NYU Langone Health

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| **Official Title:** | AN OPEN-LABEL, TREATMENT, INVESTIGATOR-INITIATED STUDY, ON THE DURATION AND EFFICACY OF AZSTARYS SERDEXMETHYLPHENIDATE AND DEXMETHYLPHENIDATE) ON ADULT ADHD SYMPTOMS AND EXECUTIVE FUNCTION THROUGHOUT THE DAY INTO EARLY EVENING |
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# AN OPEN-LABEL, TREATMENT, INVESTIGATOR-INITIATED STUDY, ON THE DURATION AND EFFICACY OF AZSTARYS SERDEXMETHYLPHENIDATE AND DEXMETHYLPHENIDATE) ON ADULT ADHD SYMPTOMS AND EXECUTIVE FUNCTION THROUGHOUT THE DAY INTO EARLY EVENING

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| **Principal Investigator:** | Lenard Adler, MD<br>Department of Psychiatry<br>NYU Grossman School of Medicine,<br>One Park Ave, New York, NY 10016<br>Lenard.Adler@nyulangone.org<br>212-263-3580 |
| **Additional Investigators:** | Marianne Guschwan, MD<br>Department of Psychiatry<br>NYU Grossman School of Medicine,<br>One Park Ave, New York, NY 10016<br>Marianne.Guschwan@nyulangone.org<br>212-263-3580<br><br>Deepti Anbarasan, MD<br>Department of Psychiatry<br>NYU Grossman School of Medicine,<br>One Park Ave, New York, NY 10016<br>Lenard.Adler@nyulangone.org<br>212-263-3580 |
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| **IND Number:** | N/A |
| **Regulatory Sponsor:** | Lenard Adler MD |
| **Study Product:** | Azstarys (*Serdexmethylphenidate and Dexmethylphenidate*) |
| **Study Product Provider:** | Corium, LLC |
| **ClinicalTrials.gov Number** | Pending |

**Initial version:** 08 June 2022 (Initial concept approved by Corium LLC)
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**Amended:** 12/18/2023 Sponsor approved

**Statement of Compliance**
This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonization ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Corium LLC and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

**Table of Contents**

**List of Abbreviations**

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| ACDS | Adult ADHD Clinical Diagnostic Scale |
| AE | Adverse Event/Adverse Experience |
| AISRS | Adult ADHD Investigator Symptom Rating Scale |
| AMSES | ADHD Medication Smoothness of Effect Scale |
| ASRS | Adult ADHD Self-Report Scale |
| BRIEF-A | Behavior Rating Inventory of Executive Function- Adult Version |
| CGI-S | Clinical Global Impression: Severity of Illness |
| CFR | Code of Federal Regulations |
| CM | Concomitant Medications |
| CRF | Case Report Form |
| CSOC | Clinical Study Oversight Committee |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CT | Clinical Trial |
| d/c'd | Discontinued |
| DCC | Data Coordinating Center |
| DEA | Drug Enforcement Administration |
| DHHS | Department of Health and Human Services |
| DR | Dose Related |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders 5$^{th}$ Edition |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiograph |
| EPIC | Electronic Medical Health Records |
| ET | Early Termination |
| F/U | Follow Up |
| FDA | Food & Drug Administration |
| FFR | Federal Financial Report |
| Freq | Frequency |
| FWA | Federal wide Assurance |

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| GCP | Good Clinical Practice |
| GEE | Generalized Estimating Equation |
| GLM | General Linear Model |
| HCG | Human Chorionic Gonadotropin Pregnancy Test |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| HT | Height |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| MAOI | Monoamine Oxidase Inhibitors |
| MAS | Mixed Amphetamine Salts |
| MAS XR | Mixed Amphetamine Salts Extended Release |
| MHX | Medical History |
| MI | Myocardial Infarction |
| MINI | Mini International Neuropsychiatric Interview |
| Mg | Milligram |
| mmHg | Millimeters of Mercury |
| MOP | Manual of Procedures |
| N | Number (typically refers to participants) |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| OHSR | Office of Human Subjects Research |
| PE | Physical Exam |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SOP | Standard Operating Procedure |
| Serd-mph | Serdexmethylphenidate and Dexmethylphenidate |

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| TASS | Time-Sensitive ADHD Symptom Scale |
| US | United States |
| WT | Weight |

**Protocol Summary**

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| Title | AN OPEN-LABEL TREATMENT, INVESTIGATOR-INITIATED STUDY, ON THE DURATION AND EFFICACY OF AZSTARYS SERDEXMETHYLPHENIDATE AND DEXMETHYLPHENIDATE) ON ADULT ADHD SYMPTOMS AND EXECUTIVE FUNCTION THROUGHOUT THE DAY INTO EARLY EVENING |
| Brief Summary | One purpose of this trial is to extend the safety and efficacy evidence basis for Azstarys in adult with ADHD. This open-label, treatment study will examine the safety and efficacy of Azstarys on ADHD symptoms using the AISRS 18-item total score on the AISRS-expanded; the Adult ADHD Investigator Symptom Rating Scale. We will also examine Executive Functioning throughout the day to later in the day (early evening -12 hours after first morning dosing). 30 subjects will be consented to gain 20 subjects, which will all start on a Two-week observation stabilization period for patients before starting treatment with Azstarys. If they are found to have ≥30% change in their total AISRS (18-items) scores of AISRS-expanded during the Two-week observation stabilization period, they are discontinued from the study.<br><br>If there is not a ≥30% change in subject's 18 item total AISRS scores of AISRS-expanded, they will move on to treatment of Azstarys and will be dispensed three weeks of Azstarys (flexible dose) starting at 39.2 mg serd-mph/7.8 mg d-mph up to 52.3 mg serd-mph/10.4 mg d-mph.<br><br>We will have viable data for at least 15 completers. Subjects will come in weekly and have their ADHD assessed with the AISRS EXPANDED and CGI. We will assess their total ADHD symptoms about twelve hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS) and Smoothness of Effect Scale (AMSES) (Three-time daily on assessment visit day) at V3, V4, V5 and V6. We will also look at clinical symptoms of Executive Function and emotional dyscontrol, as measured by the BRIEF-A and ASRS-expanded at screening baseline start and end of Azstarys dosing epoch. |
| Phase | Investigator-initiated clinical study phase 4 |
| Objectives | The primary objective is to examine the efficacy of Azstarys on ADHD symptoms The primary measure of ADHD symptoms will be the total score on the AISRS (18 items) of AISRS-expanded.<br><br>The secondary objectives are to examine changes after Azstarys treatment in:<br>1. Overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS EXPANDED and overall impairment via the clinical global impression-severity (CGI-S) scale<br><br>2. Clinical symptoms of executive function and emotional dyscontrol, as measured by the BRIEF-A. (BRIEF: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, |

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| | Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor).<br><br>3. Adult ADHD Self Report Symptom Rating Scale (ASRS) Symptom Checklist, which has high validity in assessment of core 18 adult ADHD Diagnostic and Statistical Manual of Mental Disorders (DSM) symptoms and EFD and EC symptoms. The ASRS v1.1 Symptom Checklist(ASRS 31-item scale) is designed to provide clinicians with an inventory of adult ADHD symptoms as the first part of a diagnostic evaluation or to be used in monitoring treatment response<br><br>4. Total ADHD symptoms about twelve hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS)and Smoothness of Effect Scale (AMSES) (3x day on assessment visit day;1 hour, 4 hours, 12 hours after dosing) |
| Methodology | *OPEN-LABEL TREATMENT INVESTIGATOR-INITIATED STUDY* |
| Endpoint | We will examine potential differential effects of Azstarys in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF-A >= 65 at baseline). We will also examine self-report of ADHD symptoms (on ASRS) versus clinician report (AISRS) and changes in self-report measures of executive function and emotional dyscontrol on the AISRS expanded, and ASRS-expanded versus these measures on the BRIEF-A. |
| Study Duration | 21-24 months |
| Participant Duration | Subjects will be in the study approximately 8 weeks; 0-3 weeks (screening) 2 weeks (two-week observation stabilization period) and 3 weeks, open-label azstarys / serdmph) |
| Duration of IP administration | 3 weeks Open-label Azstarys |
| Population | Male or female between the ages of 18-60, inclusive, of all races and ethnicity, meeting DSM 5-TR criteria for a primary diagnosis of ADHD (predominantly inattentive presentation or combined presentation) as diagnosed via the Adult ADHD Clinician Diagnostic Scale version 1.2 (ACDS v1.2). Subjects must be in |

