Corium

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Corium Protocol KP415.P01 Statistical Analysis Plan

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Corium LLC

STATISTICAL ANALYSIS PLAN

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

KP415.P01

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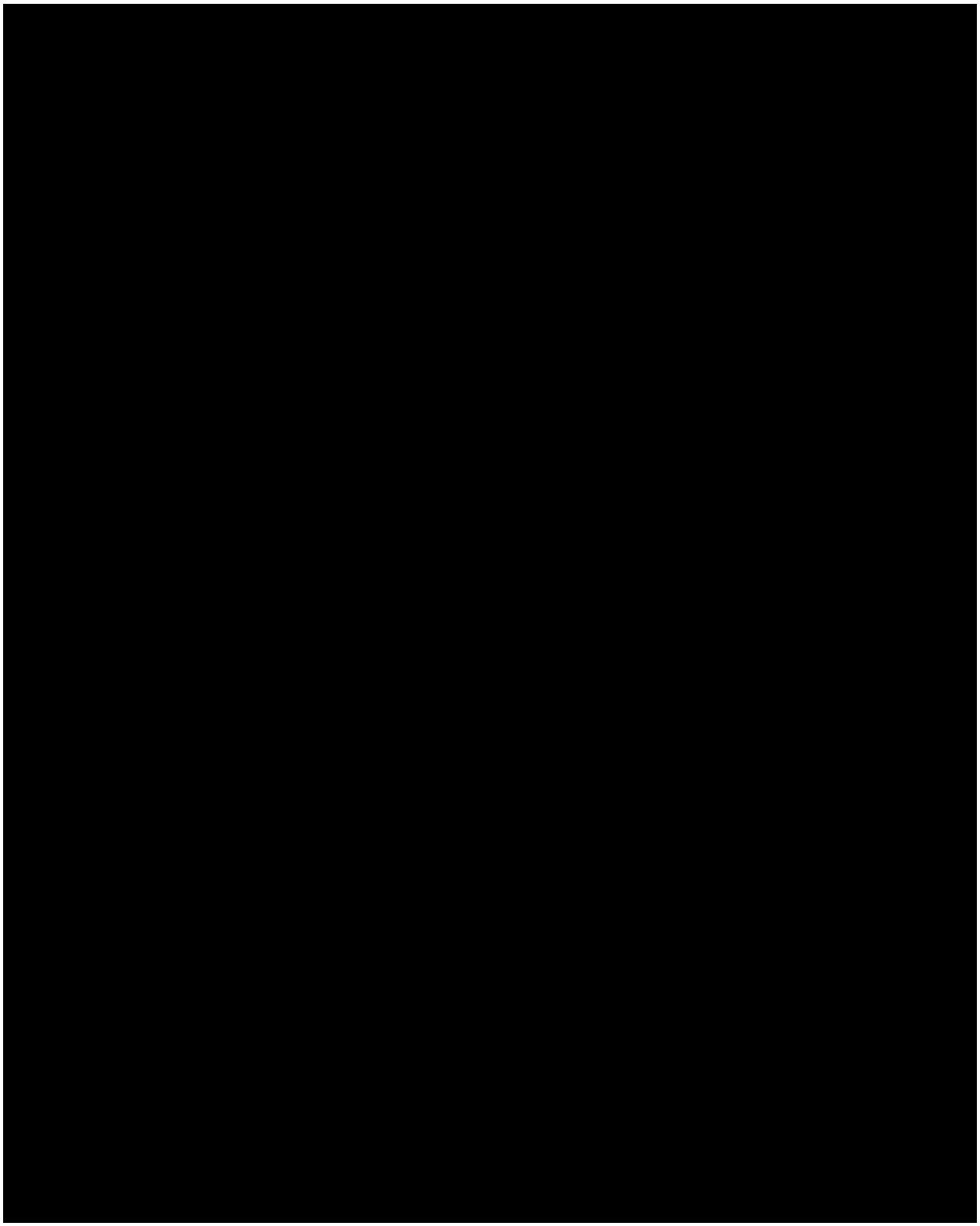
SIGNATURE PAGE



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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	ADHD Rating Scale
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
BSSR	Blinded Sample Size Re-estimation
CGI-I	Clinical Global Impressions–Improvement
CGI-S	Clinical Global Impressions–Severity
CI	Confidence Interval
CRF	Case Report Form
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EDC	Electronic Data Capture
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
MCMC	Markov chain Monte Carlo
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
MPH	Methylphenidate
NCI	National Cancer Institute
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class

1. INTRODUCTION

This is a multicenter, dose-optimized, randomized, double-blind, efficacy and safety study with Azstarys® in children 4 to 12 years of age with attention-deficit/hyperactivity disorder (ADHD). The goal of the study is to evaluate the efficacy and safety and tolerability of Azstarys® in treating subjects with ADHD.

This statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses for Protocol KP415.P01. The statistical analyses described here are based on Version 4.0 of the protocol dated 14 November 2022.

2. STUDY SUMMARY

2.1. Study Objectives

The primary objective is:

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

The secondary objective is:

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

2.2. Study Design

This is a multicenter, dose-optimized, randomized, double-blind, efficacy and safety study with Azstarys (SDX/dMPH) in children 4 to 12 years of age with attention-deficit/hyperactivity disorder (ADHD).

The study consists of 3 phases: up to 30 days in Screening Phase, 28 days in Double-Blind Treatment Phase, and a Follow Up Phone Call 5±2 days after administration of the last dose of the Treatment Phase.

