyses will be defined in the SAP.

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 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 or other identified safety information (e.g., Azstarys® Prescribing Information document).

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. AEs 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. AE 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. AE 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

A serious adverse event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

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

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. SAEs 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 (see Section 18.1.2).

All serious events reporting by Sponsor will adhere to 21 CFR 312.32 for IND drugs (7-day or 15-day alerts) and 21 CFR 314.80 for marketed drugs (15-day alerts). Unexpected fatal or life-threatening SAEs considered probably or possibly related to the study drug by the Sponsor will should be reported to the FDA by 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 site shall be referred in a timely basis to other care providers. Records of diagnostic and therapeutic interventions shall be requested in compliance with HIPAA requirements, and those received shall be retained in the subject's file.

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

18.4. Overdosage

For the purposes of this clinical trial, overdosage is defined as the administration of a supratherapeutic dose, a daily dose of study drug larger than the highest dose used in the study, i.e., >39.2 mg/7.8 mg Azstarys® product. 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 methylphenidate 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 electronic data capture (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. All forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed and dated. An eCRF must be completed for each participant 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 Investigators must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to, protocol, eCRFs, AE reports, subject source data (including records of subjects, subject visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, and monitor visit logs.

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

20.3. Access to Source Data/Documents

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

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), 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. INSURANCE

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

24. COMPLETION OF STUDY

The end of the study will be at the time of the last subject, last visit. Alternatively, the study may be stopped early as determined by the early stopping rules (see Section 8.7). The IRB will be notified about the end of the study according to regulatory requirements.

25. STUDY ADMINISTRATIVE INFORMATION

25.1. 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.

26. REFERENCES

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Appendix A: Instructions for Oral Administration of Study Drug

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

1. Swallow capsule whole with a cup of water. The capsule needs to be swallowed whole (without crushing, cutting, 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.