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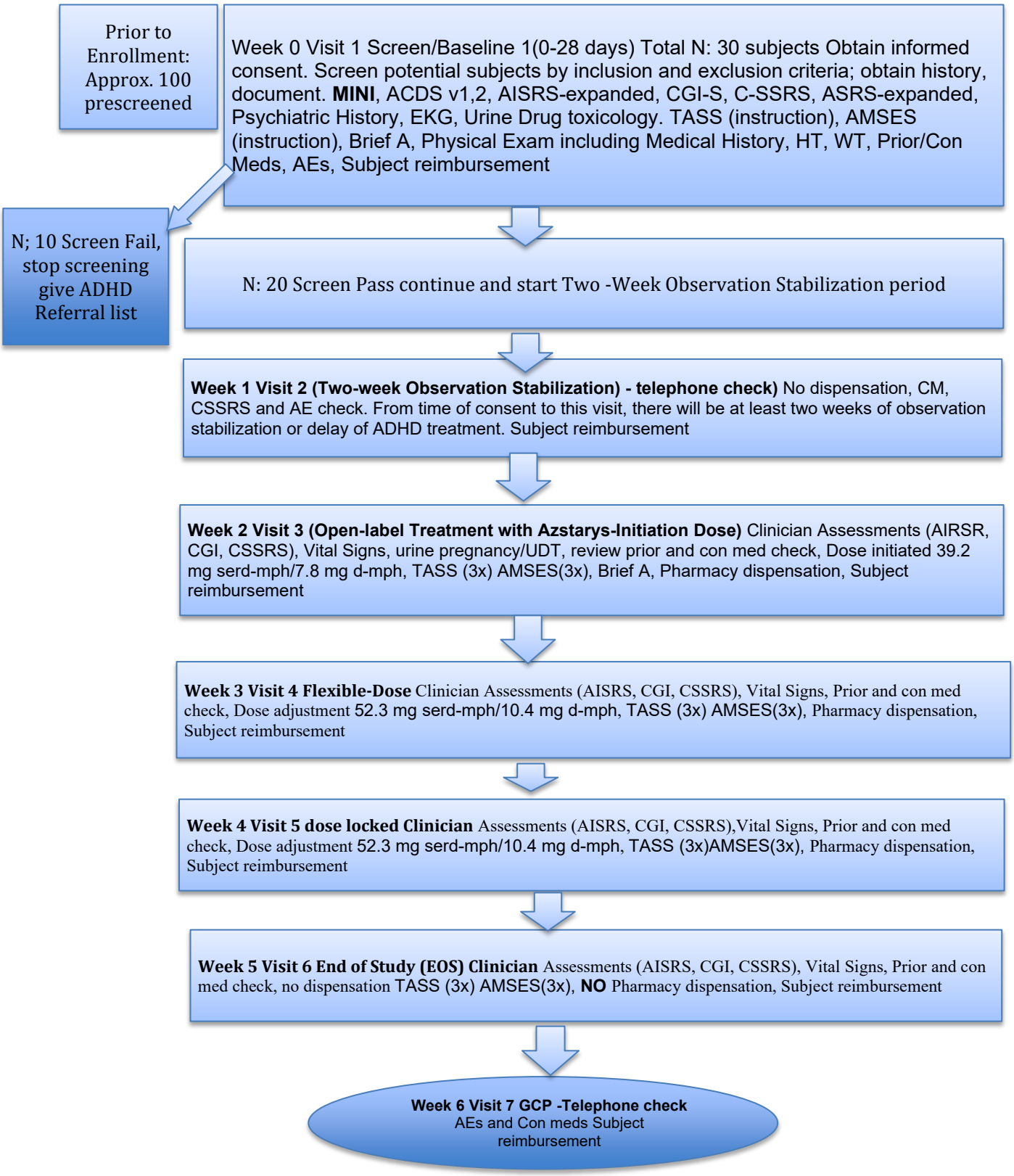
| | good health as determined by the principal investigator without any comorbid psychiatric conditions requiring treatment for at least 2 months |
| Study Sites | NYU |
| Number of participants | Approximately 30 participants expected to be enrolled / consent at NYU |
| Description of Study Agent / Procedure | Azstarys:(SDX/d-MPH) is FDA-approved and contains a molar ratio of 70% serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), and 30% d-MPH HCl. SDX. It is a Schedule II controlled substance.<br><br>After a two-week stabilization-observation period, weekly Azstarys will be given orally starting at 39.2 mg serd-mph/7.8 mg d-mph/day with titration up to 52.3 mg serd-mph/10.4 mg d-mph based on clinical response and potential adverse events, for a total of three weeks on Azstarys. |
| Reference Therapy | *No Reference Therapy* |
| Key Procedures | Psychological Assessments; MINI, ACDS, AISRS EXPANDED CGI, CSSRS, ASRS-expanded, TASS, AMSES, BRIEF-A and Physical Assessment Vital Signs, EKG, Physical Exam including medical history, UDT and urine pregnancy. |
| Statistical Analysis | For our primary analysis, which uses a two-sided test with a type I error of 0.05, it shows that 15 evaluable patients will give power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size it is half of the 1.2 effect size reported by Spencer et al. 2008 and thus is at the lower end of what we should expect to see in this study |

## FLOW DIAGRAM



## 1. Key Roles

Principal Investigator
Lenard A Adler MD
NYU
United States
Tel: 212 263-3580
Email: Lenard.Adler@nyulangone.org

Sub-Investigator
Marianne T. Guschwan MD
NYU
United States
Tel: 212 263-3580
Email: Marianne.Guschwan@nyulangone.org

Sub-Investigator
Deepti Anbarasan, MD
NYU
United States
212-263-3580
Deepti.Anabarasan@nyulangone.org

Independent Medical Monitor
Donald C. Goff, MD
NYU
United States
Tel: 646-754-4843
Email: Donald.goff@nyulangone.org

**Key Study Personnel:**
Terry Leon RN, MS
NYU
Tel: 646-754-4841
Email: Terry.Leon@nyulangone.org

**Corium LLC**

*NOTE: Non-traditional volunteers in the study will not interact with subjects for research purposes.*

## 2. Introduction, Background Information and Scientific Rationale

### *2.1. Background Information and Relevant Literature*

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by problems with sustaining attention, organization, planning, procrastination, daydreaming, restlessness, impulsivity and hyperactivity. Adult ADHD is a common and highly impairing disorder affecting 4.4% of the US population (Kessler RC et al. 2006). Recent factor analyses (Adler et al. 2017) have highlighted the importance of co-travelling symptoms of executive function deficits (organization, planning, time management and working memory) in addition to the core symptoms

of inattention and hyperactivity-impulsivity noted in the DSM (DSM –5) (American Psychiatric Association 2013). Furthermore, it has been posited that executive function deficits define the impairment in ADHD (Barkley and Murphy 2010). Psychostimulants are a mainstay of pharmacotherapy for adult ADHD, and five sustained release preparations have been FDA approved for adult ADHD.

One of these preparations, Serdexmethylphenidate/dexmethylphenidate (SDX/d-MPH) is a recently approved ADHD product (Azstarys) containing a molar ratio of 70% serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), and 30% d-MPH HCl. SDX, a Schedule II controlled substance, is pharmacologically inactive until gradually converted to active d-MPH in the lower intestinal tract. The pharmacokinetic profile of SDX/d-MPH exhibits a singled-MPH concentration peak, followed by a gradual elimination curve characterized by a long half-life (T1/2: 11.7 hours) (Corium2021).

After oral administration, early exposure to d-MPH is governed primarily by the d-MPH component, and mid- to late-day exposure is determined primarily by the gradual conversion of inactive SDX to active d-MPH. Whereas most once-daily stimulant products utilize a formulation-based approach to impart delayed and/or ER properties, SDX/d-MPH utilizes a prodrug approach to produce a unique, extended-duration pharmacokinetic profile. A similar approach to prolonging drug exposure has been successfully achieved with the d-amphetamine prodrug, lisdexamfetamine (Vyvanse) (Kollins et al. (2021)).

In the child study, the change from baseline (predose Visit 5) in SKAMP-C scores averaged over the laboratory classroom day (Visit 6) was significantly lower (i.e., improved) for the SDX/d-MPH group compared with the placebo group (least-squares [LS] mean treatment difference [95%CI]: -5.41 [-7.10 to -3.71]; $p < 0.001$; Table 2). A post hoc analysis in which predose Visit 6 was used as the SKAMP-C baseline resulted in similar treatment differences for the primary endpoint (LS mean treatment difference [95% CI]: -7.27 [-9.00 to -5.53]; $p < 0.001$; Table 2). Notably, on the morning of the laboratory classroom day (Visit 6), mean predose SKAMP-C score change from baseline was higher (i.e., more severe symptoms) in the SDX/d-MPH group compared with the placebo group, a difference that reached statistical significance (LS mean difference [95% CI]: 2.37 [0.07 to 4.68], $p = 0.044$) (Kollins et al. (2021).

It would be important to add to the evidence basis for using Azstarys. The Azstarys clinical efficacy data information on overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the total AISRS 18 item of AISRS-Expanded and overall impairment via the clinical global impression-severity (CGI-S) scale. The Clinical Global Impression Severity (CGI-S) scale is a validated, highly utilized measure of impairment in studies of adult ADHD and has been employed in prior ADHD studies. In addition, adult symptom information will be collected using the Time-Sensitive ADHD Symptom Scale (TASS) and the Smoothness of Effect Scale (AMSES).

Data from this study will help us examine co-travelling symptoms of executive dysfunction and emotional dyscontrol by using the ADHD symptoms scale validated for DSM-5 (AISRS- expanded) and the (BRIEF-A). We will also re-assess ADHD clinical symptoms later in the day via the Time-Sensitive ADHD Symptom Scale (TASS) and Smoothness of Effect Scale (AMSES) (Three times a day on assessment visit days).