Approximately 230 eligible subjects will be randomized 1:1 to Azstarys or placebo stratified by gender. Randomization will be applied within two age cohorts: Cohort 1 (4 - <5 years and 10 months), Cohort 2 (6 - <12 years and 10 months). For Cohort 1, 130 subjects (65 per arm) will start at 13.1 mg/2.6 mg or matching placebo in order to have approximately 120 completers (60 per group). Subjects in Cohort 1 may be titrated up to doses of 26.1 mg/5.2 mg, 39.2 mg/7.8 mg Azstarys (SDX/dMPH), or matching placebo. For Cohort 2, 100 subjects (50 per arm) will start at 39.2 mg/7.8 mg or matching placebo in order to have approximately 90 completers. Subjects in Cohort 2 may be titrated up or down to doses of 26.1 mg/5.2 mg, 52.3 mg/10.4 mg Azstarys (SDX/dMPH) or matching placebo. The daily dose may be changed or remain the same throughout the Double-Blind Treatment Phase based on a combination of individual tolerability and effect assessed by the Investigator.

Subjects in Cohort 1 who are eligible will have the option to participate and roll-over into a 12-month open-label safety study with Azstarys (SDX/dMPH) (Study KP415.P02) after the Double-Blind Treatment Phase.

2.2.1. Number of Subjects

Up to 230 eligible subjects will be enrolled. Up to 130 subjects (65 per arm) will be enrolled into Cohort 1 (4 - <5 years and 10 months) with the intention to complete with approximately 120 subjects, and up to 100 subjects (50 per arm) will be enrolled into Cohort 2 (6 - <12 years and 10 months) with the intention to complete with approximately 90 subjects. Approximately 20 sites will participate in this study.

2.2.2. Randomization and Blinding Procedures

Randomization will be carried out using an interactive web response system (IWRS), with central randomization following a 1:1 ratio between Azstarys and placebo. Randomization will occur within each age cohort and will be stratified by gender.

Study drug will be blinded during the Treatment Period. Neither the subject, the Investigator, nor the Sponsor will know the subject's treatment assignment. Upon completion of the study and after the database is locked according to the Sponsor (or designee) operating procedures, the randomization codes will be provided to the statistician to unblind the study. The blind for individual subjects can be broken before study unblinding at the request of the Investigator only if a specific emergency treatment would be dictated by knowing the treatment status of a subject.

2.2.3. Sample Size Justification

Sample size calculations were based on data from a previous study (efficacy study with Azstarys® in subjects 6 to 12 years of age). The power and proposed sample size in each age cohort was calculated based on a two-sample t-test for the comparison of change from baseline to 28 days post-baseline in ADHD Rating Scale total score as follows (with no multiplicity correction for the two age cohorts):

- 90% power to detect a 6-point treatment difference with a standard deviation (SD) of 10 points using two-sided α=0.05 in the Younger Cohort (4 - <5 years and 10 months) yields N=60 per treatment group in a 1:1 ratio for Active and Placebo for a total sample size of 120 younger subjects.

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

Combining the two age cohorts for a total of 105 subjects per treatment group yields 99% overall study power to detect a between-treatment difference of 6 points with a SD of 10 points using

two-sided α=0.05 for a total sample size in the study of 210 subjects. Assuming up to 10% of the subjects discontinue prior to completing the 28-day treatment period, up to 230 subjects will be randomized.

A blinded sample size re-estimation will be conducted when 50% of subjects in Cohort 1 (4 - <5 years and 10 months) have completed the Double-Blind Treatment Phase in order to check the between-subject variability assumption. The sample size will be increased if the estimated SD is larger than the assumed 10 points. If the estimated SD is smaller than the assumed 10 points, no adjustments to the sample size will be made and enrollment will continue until the total estimated sample size of 230 subjects is accrued. Details of the blinded sample size re-estimation are provided in Section 3.10.

2.2.4. Efficacy Assessments

2.2.4.1 ADHD Diagnosis

The ADHD-Rating Scale (ADHD-RS): The Preschool Version of ADHD-RS-IV will be used for Cohort 1 (4 - <5 years and 10 months) and ADHD-RS-5 will be used for Cohort 2 (6 - <12 years and 10 months). The ADHD-RS-IV and ADHD-RS-5 each contain 18-item scales based on Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2013) criteria of ADHD which rate the frequency of behaviors on a 4-point scale ranging from 0 (never or rarely) to 3 (very often). The ADHD-RS total score ranges from 0 to 54. The 18 behavior items are further divided into two 9-item subscales: hyperactivity/impulsivity and inattention. The ADHD-RS-5 also contains items related to the severity of the 18 behaviors that are rated from 0 (no problem) to 3 (severe problem). Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver at each visit. ADHD-RS scores should be collected using an ePRO device; for instances when the ePRO device is not available, ADHD-RS scores may be collected on paper CRFs.

The ADHD Presentation (Predominantly Inattentive, Hyperactive-Impulsive, or Combined) will be collected for each subject at the Screening Visit only.

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

The MINI Kid will be used to confirm the diagnosis of ADHD and identify comorbid psychiatric conditions at the Screening Visit only. MINI Kid data will be captured on paper CRFs.

2.2.4.3 Clinical Global Impressions–Severity (CGI-S)

The CGI-S is a clinician-rated scale that evaluates the severity of psychopathology (ADHD symptoms in the study) on a scale from 1 (not at all ill) to 7 (among the most severely ill). Refer to Table 2 for details on the scheduled collection time points. The CGI-S rating will be collected using an ePRO device.

2.2.4.4 Clinical Global Impressions–Improvement (CGI-I)

The CGI-I is a clinician-rated scale that evaluates the improvement of psychopathology (ADHD

symptoms in the study) on a scale from 1 (very much improved) to 7 (very much worse). The CGI-I will be performed in accordance with Table 2: Schedule of Events. Since the CGI-I is an assessment of improvement versus baseline, there will be no CGI-I assessment at baseline (Visit 2). The CGI-I rating will be collected using an ePRO device.

2.2.5. Safety Assessments

Safety assessments include adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, electrocardiogram (ECG), Children's Sleep Habits Questionnaire (CSHQ) and Columbia-Suicide Severity Rating Scale (C-SSRS). These assessments will be conducted according to Table 2: Schedule of Events.

2.2.5.1 Adverse Events

All AEs will be collected from the administration of the first dose of study drug until either the Follow-Up Phone Call or Early Termination visit. SAE assessments are to be performed up to at least 30 days after last dose for events considered definitely, probably, or possibly related to study drug. All AEs, including SAEs, will be followed to resolution when possible.

2.2.5.2 Clinical Laboratory Measures

Clinical laboratory measures will include those listed in Table 1. Refer to Table 2 for details on the scheduled collection time points.

Table 1: Protocol-Required Clinical Laboratory Evaluations

Laboratory Assessments	Parameters
Hematology	Red Blood Cell Count, White Blood Cell Count With Differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), Hemoglobin, Hematocrit and Platelets.
Serum Chemistry	Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Albumin, Alkaline Phosphatase, Bicarbonate, Total Bilirubin, Blood Urea Nitrogen, Phosphorus (Inorganic), Calcium, Chloride, Creatine Phosphokinase, Creatinine, Gamma Glutamyl Transferase, Glucose, Lactate Dehydrogenase, Potassium, Sodium, Total Protein, and Thyroid Stimulating Hormone (TSH) at Screening only.
Urinalysis	Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, pH, Protein, and Urobilinogen; Urine Screen at Screening for Drugs of Abuse (Amphetamines, Methamphetamines, Benzodiazepines, Barbiturates, Cannabinoids, Cocaine, Opioids Including Oxycodone) and Methylphenidate; Pregnancy Test.

2.2.5.3 Vital Signs, Body Weight and Height

Vital sign measurements at each visit will include systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and oral temperature (°C). Measurements will be obtained after the subject has been seated for 3 minutes. Blood pressure data will be analyzed using guidelines based on the average of 3 blood pressure measurements at least 2-5

minutes apart. Body weight (kg) and height (cm) will also be measured and collected at each visit.

2.2.5.4 Physical Examinations

A complete physical examination will include assessments of the subject's general appearance, skin, head and neck, musculoskeletal/extremities, heart, lungs, abdomen and a brief examination of the neurological system. Refer to Table 2 for details on the scheduled collection time points.

2.2.5.5 Electrocardiogram (ECG)

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. ECG measurements will include: heart rate (bpm), QT Interval (msec), RR Interval (msec) and ECG evaluation (normal; abnormal, not clinically significant; abnormal, clinically significant). Refer to Table 2 for details on the scheduled collection time points.

2.2.5.6 Children's Sleep Habits Questionnaire (CSHQ)

The modified, abbreviated Children's Sleep Habits Questionnaire (CSHQ) will be used to assess the sleep behavior during the Treatment Phase. The CSHQ is a retrospective, 33-item questionnaire to examine sleep behavior in small children. Items are rated on a 3- point scale of "Usually", "Sometimes" and "Rarely" for occurrences in a number of key sleep domains (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness). Scores will be obtained during a clinician-directed interview with the parent/guardian/caregiver. The total Sleep Disturbance Score is the sum of the frequency ratings of the 33 items. Refer to Table 2 for details on the scheduled collection time points.

2.2.5.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS, Pediatric Version) will be used to assess suicidal ideation. The "Children's Baseline/Screening" version will be assessed at Screening, and the "Children's Since Last Visit" version will be assessed at all other visits. For subjects too young to comprehend the concept of suicidal ideation, the C-SSRS questionnaire will be filled in by the parent/guardian/caregiver. Refer to Table 2 for details on the scheduled collection time points.

Table 2 : Schedule of Events

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

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

ADHD = Attention-Deficit/Hyperactivity Disorder; CGI-S/I = Clinical Global Impressions – Severity/Improvement; CHSQ = Children's Sleep Habits Questionnaire ET = Early Termination; ECG = electrocardiogram; MPH = methylphenidate; see footnotes for other abbreviations.

1. ADHD Diagnosis based on the Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (combined, inattentive, or hyperactive/impulsive presentation) and by the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI Kid).
2. Study inclusion/exclusion criteria will be evaluated at Screening and Visit 2.
3. Medical History: A complete medical history including chronic conditions, relevant surgical procedures (with start date), and history of drug use.
4. Physical Examination: at Screening and at the end of the Treatment Period or ET (if possible).
5. Height will be recorded in centimeters (cm) using a stadiometer with the subject's shoes removed. Height will be recorded at Screening, Visit 2, and at the end of the Treatment Period. Body weight will be measured in kilograms (kg) using a calibrated scale; subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed. Weight will be recorded at every visit.

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

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

3. STATISTICAL METHODS

3.1. General Methods

3.1.1. Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows.

3.1.2. Reporting Numerical Values

All clinical study data will be presented in subject data listings. Relevant descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of non-missing values. If there are missing values, the number missing will be presented, but without a percentage. Unless otherwise specified, all tests will be 2-tailed at a 0.05 level of significance. All confidence intervals (CIs) will be two-sided 95% CIs.