### *2.2. Name and Description of the Agent*

Serdexmethylphenidate/dexmethylphenidate (SDX/d-MPH) is a recently approved ADHD product (Azstarys) containing a molar ratio of 70% serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), and 30% d-MPH HCl. SDX, a Schedule II controlled substance, is pharmacologically inactive until gradually converted to active d-MPH in the lower intestinal tract. The pharmacokinetic profile of SDX/d-MPH exhibits a singled-MPH concentration peak, followed by a gradual elimination curve characterized by a long half-life (T1/2: 11.7 hours) (Corium2021). After oral administration, early exposure to d-MPH is governed primarily by the d-MPH component, and mid- to late-day exposure is determined primarily by the gradual conversion of inactive SDX to active d-MPH.

Whereas most once-daily stimulant products utilize a formulation-based approach to impart delayed and/or ER properties, SDX/d-MPH utilizes a prodrug approach to produce a unique, extended-duration pharmacokinetic profile. A similar approach to prolonging drug exposure has been successfully achieved with the d-amphetamine prodrug, lisdexamfetamine (Vyvanse). (Kollins et al. (2021)).

#### 2.2.1. Preclinical Data

In the child study investigating Azstarys; SDX/d-MPH showed significant improvement in ADHD symptoms compared with placebo in children 6–12 years of age, with a rapid onset and extended duration of treatment effect. SDX/d-MPH was safe, with AEs comparable with those observed with other stimulant treatments. (Kollins et al. (2021))

One purpose of this trial is to extend the evidence basis for Azstarys in adult ADHD. The efficacy data available to date on Azstarys is in treatment of childhood ADHD, although FDA approval in ADHD is in age 6 and up. Given the high prevalence and impairment from adult ADHD, it is critical to gather data as to overall efficacy and effects throughout the day of Azstarys. Extended-release ER stimulants are often preferred because of their duration of effect reduced need for multiple does attendance for better tolerability and decreased potential for abuse and diversion compared with short acting stimulants. (Kollins et al. (2021), CADDRA, (2018))

#### 2.2.2. Clinical Data to Date

In the child study, the change from baseline (predose Visit 5) in SKAMP-C scores averaged over the laboratory classroom day (Visit 6) was significantly lower (i.e., improved) for the SDX/d-MPH group compared with the placebo group (least-squares [LS] mean treatment difference [95%CI]: -5.41 [-7.10 to -3.71]; $p < 0.001$; Table 2). A post hoc analysis in which predose Visit 6 was used as the SKAMP-C baseline resulted in similar treatment differences for the primary endpoint (LS mean treatment difference [95% CI]: -7.27 [-9.00 to -5.53]; $p < 0.001$; Table 2). Notably, on the morning of the laboratory classroom day (Visit 6), mean predose SKAMP-C score change from baseline was higher (i.e., more severe symptoms) in the SDX/d-MPH group compared with the placebo group, a difference that reached statistical significance (LS mean difference [95% CI]: 2.37 [0.07 to 4.68], $p = 0.044$) (Kollins et al. (2021))

Recent factor analyses (*Adler et al. 2017*) have highlighted the importance of co-travelling symptoms of executive function deficits (organization, planning, time management and working memory) in addition to the core symptoms of inattention and hyperactivity-impulsivity noted in the DSM (DSM-5) (*American Psychiatric Association 2013*). Furthermore, it has been posited that executive function deficits define the impairment in ADHD (*Barkley and Murphy 2010*). Psychostimulants are a

mainstay of pharmacotherapy and five sustained-release preparations have been FDA approved for adult ADHD.

It would be important to add to the evidence basis for using Azstarys. The Azstarys clinical efficacy data information on overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS Expanded and overall impairment via the clinical global impression-severity (CGI-S) scale. The Clinical Global Impression Severity (CGI-S) scale is a validated, highly utilized measure of impairment in studies of adult ADHD and has been employed in prior ADHD studies. In addition, adding more adult symptom information using the Time-Sensitive ADHD Symptom Scale (TASS) and the Smoothness of Effect Scale (AMSES) would be beneficial.

Data from this study will help us examine co-travelling symptoms of executive dysfunction and emotional dyscontrol by using the ADHD symptoms scale validated for DSM-5 (AISRS- expanded) and the (BRIEF-A). We will also re-assess ADHD clinical symptoms throughout the day into early evening via the Time-Sensitive ADHD Symptom Scale (TASS) and Smoothness of Effect Scale (AMSES) (Three times daily on assessment visit days).

### 2.2.3. Dose Rationale

Dosing will be established from Kollins et al. 2021 trial. The study will not need an IND as Azstarys is approved for ages 6 and up and we are within FDA approved dosing. The recommended starting dosage of Azstarys is 39.2 mg serdexmethylphenidate/ 7.8 mg dexmethylphenidate once daily in the morning. Increase the dosage after one week to a dosage of 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate per day. The maximum recommended dosage is 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate once daily.

Preclinical and Clinical Studies

Serdexmethylphenidate is a prodrug of dexmethylphenidate. Following a single dose administration of 52.3 mg/10.4 mg AZSTARYS and 40 mg of a dexmethylphenidate hydrochloride extended-release (ER) capsule in healthy volunteers under fasted conditions:

- The mean peak plasma concentration (Cmax) of dexmethylphenidate was 14.0 ng/mL and 28.2 ng/mL, respectively.
- The mean area under concentration curve (AUC) of dexmethylphenidate was 186 hour*ng/mL and 248 hour*ng/mL, respectively.

The plasma PK profiles of dexmethylphenidate following administration of AZSTARYS or dexmethylphenidate hydrochloride extended-release (ER) capsule

In Adults and Pediatric Patients 13 to 17 years of age with ADHD, the efficacy of 52.3 mg/10.4 mg AZSTARYS in adults and pediatric patients 13 to 17 years of age was established by pharmacokinetic bridging between AZSTARYS (52.3 mg/10.4 mg) and dexmethylphenidate hydrochloride extended-release capsules.

### *2.3. Rationale*

The primary objective of this proposal is to extend the efficacy evidence of Azstarys in Adults with ADHD. The primary measure of ADHD symptoms will be the total score on the Adult ADHD Investigator Symptom Rating Scale (AISRS) 18 item scale. Improvement will be examined by the change in AISRS between Visit 3 Initiation (Azstarys) and Visit 6 End of Treatment (Azstarys).
The Adult ADHD Investigator Symptom Rating Scale-expanded (AISRS) employs adult-stem

questions and rates the 18 DSM 5 symptoms of ADHD; Although, Azstarys is approved for ages 6 and up, there are no adult studies examining efficacy just for adults.

Secondary objectives of this protocol are to reexamine changes after Azstarys treatment in; the overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets symptoms of Executive function deficits (EFD) and Emotional dysfunction(ED )subscales on AISRS expanded and overall impairment via the Clinical Global Impression-Severity (CGI-S) scale. In clinical symptoms of executive function, as measured by the BRIEF-A function (BRIEF: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor). Also, subject self-report of symptoms via expanded Adult ADHD Self Report Symptom Rating Scale (ASRS) Symptom Checklist, which has high validity in assessment of core 18 adult ADHD Diagnostic and Statistical Manual of Mental Disorders (DSM) symptoms and EFD and EC symptoms. The ASRS v1.1 Symptom Checklist (ASRS 31-item scale) designed to provide clinicians with an inventory of adult ADHD symptoms as the first part of a diagnostic evaluation or to be used in monitoring treatment response. We will look at the total ADHD symptoms about twelve hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS) and Smoothness of Effect Scale (AMSES) (done three times a day on assessment visit days) (Spencer et al 2008, Adler et al 2017). and in clinical symptoms of Executive Function and emotional dyscontrol, as measured by the BRIEF-A and AISRS-expanded.

Hypotheses: In subjects with adult ADHD after 3-week Azstarys treatment (from end of a two week observation stabilization period to Week 5 Visit 6), there will be significant improvement in:

1) Overall symptoms of adult ADHD as measured by the total score on the Adult ADHD Investigator Symptom Rating Scale (AISRS) (primary effect).
2) Overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS EXPANDED and overall impairment via the clinical global impression-severity (CGI-S) scale. (secondary effect).
3) In clinical symptoms of Executive Function, as measured by the BRIEF-A. (secondary effect).
4) In expanded Adult ADHD Self Report Symptom Rating Scale (ASRS) Symptom Checklist treatment response (secondary effect)
5) Total ADHD symptoms twelve hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS) and Smoothness of Effects Scale (AMSES) (secondary effect).

In the child studies investigating Azstarys; SDX/d-MPH showed significant improvement in ADHD symptoms compared with placebo in children 6–12 years of age, with a rapid onset and extended duration of treatment effect. SDX/d-MPH was safe, with AEs comparable with those observed with other stimulant treatments. (Kollins et al. (2021)).

The efficacy data available to date on Azstarys is in treatment of childhood ADHD. Given the high prevalence and impairment from adult ADHD, it is critical to gather data as to overall efficacy and effects throughout the day of Azstarys in adults. Extended-release ER stimulants are often preferred because of their duration of effect reduced need for multiple does attendance for better tolerability and decreased potential for abuse and diversion compared with short acting stimulants (Kollins et al. (2021), CADDRA (2018)).

The TASS showed high internal consistency and concurrent validity with the clinician-administered ADHD-RS and is a valid and reliable scale for measuring change in ADHD symptoms over the course of a day in adults. (Spencer et al 2008)

The Adult ADHD Medication Smoothness of Effect Scale (AMSES) is a 6-item, frequency-based, self-report scale that was recently developed to assess the consistency and duration of effect of ADHD medication throughout the day (L. A. Adler, Lynch, Shaw, et al., 2010). The AMSES compares the effectiveness of ADHD medication shortly after dosing with the effectiveness later in the day (Adler et al 2017)

## *2.4. Potential Risks & Benefits*

### 2.4.1. Known Potential Risks

AZSTARYS is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. It has been FDA-approved for children 6 years of age and adults up to 65 years of age. The most common adverse events reported in adult were decreased appetite, insomnia, nausea, vomiting, dyspepsia, abdominal pain, decreased weight, anxiety, dizziness, irritability, affect lability, tachycardia, and increased blood pressure.

AZSTARYS is contradicted for patients with known hypersensitivity to serdexmethylphenidate, methylphenidate, or other components of AZSTARYS. Bronchospasm, rash, and pruritus have been reported in patients who received AZSTARYS. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products.

AZSTARYS is also contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crisis.

The following adverse reactions have been associated with the use of amphetamines and central nervous system stimulants including AZSTARYS.

1. Potential for Abuse and Dependence: Central Nervous system stimulants including AZSTARYS, other methylphenidate-containing products, and amphetamines, have a high potential for abuse. We will assess risk of abuse and monitor for signs of abuse while in the study.
2. Cardiovascular: Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems. Further, evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during AZSTARYS treatment.
3. Blood Pressure and Heart Rate Increases: We will monitor weekly blood pressure and pulse.
4. Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed.

5. Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants.
6. In children: Long-term Suppression of Growth: Monitor height and weight at appropriate intervals in pediatric patients.
7. Psychiatric Adverse Reactions: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. We will evaluate for bipolar disorder using the MINI prior to AZSTARYS use.

**Post marketing Experience:** The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

- Blood and Lymphatic System Disorders: pancytopenia, thrombocytopenia, thrombocytopenic purpura
- Cardiac Disorders: angina pectoris, bradycardia, extrasystole, supraventricular tachycardia, ventricular extrasystole, palpitations, increased heart rate
- Eye Disorders: diplopia, mydriasis, visual impairment, blurred vision
- General Disorders: chest pain, chest discomfort, hyperpyrexia
- Gastrointestinal Disorders: dry mouth Hepatobiliary disorders: hepatocellular injury, acute hepatic failure
- Immune System Disorders: hypersensitivity reactions such as angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritus NEC, rashes, eruptions, and exanthemas NEC
- Investigations: alkaline phosphatase increased, bilirubin increased, hepatic enzyme increased, platelet count decreased, white blood cell count abnormal
- Musculoskeletal, Connective Tissue and Bone Disorders: arthralgia, myalgia, muscle twitching, rhabdomyolysis, muscle cramps
- Nervous System: convulsion, grand mal convulsion, dyskinesia, serotonin syndrome in combination with serotonergic drugs, nervousness, headache, tremor, drowsiness, vertigo
- Psychiatric Disorders: disorientation, libido changes, hallucination, hallucination auditory, hallucination visual, logorrhea, mania, restlessness, agitation
- Skin and Subcutaneous Tissue Disorders: alopecia, erythema, hyperhidrosis
- Urogenital System: priapism
- Vascular Disorders: Raynaud's phenomenon

**Risk of observation stabilization period:** The subject will be required to not take any ADHD medications or delay start of ADHD medication if newly diagnosed and their symptoms may return and or get worse.

If subject is currently prescribed ADHD medication, and has not taken their medication in past week, they will be asked not to restart their current medication, during this time, their ADHD symptoms may worsen. The study doctor and the study staff will monitor ADHD symptoms while subjects are not on ADHD medications. Subjects are not allowed to take any ADHD medication other than Azstarys while in this Azstarys trial.

Once two-week observation is complete, and subjects are still eligible to move to W2 Visit 3 Initiation Dose, they will be prescribed Azstarys. If subject is not eligible to move onto W2 Visit 3, these subjects are instructed by the study clinician to start ADHD medications and would be given the Adult ADHD referral list,

**Risk of Safety Clinical assessments**: Potential risks associated with an EKG include an initial feeling of coldness when the test material (sticky pads and gel) touches the skin, localized rash or skin irritation from the test material.

**Risk in Pregnancy:**
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including AZSTARYS, during pregnancy. Subjects who are pregnant, planning to be pregnant or men planning to make a woman pregnant will not be eligible for the study and will not be dispensed AZSTARYS.

Because the effect of Azstarys on sperm are unknown, subjects will be required to use a medically accepted method of birth control while they participate in the study and for at least 90 days after the end of study treatment, using one of the methods described above. If subject or their partner becomes or thinks they may have become pregnant during their time in the study or within 30 days after last dose, we ask that they tell the principal investigator right away.

If found to be pregnant after starting the study. We will contact National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

There are no available data on AZSTARYS use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. AZSTARYS contains dexmethylphenidate and serdexmethylphenidate, a prodrug of dexmethylphenidate. Dexmethylphenidate is the d-threo enantiomer of racemic methylphenidate. Published studies and post marketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants use during pregnancy (More details are covered in the investigator's brochure).

Patients will be told to take medication once daily in the morning and report if they have any of these effects at each visit.

**Risk of loss of Confidentiality**: Possible loss of confidentiality related to urine screens and clinical data obtained during this study is recognized. As a guard against the loss of confidentiality, all information will be stored in locked files, which can be accessed only by members of the research staff for this project.

### 2.4.2. Minimizing Risks

The above risks are minimized through standard of care monitoring. This monitoring will occur weekly three times on days of assessments to ensure subject safety. We will assess risk of abuse and monitor for signs of abuse throughout the study. Subjects are asked by research staff, how they are feeling since last time at the clinic or last phone call. Subject will be asked about drugs of abuse at screening and at start of open label initiation of Azstarys. They are also asked to supply a urine sample for urine drug toxicology. Patients are instructed to take medication once daily in the morning and report if they have any effects at each visit. Subjects are asked three times throughout

the day at every weekly visit regarding any adverse events. They are also encouraged to reach out to us even if adverse events happen outside their usual weekly visit.

As a guard against the loss of confidentiality, all information will be stored in locked files, in locked rooms, secure share drive which can be accessed only by members of the research staff for this project. Subjects that are at an increased risk of physical or mental harm will be evaluated and withdrawn from the study. Those with efficacy issues needing treatment will be referred to treatment in their community. Women who become pregnant will be followed until birth or termination of fetus.

### 2.4.3. Known Potential Benefits

Azstarys is FDA approved and is known to be effective in those 6 years of age and older. Azstarys is used for long term treatment of adults with ADHD. While there may not be a direct benefit to specific the patients, it is hoped that the knowledge gained will add to the current adult data and benefit others in the future. If subject would like to continue treatment with Azstarys, they are able to ask their personal non-study physician for continuation of treatment. We will do our best to accommodate a seamless transition to treatment with their physician once done with the study. The subject is able to access information on accessing Azstarys at reduced rates. The Azstarys will be prescribe by their own provider (https://azstarys-pro.com/adult-adhd)

In addition, this study will extend the evidence basis for Azstarys in adult ADHD. The efficacy data available to date on Azstarys is in treatment of childhood ADHD, although FDA approval in ADHD is in age 6 and up. Given the high prevalence and impairment from adult ADHD, it is critical to gather data as to overall efficacy and effects throughout the day of Azstarys. Extended-release ER stimulants are often preferred because of their duration of effect reduced need for multiple does attendance for better tolerability and decreased potential for abuse and diversion compared with short acting stimulants. (Kollins et al. (2021), CADDRA, 2018).

## 3. Objectives and Purpose

### *3.1. Primary Objective*

The primary objective of this proposal is to examine the efficacy of Azstarys on ADHD symptoms throughout the day into early evening. The primary measure of ADHD symptoms will be the AISRS 18 item total score on the AISRS-expanded; the Adult ADHD Investigator Symptom Rating Scale.

### *3.2. Secondary Objectives*

The secondary objectives of this study are to examine changes after Azstarys treatment in:

1. Overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS EXPANDED and overall impairment via the clinical global impression-severity (CGI-S) scale.
2. Total ADHD symptoms about twelve hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS) and Smoothness of Effect Scale (AMSES) (done three times a day on assessment visit days)
3. In clinical symptoms of Executive Function and emotional dyscontrol, as measured by the BRIEF-A and AISRS-expanded.

# 4. Study Design and Endpoints

## *4.1. Description of Study Design*

This is a phase four, two-week observation stabilization period, open-label, three-week treatment looking at duration and efficacy of AZSTARY on adults with ADHD symptoms and adult executive functions throughout the day into early evening.

We will introduce a two-week observation stabilization lead-in to all consented eligible subjects.

Subjects, who after two weeks observation stabilization, had change of ADHD symptoms equal or greater than 30% on total AISRS 18 item of AISRS-Expanded from screening Week 1 Visit 2 to start of Week 2 Visit 3 will not continue to treatment and completion of Week 2 Visit 3. If the subject does not experience a 30% change in their total AISRS 18 item of AISRS-Expanded scores during baseline the subject will then continue and initiate to a three-week open-label treatment with Azstarys. AZSTARYS will start at dose of 39.2 mg serd-mph/7.8 mg d-mph/day with titration up to 52.3 mg serd-mph/10.4 mg d-mph based on clinical response and potential adverse events.