Means, medians, and CIs will be reported to one decimal place more than the data reported on the case report form (CRF) or by the laboratory/vendor up to a maximum of two decimal places. Standard deviations will be reported to one additional decimal place. A maximum of three decimal places will apply to all summary statistics. P-values will be displayed to four decimal places. If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

3.1.3. Baseline Value and Changes from Baseline

The baseline value will be defined as the last non-missing value prior to the administration of the first dose of study drug. If an assessment is obtained on the same day as first dose of study drug and times are not available for both assessment and dosing, it will be assumed that the assessment is prior to dosing. Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each subject (i.e., post-dose – baseline). Percent change from baseline will be calculated by dividing change from baseline by the baseline value given it is not missing or zero, and then multiplying by 100 for each subject (i.e., [change from baseline/baseline] x 100).

3.1.4. Handling of Missing/Incomplete Values

For all baseline and safety endpoints, no substitutions will be made for missing/incomplete data points, except for adverse event and medication dates, as described below. Handling of missing values for the efficacy endpoints is also described below.

3.1.4.1 Adverse Events or Medication Missing Dates

Partial dates for AEs and medications will be imputed for the ease of determining whether adverse events were treatment-emergent and whether medications were concomitant to study drug.

Missing or partial dates for AEs and medications will be handled as follows in the safety

analysis:

Start Date	Missing day: If month and year are equal to the month and year of first dose date, set start date to the first dose date. Otherwise, set the day to the first of the month. Missing month and day: If year is equal to the year of first dose date, set start date to the first dose date. Otherwise, set the month and day to Jan 1. Missing year, month, and day: Set start date to the first dose date.
End Date	Missing day: set end date to the last day of the month. Missing month and day: set to Dec 31. Missing year, month, and day: no imputation

If imputation of a start date (and end date if both were imputed) results in a start date occurring after the end date, the imputed start date will be reset to equal the end date. If an imputed start or end date occurs after the database lock date, the imputed date will be reset to the database lock date. Imputed partial dates will only be used for identifying whether an AE was treatment-emergent or a medication was concomitant. Listings will display the partial dates as recorded on the electronic CRF.

3.1.4.2 Assigning Missing Scores in ADHD-RS

Electronic Patient Reported Outcome (ePRO) data are entered in the Patient Cloud using the device (iPad) provided by Medidata Rave EDC. Paper PRO eCRFs are available only in the rare event the device is not working.

Scores for the following items will be set to missing for subjects who indicated their absence from school at the time of the assessment.

- Completing or returning homework
- Performing academically in school
- Controlling behavior in school

3.1.4.2.1 Missing Items in ADHD-RS

Missing items for the ADHD-RS scales will be handled as follows:

1. If more than 3 items have missing data, the total score will be set to missing. If the total score is missing then both subscales (Inattention and Hyperactivity/Impulsivity) will be set to missing.

2. If 3 items or fewer have missing or invalid data, the values for the missing items will be imputed using the mean of the non-missing items rounded to the nearest integer for the purpose of calculating the total score and subscale scores.

For the primary efficacy analysis, the change from baseline in ADHD Rating Score (ADHD-RS) total score will be analyzed using a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA) model in which the missing data are handled implicitly under the assumption of Missing-At-Random (MAR).

3.1.4.2.2 Multiple Imputation Method

As a sensitivity analysis for the primary efficacy analysis, missing ADHD-RS total scores data will be imputed as follows (refer to Section 6 for the sample SAS code for MI):

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

2. In step 2 of the analysis, each MI repetition will be analyzed separately to test the equality of the change from baseline in ADHD-RS total score means for Azstarys® and placebo at Visit 6.

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

3.1.5. Visit Windows

Visit windows will be used to determine analysis visits for efficacy and safety endpoints. If a subject has multiple assessments (including unscheduled visits) within a visit window, the value closest to the target day for that visit will be selected for analysis. If more than 1 assessment is equidistant to the target day, the latest value will be selected. Any additional collected values that are not used in the analysis will be included in listings.

Analysis Visit	Relative Target Study Day	Study Days
Baseline	0	See Section 3.1.3
Visit 3	7	2 - 10
Visit 4	14	11 - 17
Visit 5	21	18 - 24
Visit 6	28	≥25

3.1.6. Standard Calculations

Durations associated with ADHD Diagnosis and onset will be calculated as follows:

- Time since ADHD Diagnosis (months) = (date of informed consent – date of ADHD diagnosis + 1)/30.4375
- Time since ADHD Symptoms Onset (months) = (date of informed consent – date of ADHD symptoms + 1)/30.4375

Treatment compliance during the treatment period will utilize the following calculation:

Treatment Compliance (%) = 100*(number of capsules dispensed – number of capsules returned) / number of capsules expected to be taken.

Weight and Height Z-scores will be calculated as follows:

z-score = (observed value - mean of the reference population) / standard deviation of the reference population.

The calculation of the weight and height z-scores (and percentiles) is based on a SAS® program from the CDC[1] which utilizes the United States 2000 CDC Growth Charts (ages 2 to <20 years; updated in the year 2000) as the reference population, developed with data from five national health examination surveys (Kuczmarski[2]).

3.2. Analysis Populations and Subgroups

3.2.1. Definition of Analysis Populations

3.2.1.1 Intent to Treat (ITT) Population

The ITT Population will consist of all randomized subjects who received at least one dose of study medication and have a baseline and at least one post-randomization ADHD-RS Total Score. All efficacy analyses will be conducted in the ITT Population.

3.2.1.2 Safety Population

The Safety Population will consist of all randomized subjects who received at least one dose of study medication and who have at least one post-dose safety assessment. Safety endpoints will be analyzed using the Safety Population.

3.2.1.3 Per-Protocol (PP) Population

The PP Population will consist of all randomized subjects who received at least one dose of study medication and have the baseline and at least one post-randomization ADHD-RS Total Score, and did not use prohibited medications deemed to impact efficacy. The PP Population will be used for sensitivity analyses of the primary efficacy endpoint.

3.2.2. Definition of Subgroups

No subgroup analyses are planned for this study.

3.3. Analysis Variables

3.3.1. Efficacy Variables

Efficacy variables will include:

- Change from baseline in ADHD-RS total score
- Change from baseline in ADHD-RS for hyperactivity/impulsivity score
- Change from baseline in ADHD-RS for inattention score
- Change from baseline in CGI-S score
- CGI-I score

3.3.2. Safety Variables

Safety variables will include:

- Incidence of treatment emergent adverse events (TEAEs)
- Incidence of TEAEs leading to treatment discontinuation
- Incidence of serious adverse events (SAEs)
- Change from baseline in clinical laboratory values (hematology, chemistry)
- Incidence of shift from baseline (hematology, chemistry, urinalysis)
- Change from baseline in vital signs (systolic and diastolic blood pressure, pulse, respiratory rate and temperature)
- Change and percent change from baseline in body weight, height, weight and height z-scores, and weight and height percentiles
- Change and percent change from baseline in CSHQ scores
- Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation and/or behavior
- Change from baseline in ECGs

3.4. Subjects Disposition and Evaluability

3.4.1. Subject Disposition

Subject disposition will be summarized for all subjects randomized by treatment group and overall. Disposition will also be summarized separately for each age cohort. The number and percentage of subjects randomized, dosed, included in each analysis population, completing treatment and completing the study will be presented. The number and percentage of those who discontinue treatment and discontinue from the study, along with the reasons for discontinuation will be presented. The number of subjects screened and reasons for screen failure will also be summarized.

A listing of subject disposition will also be presented.

3.4.2. Protocol Deviations

Important protocol deviations will be summarized for all subjects in the ITT population by treatment group and overall, within and across age cohorts.

All protocol deviations will be presented in a subject listing.

3.5. Demographics and Baseline Characteristics

3.5.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized for each of the analysis populations by treatment group, overall and separately for each age cohort. Frequencies and percentages will be presented for sex, race and ethnicity. Subjects of multiple races will be counted under each race once. Descriptive statistics will be presented for age, height, weight, and body mass index at baseline.

All demographics and baseline characteristics will be presented in a subject listing.

3.5.2. ADHD Diagnosis

ADHD diagnosis will be summarized for the ITT and PP Populations by treatment group and overall separately for each age cohort. Descriptive statistics will be provided for time since ADHD diagnosis (in months) and time since onset of ADHD symptoms (in months), if recorded. Frequencies and percentages will be presented for attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder from the MINI Kid diagnostic modules. Refer to Section 3.1.6 for the calculation of the time since ADHD diagnosis/symptoms onset.

All ADHD baseline characteristics will be presented in a subject listing.

3.5.3. Medical History

All relevant medical history will be coded using Medical Dictionary of Regulatory Activities (MedDRA) Version 25.1 and will be classified by system organ class (SOC) and preferred term. Medical History will be summarized for the ITT population by treatment group and overall separately for each age cohort. The number and percentage of subjects having a medical condition by SOC and preferred term will be presented. Each subject will be counted once under each SOC and preferred term within SOC. The summary will be sorted alphabetically by SOC, and within SOC, by decreasing frequency of preferred term for all subjects.

Medical history will be presented in a subject listing.

3.6. Concomitant Medications

3.6.1. Prior and Concomitant Medications

All reported prior and concomitant medications will be coded using the World Health Organization (WHO) Version B3 September 2022.

Concomitant medications are defined as medications that are being taken while on study drug. Concomitant medications will be summarized for the ITT population by treatment group and overall separately for each age cohort. The number and percentage of subjects who took at least one concomitant medication as well as the number and percentage of subjects who took each type of medication will be presented by Anatomic Therapeutic Class (ATC) level 4 term and preferred term. Each subject will be counted once under each ATC level 4 term and preferred term within ATC level 4 term. The summary will be sorted alphabetically by ATC level 4 term,

and within ATC level 4 term, by decreasing frequency of preferred term for all subjects.

All prior and concomitant medications will be presented in a subject listing.

3.7. Study Drug Exposure and Compliance

Study drug exposure and treatment compliance will be summarized for the ITT population by treatment group and overall separately for each age cohort.

3.7.1. Study Drug Exposure

Descriptive statistics will be provided for the total number of doses (capsules) received, total number of missed doses and duration of treatment (days). Number and percentage of subjects at each optimized dose level administered (i.e., 13.1 mg/2.6 mg, 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, and 52.3 mg/10.4 mg) will be presented. Reasons for missed doses will also be summarized.

3.7.2. Treatment Compliance

Treatment compliance (%) will be classified into the following categories: < 80%, 80-100%, >100 to 120%, and > 120%. The number and percentage of subjects within each of these compliance categories will be presented. Refer to Section 3.1.6 for the calculation of the treatment compliance.

3.8. Efficacy Analyses

All efficacy analyses will be performed for the ITT Population by treatment group and overall and separately for each age cohort.

3.8.1. Primary Efficacy Endpoint

3.8.1.1 Change from Baseline in ADHD Rating Scale (ADHD-RS) Total Score

Change from baseline in ADHD-RS total score will be analyzed using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model fitted using all observed data. In cases when ADHD-RS scores were not collected using an ePRO device, but were instead collected on a paper CRF, data from both modalities will be used in the primary analysis. A sensitivity analysis using only ePRO data will also be performed. Refer to Section 6 for the sample SAS code for the model.