If subject has experienced a change of 30% on total AISRS 18 item of AISRS-Expanded rating interview subject participation will end after the two-week observation period. They are given the ADHD referral list for connection to treatment in the community.

We plan to consent 30 subjects out of which about 10 will screen fail, 20 will be enrolled; asked to observation stabilization for two weeks, dispensed AZSTARY and 15 will complete all study visits. Subjects will be seen weekly except for the telephone check at Week 1 Visit 2 (Two-week stabilization observation).

## *4.2. Study Endpoints*

### 4.2.1. Primary Study Endpoints

Our primary outcome is effects on overall adult ADHD symptoms via 18 item total score of AISRS-expanded. The AISRS 18 item total score of AISRS Expanded will be will be examined for a 30% change between the W0 Visit 1 (screening/baseline visit) and Week 2 Visit 3 (Initiation Dose), which happens post the two week observation stabilization period and Week 5 Visit 6 (EOS visit).

### 4.2.2. Secondary Study Endpoints

In secondary analyses, we will also analyze the following variables:

- AISRS-expanded, evaluation of ADHD subsets IA and HI symptoms (total, inattentive and hyperactive-impulsive subsets)and overall impairment via clinical global impression severity (CGI-S) scale.
- TASS and AMSES done 1 hour, 4 hours and 12 hours post dose (for effects of Azstarys over time at different points of the day into early evening),
- Expanded Adult ADHD Self Report Symptom Rating Scale (ASRS-expanded) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets)
- Symptoms of executive function (BRIEF: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor),
- Executive dysfunction and emotional dyscontrol by using the ADHD symptoms scale validated for DSM-5 (AISRS- expanded) and the (BRIEF-A).

### 4.2.3. Exploratory Endpoints

We will examine potential differential effects of Azstarys in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF-A >= 65 at baseline). We will also examine self-report of ADHD symptoms (on ASRS) versus clinician report (AISRS) and changes in self-report measures of executive function and emotional dyscontrol on the ASRS-expanded and AISRS-expanded versus these measures on the BRIEF-A.

## 5. Study Enrollment and Withdrawal

### *5.1. Inclusion Criteria*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Adults ages 18-60 years, inclusive at the time of consent
2. Able to provide signed informed consent
3. Any gender
4. Subjects with a current primary DSM-5 diagnosis of ADHD of predominantly inattentive presentation, or combined presentations) as confirmed by the ACDS Version 1.2.5. Subjects who are not receiving any pharmacological treatment for ADHD must have an AISRS 18 item total score of AISRS expanded of ≥ 28 at screening. Subjects who were previously receiving pharmacological treatment for ADHD at screening must have a minimum total AISRS 18 item of AISRS EXPANDED score of ≥ 22 at screening
5. Dysthymia and anxiety disorders in remission but stable on psychiatric medication for three weeks or more at the discretion of principal investigator will be allowed- medication for these disorders to remain constant for the duration of the protocol.
6. Subjects, who have not used stimulant medication in the past 2 months.

### *5.1.2 Exclusion Criteria*

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Known hypersensitivity to serdexmethylphenidate, methylphenidate, or product components.
2. Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days.
3. Lifetime bipolar disorder, psychotic disorders, autism, intellectual disability except mood disorders accepted under the inclusion criteria at the discretion of the principal investigator.
4. Active suicidality within past year, or history of suicide attempt in past 2 years
5. Any history of severe past drug dependence determined by the MINI (i.e., a focus of clinical attention or a cause of substantial social or occupational difficulty)
6. Concurrent excessive substance abuse and/or history of excessive substance use within 6 months at P.I discretion/judgment
7. Use of any prescribed benzodiazepine
8. Any unstable medical or neurological condition; clinically significant medical abnormalities such as cardiovascular abnormalities, and any chronic condition of the central nervous system
9. Any psychotropic medication usage not approved by P.I.
10. Known nonresponse to MPH treatment
11. History of allergic reaction or sensitivity to MPH
12. Female of childbearing age, who are breastfeeding, pregnant, planning to be pregnant or men planning to make a woman pregnant during the study or for one-month post study
13. PI/clinician discretion

### *5.1.3 Vulnerable Subjects*

We do not plan to enroll any subject in vulnerable population.

### *5.1.4 Strategies for Recruitment and Retention*

We plan to enroll approximately 30 subjects out of which we anticipate 10 will screen fail, 20 will initiate Azstarys treatment, and 15 will complete the study.

We will advertise within and outside New York Langone Medical Center. We use iConnect through EPIC to help identify subjects. There are print advertisements created and approved to help with recruitment on Studykik.

The Phone Script will be used to describe the study to potential subjects. We will then use the prescreen to evaluate eligibility. Trained and qualified research staff will conduct prescreen in a private location and ask potential subject if they are in an area where they can talk about their mental and physical health freely. If they are not in a secure location, prescreen can be conducted at another time agreeable to the subject or a redcap link can be sent instead which they will complete at their convenience.

Research Staff will conduct the prescreen interview (phone/redcap) and review the collected data with the PI at weekly team meetings. If potentially eligible, research staff will schedule the potential subject for the study specific screening visit. The pre-screening interview procedures collect the minimum amount of PHI necessary to determine study eligibility. Names, dates, phone numbers, and email are required to determine eligibility, contact participants regarding their eligibility status after consult with study clinicians, and to facilitate re-contact for future research purposes (optional). All data is collected though secure mechanisms, such as phone, WebEx and REDCap.

Potential participants will be asked whether they would like their information retained so they can be contacted for future research purposes. Study personnel administering the pre-screening interview will document opt-in / opt-out status in a restricted tracking log. If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858. Information collected from participants who opt out of future contact will be destroyed once the pre-screening interview has ended.

Identifiers from the pre-screen will be destroyed if the participant is not eligible for a screening visit unless the participant authorizes saving their information for contact regarding future research opportunities.

Data for eligible participants will be coded with a unique identifier and stored securely as described in the protocol.

This study will accept patient referrals from other clinicians if the patients have given their treating physician permission to allow their contact information to be shared with the study team. Patients will be contacted using the methods described above.

### *5.1.5 Informed Consent Process*

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The

investigator and/or designee will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their health care provider, family or friends prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

**REMOTE**
A link to REDCap will be emailed to potential subjects after clearing the screen. If the potential subject does not want to undergo remote consent or has trouble with the remote consenting procedures, they will be consented in person (see section below).

For those who are willing and able to undergo remote consent, the research staff will schedule a Webex meeting with the subject. During the Webex meeting the research staff will explain details of the study including the risks and benefits while sharing screen of the inform consent and asking page by page if subject understands and has any questions. Once the subject is fully informed and does not have any questions, they will be asked to sign the informed consent via REDCap. Once the study staff has completed the informed consent process and the subject has signed the consent, the subject can now proceed with the rest of the screening procedures.

The REDCap eConsent link will be submitted to the IRB for review in Research Navigator via Modification before use in the study. Language consistency with the IRB-approved consent will be reviewed and approved by the IRB before use.

**IN PERSON**
Potential subjects who are unwilling or unable to undergo remote consenting procedures will be scheduled for an in person-screening visit. Subjects will be provided a copy of the ICF in person. The research staff will assist the subject in person how to use the WebEx feature on their phone or laptop for future visits with the study doctor.

### *5.1.6 Duration of Study Participation*
Subjects participation in the study will last approximately 8 weeks.

### *5.1.7 Total Number of Participants and Sites*
This is an investigator-initiated study. NYU is the only site. Recruitment will end when approximately 30 participants are enrolled/signed consent. We expect approximately 30 participants will be enrolled in order to produce 15 evaluable participants that reach end of treatment W5 V6.

## *5.2. Participant Withdrawal or Termination*

### 5.2.1. Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Patients will be withdrawn if, in the opinion of the study doctor, it is no longer safe for the patient to participate in the study. We can get verbal permission to follow-up with the patient in the event they suffer adverse events. We will document three attempts to contact the patient via phone. If unable to contact, we will send the patient a certified letter.
- The subjects who experience ≥30% change in their total AISRS-expanded;(18-item only) scores post-two-week observation stabilization period; Week 2 Visit 3

Subjects will enter the two-week observation stabilization period of the study, where they will not take any ADHD medications. If they were taking ADHD medications, they are asked to stop. If they are newly diagnosed with ADHD, they are asked not to start any ADHD medications.

Subjects who experience a greater than a 30% change in their total AISRS-expanded (18-item only) scores post-two-week observation period; Week 2 Visit 3. are discontinued from the study. We anticipate that, based on the literature, 10% or fewer of patients will be discontinued and that the overall discontinuation rate in the trial will be 20%.

Subjects who experience an equal or greater than 30% change in their total AISRS-expanded (18 –item only) scores from Week 0 Visit 1 baseline to Week 2 Visit 3 (Post-Two-week Stabilization Period, start of Azstarys Treatment) will be given ADHD Program Referral list and diagnostic letter. Those that did not have an equal/greater 30% change in their AISRS-expanded (18 –item only) were continued to open-label Azstarys.