The dependent variable will be change from baseline in ADHD-RS (ADHD-RS IV for Cohort 1 and ADHD-RS-V] for Cohort 2) total score for all post-baseline assessments for each subject. The model will include fixed effects for treatment, age cohort, gender (stratification factor for randomization), baseline ADHD-RS total score, analysis visit and analysis visit-by-treatment interaction as well as a random effect for the subject. The mixed model will utilize restricted maximum likelihood estimation with the Kenward-Roger method used to compute the denominator degrees of freedom for tests of fixed effects. The model will assume an unstructured covariance matrix. If the model does not converge under the unstructured covariance matrix when using the SAS PROC MIXED default Newton-Raphson algorithm, other numerical methods such as the Fisher scoring algorithm will be tried.

If the model using the unstructured covariance matrix still fails to converge, the following structures will be executed sequentially until convergence is attained: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order autoregressive, Toeplitz, Compound Symmetry, and first-order autoregressive. If a structured covariance is used, then a robust sandwich estimator will be utilized for estimating the variance of the treatment effect estimate.

The least-squares (LS) mean and 95% CI for the change from baseline in ADHD-RS total score will be extracted from the model for each post-baseline visit and presented by treatment group. The Visit 6 difference between least square (LS) means of Azstarys® and placebo will also be presented along with the corresponding 95% CI and two-sided p-value. Treatment difference statistics will also be presented for the earlier post-baseline visits, but considered descriptive only.

The presentation will also include descriptive statistics of ADHD-RS total score for baseline and post-baseline visits, as well as the corresponding changes from baseline based on observed data.

The primary estimand for this study is the difference in LS means of Azstarys® and placebo with respect to change from baseline in ADHD-RS total score at Visit 6, based on the primary endpoint MMRM model fitted to the ITT population. There will be no adjustments made for the use of prohibited therapies or other intercurrent events. The p-value associated with the primary estimand will be used to test the primary hypothesis of this study, that mean change from baseline to Visit 6 ADHD-RS total score for Azstarys® is different from that of placebo. If Azstarys® is shown to be statistically superior to placebo, then the superiority of Azstarys® to placebo will be tested for each cohort separately at a two-sided 0.05 level of significance.

LS mean changes from baseline over time with 95% CI from the analysis model will be plotted by treatment group and presented side by side for each age cohort.

3.8.1.2 Sensitivity Analyses of Primary Efficacy Results

Robustness of the primary efficacy endpoint in the presence of missing data or early treatment discontinuations will be explored by the following sensitivity analyses.

- MMRM on observed values (ePRO and paper) using multiple imputation method as described in Section 3.1.4.2.2
- MMRM on ePRO data only using multiple imputation method as described in Section 3.1.4.2.2
- MMRM on observed values for subjects with non-missing ADHD-RS Total Score at Visit 6 (i.e., completers only case)
- MMRM on observed values for subjects in PP Population

If the primary analysis renders a significant treatment difference, a tipping point analysis will be performed in order to examine the sensitivity of inferences to departures from the missing at random (MAR) assumption. As missing values following early discontinuations may not be consistent with a MAR assumption, a sensitivity analysis using multiple imputation under a missing not at random (MNAR) assumption will be performed searching for a tipping point that reverses the primary analysis conclusion.

The imputed values for Azstarys® subjects' visits post discontinuation will be made worse by adding a delta defined as k times the treatment difference between Azstarys® and placebo obtained from the MI steps described in Section 3.1.4.2.2, where k is a shift parameter that is incremented in order to identify the point at which the primary analysis result becomes non-significant (the tipping point). Consideration will then be given to how plausible the imputed values are at the tipping point. If not plausible, then the conclusion for the primary analysis under the MAR assumption is supported.

The tipping point analysis will be conducted as follows:

Generate scenarios with varying values of k (e.g., 20%, 40%, etc.) until the significance of the prespecified analysis assuming MAR is overturned (e.g., from p-value <0.05 to p-value ≥0.05). The worsening by adding k times the treatment differences is applied to all the post-discontinuation imputed values for each set of "complete" data from MI step 3 described in Section 3.1.4.2.2. As an example, if a subject from the Azstarys treatment group had 2 post-discontinuation visits imputed, the values of both of these 2 imputed visits would be made worse by adding k times the Azstarys versus Placebo treatment difference at each of these 2 visits.

Note that when k = 0%, this approach produces an analysis that is consistent with MAR and is equivalent to the primary analysis with MI. When k = 100%, this approach produces an analysis that is equivalent to "jump to reference," since the treatment differences are removed. When k >100%, the analysis reflects a "worse-than-control" scenario.

3.8.2. Secondary Efficacy Endpoints

3.8.2.1 Change from Baseline in ADHD-RS for Hyperactivity/Impulsivity and Inattention

If the primary endpoint comparison for change from baseline in ADHD-RS total score is significant overall and for Cohort 1, the superiority of Azstarys® to placebo with respect to the secondary efficacy endpoints will be tested for Cohort 1 only using a fixed sequence testing procedure (first for ADHD-RS for hyperactivity/impulsivity and then for ADHD-RS for inattention) to maintain Type 1 error control.

Change from baseline in ADHD-RS for hyperactivity/impulsivity and ADHD-RS for inattention will be summarized in a MMRM ANCOVA analogous to the primary efficacy analysis described in Section 3.9.1.1, except that the dependent variables will be change from baseline in ADHD-RS score for hyperactivity/impulsivity score and change from baseline in ADHD-RS score for inattention.