### 5.2.2. Handling of Participant Withdrawals or Termination

Patients can withdraw or take back their permission to use and share their health information at any time. When the patient withdraws their permission, they will not be able to take back information that has already been used or shared with others. In order to withdraw their permission from the study, patients must send a written notice to the principal investigator for the study noted on page one of their consent form. If patient withdraws their permission, he/she will not be able to stay in this study.

Patients will be withdrawn if, in the opinion of the study doctor, it is no longer safe for the patient to participate in the study. We can get permission to follow-up with the patient in the event they suffer adverse events. We will document three attempts to contact the patient via phone and [safe] email. If unable to contact, we will send the patient a certified letter.

These are the possible reasons for termination from the study:

- Adverse events
- Lack of efficacy
- Lost to follow-up

- Pregnancy
- Withdrawal by subject
- Noncompliance
- Protocol violation
- Physician discretion

5.2.3 **Premature Termination or Suspension of Study**
This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Corium LLC. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Corium LLC, IRB and/or FDA.

## 6. Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention: AZSTARYS (serdexmethylphenidate and dexmethylphenidate) capsules, for oral use, CII [controlled substance]

### *6.1. Study Agent(s) and Control Description*
**AZSTARYS** (serdexmethylphenidate and dexmethylphenidate) capsules, for oral use, CII [controlled substance] is a recently approved ADHD product (Azstarys) containing a molar ratio of 70% serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), and 30% d-MPH HCl. SDX, a Schedule II controlled substance, is pharmacologically inactive until gradually converted to active d-MPH in the lower intestinal tract.

Subjects will be pick up Azstarys capsules (serdexmethylphenidate/dexmethylphenidate): 39.2 mg/7.8 mg, 52.3 mg/10.4 mg from Turtle Bay Pharmacy.

**Azstarys**
39.2 mg/7.8 mg Capsules – dark blue cap/grey body, imprinted with “429” on cap and “KP415” on the body
52.3 mg/10.4 mg Capsules – orange cap/grey body, imprinted with “5612” on cap and “KP415” on the body

### 6.1.1. Acquisition
Azstarys will be prescribed by Dr Adler or another study doctor. Subjects will acquire study medication from Turtle Bay Pharmacy, located at 901 2nd Ave, New York, NY, United States, New York (212) 752-5151.

Subject will purchase the Azstarys medication with NYU ClinCard / Mastercard. The cost for one week (7 pills) of Azstarys is $120. The full amount of pharmacy cost will be added to the ClinCard after Dr Adler sees each patient and reports the subject is eligible for dispensation.

After treatment with Azstarys and completion of study, if requested by subject, there are medication saving opportunities. Subjects wanting to continue Azstarys though their own non-study doctors can find money savings coupons at the Azstarys support site. https://azstarys.com/savings-and-support.

**6.1.2. Formulation, Appearance, Packaging, and Labeling** Azstarys will be stored and dispensed per FDA standards (CFR - Code of Federal Regulations Title 21).

Turtle Bay Pharmacy is located at 901 2nd Ave, New York, NY, United States, New York (phone: 212-752-5151).

**6.1.3. Product Storage and Stability**
Azstarys will be stored and dispensed from the local pharmacy. They will store the drug per standard procedures for controlled substances (e.g., protect from moisture, dispense in tight container).

**6.1.4. Preparation**
Turtle Bay Pharmacy will receive Azstarys in bulk stock bottles at the starting dose of 39.2 mg serd-mph/7.8 mg d-mph and 52.3 mg serd-mph/10.4 mg d-mph. Pharmacy will dispense per *their standard operating procedure (SOP).*

**6.1.5. Dosing and Administration**
After a two-week, observation stabilization period, all subjects will receive three weeks of treatment with Azstarys (39.2 mg serd-mph/7.8 mg d-mph–) up to 52.3 mg serd-mph/10.4 mg /day.

The purpose of having a two-week observation period is to exclude subjects, who have highly variable ADHD in order to assess if their improvement is from changes in ADHD or from medication effects, This would limit the exposure of these participants to unnecessary research procedures.

**6.1.6. Route of Administration**
Subjects will take medication by mouth in the morning. Subjects take Azstarys capsule at 7am +/- 30 mins once a day in the morning. Azstarys can be taken with or without food. Subjects are asked to take Azstarys capsule whole in the morning

**6.1.7. Starting Dose and Dose Escalation Schedule**
During the two-week observation stabilization, medication is not dispensed; subjects are required not to take any medication for ADHD. If newly diagnosed, subject not to start any medication for ADHD.

During Azstarys treatment (three weeks), open-label Azstarys will be dispensed at a dose of 39.2 mg serd-mph/7.8 mg d-mph/day at Week 2 Visit 3, Initiation Dose - Post-Two-week Observation Stabilization.

Subjects are titrated up (in the judgment of the investigator) up to 52.3 mg serd-mph/10.4 mg d-mph/day based upon clinical response and tolerability for Week 3 visit 4. Then they will be locked at Week 4 visit 5 and holding at that dose from (W4 V5) of up to up to 52.3 mg serd-mph/10.4 mg d-mph at (W5 V6). At Week 5 Visit 6 there is no dispensation of Azstarys.

Patients a seen weekly throughout the trial; except for Week 1 Visit 3 and Week 6 Visit 7 telephone check-in for safety measures.

Dispensation

- W2 V3- 39.2 mg serd-mph/7.8 mg d-mph
- W3 V4- up to 52.3 mg serd-mph/10.4 mg d-mph
- W4 V5- up to 52.3 mg serd-mph/10.4 mg d-mph/hold dose
- W5 V6 – no dispensation

Azstarys is approved for ages 6 and up and we are within FDA approved dosing.

### 6.1.8. Dose Adjustments/Modifications/Delays

All subjects will be in an observation stabilization period / not start any meds for ADHD during this two-week period, if they have not experienced a greater than a 30% change in their total AISRS-expanded(18-item only) scores at Week 2 Visit 3 Initiation Dose; Post Observation Stabilization Period, subjects are dispensed drug Azstarys 39.2 mg serd-mph/7.8 mg d-mph. Once on Azstarys, subjects are titrated up to 52.3 mg serd-mph/10.4 mg d-mph at the Principal Investigator's discretion-pending efficacy and safety. Subjects that experience adverse events (abnormal EKG, abnormal vital signs or any AEs that are known to be associated with Azstarys) will not be eligible to start the study or if they are already in the study their dose will be held at current dosage, or they will be withdrawn from the study.

### 6.1.9. Duration of Therapy

Observation Stabilization epoch (two weeks), open-label Azstarys treatment (three weeks)

### 6.1.10. Tracking of Dose

Study team will review pharmacy Standard Operating Procedures for dispensing of Azstarys, there will be a two-week observation stabilization lead-in and then a three-week open-label treatment with Azstarys

The two- week observation stabilization period starts at the end of screening visit after subject consents, subjects are in observation stabilization and will not start any medications for ADHD. At the end of the following week; Week 1 Visit 2 they are seen remotely via telephone call to assess compliance and safety. Subjects return to clinic in one week and dispensed initial dose of Azstarys 39.2 mg serd-mph/7.8 mg d-mph/day with titration weekly up to 52.3 mg serd-mph/10.4 mg d-mph based on clinical response and potential adverse events reported and observed at each visit.

After the end of observation stabilization period and start of Azstarys period, Patients will be seen weekly throughout the trial. Participants are given dosing instructions and will return to the clinic weekly for review of compliance. Subjects must have over 80% compliance to continue in the study.

Compliance will be tracked by counting the remaining pills in the bottle at each visit in presence of patient. Subjects are reminded to bring back their pills and empty bottles at each visit. Subjects are instructed that noncompliance without the doctor's approval would be dangerous. It may warrant reevaluation of their continued participation.

Turtle Bay Pharmacy will handle returns as per their SOPs. The research team will not be involved in any returns only documenting medication compliance. Pharmacy will also dispense study

medication to the subjects weekly. There will be medication compliance check at each visit. Subjects are asked to bring their medication to the visit and research staff will count number of pills left in the bottle. Note: we are not taking returns. If there are pills in the bottle the progress note will indicate number of pills not taken and the bottle with the extra pills is retained by the subject.

### *6.2. Study Agent Accountability Procedures*

There is no plan for an assignment/randomization method after screening; all eligible patients will go through observation stabilization of current ADHD medications and not start any for the two weeks. The two weeks of observation stabilization-stabilization period is followed by three weeks of Open-Label Azstarys. The Week W1 V2, subjects are seen remotely via telephone call to assess compliance and safety. At the start of the second week, (W2 V3), subjects are dispensed active Azstarys 39.2 mg serd-mph/7.8 mg d-mph/day with titration weekly up to 52.3 mg serd-mph/10.4 mg d-mph based on clinical response (AISRS) and potential adverse events reported and observed at each visit. There is no dispensation for W5 V6 End of Study Visit.

Corium LLC will provide Turtle Bay Pharmacy the Azstarys. Dr. Adler will prescribe weekly doses for subjects to pick up at the local pharmacy. Subjects will pay for the Azstarys themselves from a prepaid card (clinicard) given to them by the study team.