3.8.2.2 Change from Baseline in CGI-S and CGI-I

Descriptive statistics will be presented for baseline (Visit 2), all post baseline measurements (Visits 3 to 6), and changes from baseline to all post-baseline measurements of CGI-S by treatment group, overall and separately for each age cohort. A MMRM ANCOVA model will be fitted using all data as observed. The dependent variable will be change from baseline in CGI-S post-baseline assessments for each subject. The model will include fixed effects for treatment,

age cohort, gender (stratification factor for randomization), baseline CGI-S, analysis visit (Visit 3, 4, 5, and 6), and analysis visit-by-treatment interaction as well as a random effect for the subject. The mixed model will be fitted in the same manner as described above for the primary endpoint analysis. From the MMRM model, the Visit 6 difference between LS means of Azstarys® and placebo will be presented along with the corresponding 95% CI and two-sided p-value.

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

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

3.9. Safety Analysis

All safety analyses will be performed for the Safety Population by treatment group and overall and separately for each age cohort.

3.9.1. Adverse Events

All AEs will be coded using the MedDRA Version 25.1 and will be classified by SOC and preferred term. Severity will be graded as mild, moderate or severe.

TEAEs are defined as AEs that begin in the time period following the first administration of study medication through 5 days after the last dose of study medication or existing AEs that worsen in the time period following the first dose of study medication through 5 days after the last dose of study medication. Investigator assessed causality to study drug will be categorized as “probably related”, “possibly related” or “unrelated”. For summary purposes, “probably related” and “possibly related” will be considered “related.” Any missing relationships will be considered as “related” as well.

An overall summary of AEs will include the total number and percentage of subjects who experienced any TEAEs, SAEs, study drug-related TEAEs or SAEs, TEAEs leading to study drug discontinuation or study withdrawal, and TEAEs leading to death. In addition, the greatest severity of a TEAE experienced by each subject will be summarized.

A summary of TEAEs will include the number and percent of subjects who experience at least one TEAE, as well as the number and percent of subjects who experience at least one TEAE within each specific SOC and PT. A summary by PT only will also be presented. SAEs, drug-related TEAEs, TEAEs leading to study drug discontinuation or study withdrawal and TEAEs leading to death will be summarized similarly. TEAE incidences will also be summarized by

maximum severity grade.

For the presentation of AE incidences, the SOCs will be sorted by decreasing frequency, and within SOC, the PTs will be presented by decreasing frequency.

All AEs and SAEs, whether treatment emergent or not, will be listed for all subjects. A listing of AEs leading to treatment discontinuation will be provided as well.

3.9.2. Clinical Laboratory Evaluation

All laboratory results will be summarized using standard units.

For all quantitative hematology and chemistry parameters listed in Section 2.2.4.2, descriptive statistics will be presented for observed and change from baseline values at End of Treatment/Early Termination.

All clinical laboratory values will be presented in subject listings. Out of normal range values and clinically significant laboratory results will also be listed.

All pregnancy, MPH and drug abuse test results will be presented in a subject listing.

3.9.3. Vital Signs

Descriptive statistics for systolic and diastolic blood pressures, pulse rate, respiratory rate and temperature will be presented for the observed and change from baseline values at each analysis visit, using the visit windows defined in Section 3.1.5.

The incidence of clinically notable vital signs will also be summarized by analysis visit. These will be defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 90 mmHg, pulse rate ≥ 130 beats/min, and respiratory rate ≥ 30 breaths/min.

All vital sign results will be presented in a subject listing.

3.9.4. Body Weight and Height

Descriptive statistics for body weight (in kg) and height (in cm) will be presented for the observed, change and percent change from baseline values at each analysis visit.

Additionally, weight and height z-scores and percentiles will be summarized. The z-score system expresses the anthropometric value as a number of standard deviations (SDs) below or above the mean of a reference population. A positive z-score indicates that a child's weight/height is above average while a negative z-score indicates that it is below average. Since z-scores are standardized values of a normal distribution with mean 0 and SD of 1, there is a direct correlation to percentiles. A percentile indicates the percentage of observations that fall below a certain value of the reference population. A z-score of 0 corresponds to the 50^{th} percentile in the reference population; a z-score of ±1 corresponds to approximately the 16^{th} and 84^{th} percentiles, respectively; and a z-score of ±2 corresponds to approximately the 2^{nd} and 98^{th} percentiles, respectively. Refer to Section 3.1.6 for the calculation of z-scores and percentiles.

The descriptive statistics will include n, mean, standard deviation (SD), median, 1st and 3rd quartile (Q1, Q3), and range (minimum and maximum). In addition, descriptive statistics will be tabulated by sex and optimized dose.

All body weight and height results will be presented in a subject listing.

3.9.5. Physical Examinations

All physical examination results will be presented in a subject listing.

3.9.6. ECGs

Descriptive statistics will be presented for the observed and change from baseline values of heart rate, and RR and QT intervals at End of Treatment/Early Termination. Frequencies and percentages will also be provided for overall ECG interpretation (normal; abnormal, not clinically significant; abnormal, clinically significant).

All ECG results will be presented in a subject listing.

3.9.7. CSHQ

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

Descriptive statistics will also be presented by analysis visit for the change and percent change from baseline in scores for Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness by treatment overall and by age cohort.

All CSHQ results will be presented in a subject listing.

3.9.8. C-SSRS

C-SSRS outcomes at each visit will be summarized by the number and percentage of subjects in each treatment group with the following: suicidal ideation, suicidal behavior, and suicidal ideation or behavior (ideation and behavior combined).

All C-SSRS results will be presented in a subject listing.

3.10. Interim Analysis: Blinded Sample Size Re-Estimation

3.10.1. Analysis Objective

A blinded sample size re-estimation will be conducted for Cohort 1 (4 - <5 years and 10 months) when approximately 50% of Cohort 1 subjects complete their Visit 6 assessment or discontinue prior. The common within-group SD for the change from baseline to 28 days post-baseline in ADHD-RS total score, which was assumed to be 10 in the initial sample size calculation, will be re-estimated. The sample size of 130 for Cohort 1 may be increased, if the SD estimate is larger than initially assumed.