The Azstarys product will come directly from Corium LLC commercial supply to Turtle Bay Pharmacy. Once the first subject is consented, Turtle Bay Pharmacy will order one stock bottle of Azstarys that will arrive overnight. The Azstarys medication will be on site ready for dispensation.

Azstarys will be labeled according to the standard operating procedures of Turtle Bay Pharmacy. Pharmacy will reach out to Corium LLC for resupply. Expiry date will be included in the stock bottles. If expiry date changes at any time, Corium LLC will send us documentation regarding product safety and change of the expiry date

Pharmacy will complete accountability logs per their SOPS. Additionally, research team will document subject dosages, compliance in source documentation records. The retail pharmacy will have their label compliant with all dispensing labeling requirement.

#### 6.2.1. Procedures for Training of Clinicians on Procedural Intervention

All team member conducting any study procedure will have certification and training to conduct the procedures and have been deemed competent to perform the procedure per the study principal investigator per the delegation logs.

***Study Flow for Hybrid Study Visits***

**During Screening/Baseline Visit (Week -3-0)**

**Screening:**

The screening visit can be conducted hybrid and completed in two parts: remote and in-clinic. The remote screening period can last up to 28 days. It takes time to schedule some of the parts of this study. In addition, medical records may take time to acquire. Subjects will be asked to come to the clinic for physical, EKG, vital signs, urine samples.

During the remote portion of the screening visit, informed consent will be obtained via REDCap link during a WebEx consultation meeting with study staff reviewing the inform consent process of explaining the study and all risks and benefits.

The informed consent is sent prior to the screening WebEx meeting to allow the subject time to discuss with primary care physician or family. After the consent process is complete, research staff with continue with the screening study visit. Study staff will review the inclusion and exclusion criteria, collect demographics, medical and psychiatric history, prior and concomitant medications, and confirm no co-morbid psychiatric disorders using the MINI and C-SSRS. Principal Investigator or trained clinician will confirm the ADHD diagnosis and current ADHD symptoms via the ACDS v 1.2, CGI-S, AISRS-expanded (18 item score). Subjects will receive REDCap link to complete a self-assessment of their ADHD symptoms, expanded ASRS. The screening/ baseline visit can last 21 -28 days.

During the in-clinic portion, credentialed study staff will conduct a physical examination, medical review of systems, vital signs (pulse and blood pressure), collect urine sample for urine drug screen / urine pregnancy and electrocardiogram (ECG/EKG). All or some of these clinical examinations can be waived from the screening process if subject can provide records from their primary care doctor done within the past year and the principal investigator reviews and approves them.

**Baseline:**
Principal investigator or co-investigator will review all eligibility criteria, inclusive of inclusion and exclusion criteria. Any assessments not done during screening will be done before baseline procedures. Study staff will review any new concomitant medications or adverse events and clinician will conduct a C-SSRS. Eligible participant will be given information regarding observation stabilization period and will be instructed on the TASS and AMSES.

*After all screening/baseline, procedures are completed and the principal investigator decides subject is eligible to continue in the study, subject will move to the two-week stabilization-observation phase.*

*If subject is not eligible, their participation in the study is complete and they will receive the ADHD Referral list that will list providers in the community.*

Eligible participants will begin the two-week observation stabilization period. Participants will be instructed to an observation stabilization of current medication and not to start any new ADHD medication, if newly diagnosed.

**Two-week Stabilization observation stabilization Phase (Week 1, Visit 2) Telephone check**
Research staff will review completion of procedures and assessments from Week 0 V1. Research staff will call subject at the end of the first week to review any changes in concomitant medications and adverse events (AE), if any, will be noted. Research staff will call subject for safety assessments

**Open-label Azstarys Treatment Phase (Week 2, Visit 3 Hybrid visit)**
Eligible participants will return to the study site for study assessments and dispensation of Azstarys. The following procedures and assessments will be performed during Visit 3: vital signs, urine pregnancy dipstick (for females of childbearing potential), and urine toxicology dipstick, AISRS, Expanded ASRS, CGI-S, Concomitant medications and adverse events (AE), if any, will be noted. Participants with ≥30% change in total AISRS-expanded (18-item) scores from Visit 1 to Visit 3 will be discontinued from the study. At the end of Visit 3, if subject does not have a ≥30% change

in total AISRS-expanded (18-item only) scores. Study doctor will check istop and write a prescription to local pharmacy, who will dispense to eligible participants initial dose schedule of Azstarys. Subjects will be instructed to take Azstarys 39.2mg serdmph/7.8d-mph the next morning, and to continue to take IP once daily in the morning. The TASS/AMES will be done three times on days of administration V3, V4, V5 and V6.

**Treatment Phase (Week 3-5, Visit 4-6)**

**Azstarys Flexible Dose (Week 3, Visit 4 Hybrid visit)**
Participants will return to the study site every 7 days during the AZSTARYS treatment phase. The following procedures and assessments may be performed at Visits 4-6: vital signs, AISRS-expanded, CGI-S, TASS/AMES, Expanded ASRS, C-SSRS, Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Subjects will receive a re-supply of study medication at the end of every visit during the AZSTARYS treatment phase. The dose of AZSTARYS can be clinically adjusted (in the judgement of the investigator) starting at Visit 4 based upon clinical response and side effects, up to a maximal dose of 52.3/10.4mg/day. Medication compliance will be performed at V4, V5, and V6. Participants must take 80% of the prescribed doses of study medication in order to be considered compliant. Subject will also complete their Brief A and expanded ASRS via remote links. Research staff will check for completion of links. The TASS/AMES will be done three times on days of administration V3, V4, V5 and V6. The recommended dosing is at 7am +/- 1 hour. The first TASS/AMES is done at half hour to one-hour post dose (7:30 to 8 am +/- 1 hour), the second TASS/AMES is done 4 hours post dose (11am +/- 1 hour) and the third TASS is done 12 hours post dose (7 pm+/- 1 hour). All TASS and AMSES administrations are completed three times daily on assessment visit day. Brief A and ASRS will be collected either remote or in clinic once a week.

**Azstarys Flexible Dose (Week 4, Visit 5 Hybrid visit**) is the same as Week 3 Visit 4.

**Azstarys Withdrawal/End of Treatment (Visit 6)**
Participants will return to the study site for Visit 6 within 7 days of Visit 5. The following procedures and assessments will be performed at Visit 6: vital signs, AISRS-expanded, CGI-S, TASS/AMES, Expanded ASRS, C-SSRS and BRIEF-A. Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants should report taking at least 80% of the prescribed study medication in order to be considered compliant. The TASS will be done three times on days of administration. The recommended dosing is at 7 am +/- 1 hour. The first TASS is done at half hour to one-hour post dose (7:30 to 8 am +/- 1 hour), the second TASS is done 4 hours post dose (11am +/- 1 hour) and the third TASS is done 12 hours post dose (7 pm+/- 1 hour).

Participants will be given the Adult ADHD Referral list to help with the transitioning into treatment as usual. Those that complete the study, if requested will receive a participation letter that would include their diagnosis of ADHD. If requested at this last visit, the study doctor will provide subject a prescription for one month of off study Azstarys. We can help with paper work for insurance authorization. Subject is no longer in the study and will cover cost and copayments if any of Open Label Azstarys.

**GCP FOLLOWUP: Telephone call (visit 7)**
Study staff will make a phone call to the participant within 7 days of Visit 6 as part of good clinical practices. Patient will be asked about how they are feeling. Did they transition into treatment as usual? Concomitant medications and AEs, if any, will be noted.

**Unscheduled Visits approved by the principal investigator will be documented in source documents. These visits would be for safety labs/EKGs, early withdrawal or missed visits.*

### *6.3. Study Procedures / Evaluations*

Description of the Measures are listed below, organized by domain. The assessment schedule is summarized in the schedule of events table located at the end of this protocol. These measures will be administered by a trained licensed psychologist, nurse, or MD.

***Optional:*** Participants will be invited to complete the audio / video consent form if they consent to having their clinical interviews video and / or audio-recorded to ensure clinical adherence and to monitor inter-rater reliability. The recordings will be stored on an MCIT-managed shared drive, with no identifiers. Subjects will be asked to use a pseudo name.

**6.3.1.1.** Clinical Interview: ADHD diagnosis and severity will be assessed with Adult ADHD Clinical Diagnostic Scale-Version 1.2 (ACDS v1.2), a semi-structured diagnostic interview widely used in adult ADHD studies to evaluate both childhood and adult symptoms of ADHD, the Clinical Global Impression Scale (CGI-S), a widely used clinician-rated measure of global ADHD impairment and severity and Mini International Neuropsychiatric Interview (MINI) a short psychiatric interview.

**6.3.1.2.** Mood and ADHD: ADHD symptoms will also be measured using the Adult ADHD Investigator Symptom Rating Scale (AISRS) and the 18-question Attention Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 (DSM-5 ASRS). Severity of executive function will be assessed via the Behavioral Rating Inventory of Executive Function- Adult version (BRIEF-A) self-report. Suicidality and suicidal ideation will be assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS).

**6.3.1.3.** Efficacy: To evaluate the efficacy of Azstarys, we will explore correlations of TASS and AMES ratings with AISRS expanded (18 item score) ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day. We will assess 30% change in BRIEF-A measures. Furthermore, we will examine potential differential effects of Azstarys in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF-A ≥65 at baseline). We will also examine correlations in self- report of ADHD symptoms on the ASRS versus clinician report of ADHD symptoms on the AISRS, and also changes in self-report measures of executive function and emotional dyscontrol on the AISRS-expanded and ASRS-expanded versus these measures on the BRIEF-A.