3.10.2. Analysis Method

Change from baseline in ADHD-RS total score through end of treatment will be calculated for each ITT subject who completed their Visit 6 assessment or discontinued prior. The common within-group standard deviation (σ) will be estimated for the change from baseline in ADHD-RS total score to Visit 6 using the methodology of Gould and Shih[3] :

$$\sigma^2 \approx \frac{n-1}{n-2}\left(s^2 - \frac{\Delta^2}{4}\right)$$

where n=number of subjects included in interim analysis, s=standard deviation of pooled sample, and Δ=6, the treatment difference under the alternative hypothesis.

Two separate estimates of σ will be derived. One including only those subjects who had an ADHD-RS total score at Visit 6, and the other including those who had an ADHD-RS total score at Visit 6 and those who discontinued prior to Visit 6. For those who discontinued and did not have an ADHD-RS total score at Visit 6, their last ADHD-RS total score prior to discontinuation will be used. From the two estimates of σ, the one that is largest will be used for the sample size re-estimation.

This adjusted variance estimate was recommended by Friede and Kieser[4] and is similar to the estimate proposed by Zucker[5]. Friede and Kieser[6] and Waksman[7] showed this estimate to be superior to the one obtained from the EM algorithm which was also proposed by Gould and Shih[3]. All statistical analyses will be performed using SAS® Version 9.4. Subjects will not be identified by treatment group and only an overall standard deviation will be calculated. If the estimate of σ for the change from baseline to Visit 6 in ADHD-RS total score is greater than 10 but less than or equal to 12, the independent statistician will recommend an increase in the sample size to 142 for Cohort 1. If the SD is less than or equal to 10 or greater than 12, Cohort 1 will retain its original planned size of 130. The sponsor will only receive the recommendation to either keep or increase the sample size of Cohort 1 (see Section 3.10.4). The sponsor will not be provided with the estimated value of σ. Since the study will remain masked for the sample size assessment, no alpha penalty for the final analysis will be incurred.

3.10.3. Maintaining the Treatment Masking

Only the study data required for the blinded sample size re-estimation (BSSR) will be sent to Suzanne Granger, the independent statistician at PROMETRIKA. This will include a transfer of the ADHD-RS data as well as datasets which contain the randomization date for each subject and

dosing information to confirm subject inclusion in the ITT analysis set. No information regarding the randomized treatments or treatments received will be sent to PROMETRIKA. Those performing the BSSR will remain blinded.

The data used in the BSSR will be as up-to-date as possible and as clean as possible since this will not be a locked database at the time of the data snapshot. During the BSSR, all ongoing subjects will complete their scheduled study assessments and subject enrollment will continue.

At PROMETRIKA, all data, programs, and output related to the BSSR will be kept in a secure electronic study folder with access restricted to only those personnel who will perform and validate the BSSR analyses. Restricted access on this study folder will be maintained until after the study database is locked. Only once the final data analysis has been completed will this information be transferred to the Sponsor.

3.10.4. Distribution of Results

Suzanne Granger will inform Lucia Ayra, Clinical Supplies Manager and Ron Tashjian, Sr. Director Clinical Operations, and copy (cc: via email) Charles Oh, Chief Medical Officer and Santhi Adusumilli, Clinical Trial Manager of the recommendation resulting from the BSSR in a memorandum which will be sent via email as a password protected file. The only information that will be communicated is:

- increase the sample size to 142 for Cohort 1, or
- retain the original planned sample size of 130 in Cohort 1.

Lucia Ayra and Ron Tashjian will be responsible for informing Corium personnel, as needed.

4. MODIFICATIONS FROM STATISTICAL METHODS IN THE PROTOCOL

The following are modifications in this SAP to the statistical methods described in the study protocol.

- The definition of ITT Population was modified to require a baseline ADHD-RS Total Score, since primary efficacy endpoint is change from baseline in ADHD-RS total score.
- Shifts from normal range (low, normal, high) in laboratory values from baseline to post-baseline assessments will not be analyzed.
- C-SSRS data at each visit will be summarized by the number and percentage of subjects in each treatment group with suicidal ideation or suicidal behavior. Changes from baseline will not be analyzed.
- Baseline CGI-S will be included as a covariate in the MMRM analyzing CGI-I post-baseline assessments.
- In addition to analyses of the CSHQ Total Sleep Disturbance Score, descriptive statistics will also be presented by analysis visit for the change and percent change from baseline in scores for Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety,

Night Wakings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness by treatment overall and by age cohort.

5. REFERENCES

1. CDC SAS Program. Centers for Disease Control and Prevention (CDC), Division of Nutrition, Physical Activity, and Obesity, Growth Chart Training: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm.

2. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. Vital Health Stat 11(246). 2002.

3. Gould AL, Shih WJ. Sample size re-estimation without unblinding for normally distributed outcomes with unknown variance. *Communications in Statistics – Theory and Methods* 1992; 21:10, 2833-2853.

4. Zucker DM, Wittes JT, Schabenberger O, Brittain E. Internal pilot studies II: Comparison of various procedures. *Statistics in Medicine* 1999; 18:3493-3509.

5. Friede T, Kieser M. On the inappropriateness of an EM algorithm based procedure for blinded sample size re-estimation. *Statistics in Medicine* 2002; 21:165-176.

6. Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Statistics in Medicine* 2003; 22:3571-3581.

7. Waksman J. Assessment of the Gould-Shih procedure for sample size re-estimation. *Pharmaceutical Statistics* 2007; 6:53-65.

6. SAMPLE SAS CODES