**Assessments**

The Adult ADHD Investigator Symptom Rating Scale (AISRS) is an 18-item scale, clinician-administered semi-structured interview methodology developed to evaluate treatment responses (Spencer et al., 2010). The measure contains prompts and stem questions designed to capture the Diagnostic and Statistical Manual of Mental Disorders (DSM) symptoms of the disorder ADHD as they present in adulthood. Based on the responses from the patient, the administering clinicians rate the symptom severity as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. The scale has been used and validated many times in a variety of clinical drug trials (Adler & Gorny, 2015; Adler, Zimmerman, Starr, Silber, Palumbo, Orman & Spencer 2011; Goodman et al., 2017; Spencer et al., 2010). The AISRS has been expanded to include additional symptoms intended to assess executive function deficits (EFDs; nine items) and emotional dyscontrol (EC; four items). EFDs are deficiencies

of high order cognitive processes, such as self-control, self-regulation, and ability to prioritize and to plan multiple tasks. EC includes symptoms of mood lability, irritability, and emotional over-reactivity. These prompts have been written for the AISRS to help guide the rater to explore the full manifestations of symptoms in an adult with ADHD. (Silverstein et al. (2018)), once expanded the AISRS is a 34-item scale administered by a trained licensed psychologist, nurse, or MD.

The Adult ADHD Self-Report Scale (ASRS) Symptom Checklist (Expanded) is a self-report that presents the 18 DSM ADHD symptoms in adult context and rated on a frequency basis. It was developed by the World Health Organization (WHO) work group on adult ADHD and comprises an 18-item Symptom Checklist (corresponding to the 18 symptoms found in the DSM) and a six-item screener (items extracted from the symptom checklist) to help identify adults at risk of ADHD (Kessler et al., 2005; Ustun et al., 2017). The Screener and the Symptom Checklist use a 5-point Likert-type scale to rate ADHD symptoms (0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = very often). Depending on the question, "sometimes," "often," or "very often" suggests clinical impairment for that specific item. The ASRS v1.1 Symptom Checklist is designed to provide clinicians with an inventory of adult ADHD symptoms as the first part of a diagnostic evaluation or to be used in monitoring treatment response (Adler, Shaw, & Alperin, 2015; Adler et al., 2006). The ASRS has been expanded to include additional symptoms intended to assess executive function deficits (EFDs; nine items) and emotional dyscontrol (EC; four items). EFDs are deficiencies of high order cognitive processes, such as self-control, self-regulation, and ability to prioritize and to plan multiple tasks. EC includes symptoms of mood lability, irritability, and emotional overreactivity. (Silverstein et al 2018) The subject will answer 31 questions. Of those 31, 18 of the questions pertain to the 18 DSM-5 ADHD symptoms (ADHD Symptoms). The expanded version includes 9 additional items that assess Executive Function Deficits, and 4 items that assess Emotional Dyscontrol (Silverstein et al. (2018)). The assessment is self-administered and completed by subject.

The TASS scale is an 18-item scale matching the 18 DSM ADHD symptoms, with language changed to allow self-report ratings and assessment of ADHD symptoms throughout the day. It has been validated and used as a measure of change throughout the day in the Spencer et al. (2008). The research staff will administer this scale.

Smoothness of Effect Scale (AMSES) Adult ADHD Medication Smoothness of Effect Scale (AMSES) is a 6-item, frequency-based, self-report scale that was recently developed to assess the consistency and duration of effect of ADHD medication throughout the day (L. A. Adler, Lynch, Shaw, et al., 2017). The research staff will administer this scale.

The Clinical Global Impression Severity (CGI-S) scale is a validated, highly utilized measure of impairment in studies of adult ADHD and has been employed in prior ADHD studies. It is an observer-rated scale that will be used to measure symptom severity. The investigator or rater will respond to the following question: "Considering your total clinical experience with adult ADHD, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill;6 = severely ill; and 7 = among the most extremely ill patients. (Busner J, Targum SD. (2007)) The scale is administered by a trained licensed psychologist, nurse, or MD.

The BRIEF-A is a 75 item self-report scale which is highly validated and normed; it has three major scales (GEC, metacognition, behavioral regulation scales and several subscales – see stats section) – it is log transformed so scores >=65 are considered significant as they are >= 1.5 SDs above the population mean. The scale has been used as a measure of executive function in several ADHD

clinical trials (Vyvanse and Mixed Amphetamine Salts: Adler LA et al. 2014; atomoxetine: Adler LA et al. (2014)). This scale is self-administered; the subject will complete.

Study procedures and evaluations to be done as part of the study. All procedures listed here should be specific to the study and not part of standard clinical care.
Medical research staff.

- Medical history will be acquired at prescreen and screening (mental and physical medical history will be obtained by interview and/or from medical records if patient has a primary care doctor and agrees to all us to contact pcp for medical records after signing a medical release of medical information after consenting.)
- Medication history (current and past medication taken should be included; prescription and over-the-counter medications). Assessment of eligibility should include a review of permitted and prohibited medications.
- Physical examination; review of organ systems and vital signs will be done at screening visit.
- Echocardiogram will be done at screening/baseline visit.
- Urine for pregnancy (for female subjects of childbearing age) and drug screen will be done
- Assessment of study agent adherence via compliance questions.
- Administration of questionnaires or other instruments for patient-reported outcomes, either in the clinic using hard copy questionnaires or using redcap links.

### 6.3.2. Standard of Care Study Procedures

There are no procedures being conducted as regular standard of care.

### 6.3.3. Clinical Laboratory Evaluations

Pregnancy test and urine toxicology will be conducted prior to dosing. Tests will be conducted using a urine dipstick or urine cup.

Noble Medical 19525 Janacek Court, Suite 104 Brookfield, WI 53045 877-836-5713 info@noblemedical.com John Hlavachek (john@noblemedical.com)

1. NMCup-12-01-BT12 PanelCup, CLIAWaived, AMP500/BAR300/BUP10/BZO300/COC150/MET500/MDMA500/MTD300/OPI300/OXY100/ TCA1000/THC50
2. hCG Women Pregnancy Strip, 25mIU/ml, Sample: urine. 50 strips each box CLIA Waived

*Note: Urine Drug Screen and Pregnancy tests are required within 24 hours of study intervention and results available prior to administration of study product Azstarys*

## *6.4. Study Schedule*

### 6.4.1. Screening

**Prescreen**

Subjects will be prescreened with an IRB-approved script and prescreen form. This prescreen process will take place either over the telephone, or subjects can complete the pre-screen through a redcap link if they prefer. The prescreen will take about 20 minutes to conduct and decreases the burden of having subjects come into the clinic to easily screen fail for age, weight or prior medications. The prescreen form of the prescreen failures are destroyed, unless subject wants to opt

in for future study. Those who pass prescreen are given an appointment for the hybrid Screening/Baseline remote/in clinic visit. Subjects are able to opt-in or opt out.

**During Screening/Baseline Visit (Week -3-0) Hybrid both remote or in clinic.**
Research Staff will conduct the Informed consent process per clinic standard operating procedures and Inform Consent will be obtained at the screening visit before any study procedures are conducted. Study staff will review the inclusion and exclusion criteria, collect demographics, medical and psychiatric history via the MINI, prior and concomitant medications, vital signs (pulse and blood pressure) and confirm the ADHD diagnosis via the ACDS v 1.2 and AISRS-expanded(18 item score). Study staff will conduct a physical examination, medical review of systems, and electrocardiogram (ECG). A urine sample will be collected for urine drug screen to ensure no drugs of abuse. Subjects can opt out of some of these tests if they can produce medical records from Primary Care Physician documenting safety tests completed within one year and the Principal Investigator can determine eligibility based on these tests and study screening procedures. Participant will complete self-report forms.

**Screening/Baseline Visit (Week 0, Visit 1 Day -28 to 0)**

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Review inclusion/exclusion criteria.
- Obtain urine for toxicology test.
- Collect Vital Signs
- Confirm Prior and Con meds
- Assess any changes in healthy; New AEs
- CSSRS Assessed
- Provide subject with instructions for dosing, 7am +/- 1 hour and the need to answer questionnaires 30mins after dosing, 4 hours after dosing and 12 hours after dosing.
- Provide participants with a copy of ICF and ClinCard compensation.
- Schedule study visits for participants who are eligible and available for the duration of the study.

**6.4.1.1. Week 1 Visit 2** (Two-week Stabilization Observation period) - telephone check.
Research staff will call subject for a safety check and compliance with study medication regimen.

- Confirm Prior and Con meds
- Assess any changes in healthy; New AEs
- C-SSRS

### 6.4.2. Intermediate Visits (Post-2-week stabilization observation stabilization)

**Treatment Phase: Week 2 Visit 3, Week 3 Visit 4, Week 4 Visit 5 Week 5 Visit 6.** Visits 3-6 are Hybrid Visits.

Post-2-week observation stabilization period, subjects if eligible will continue to treatment period with Azstarys. Week 2 Visit 3 Initiation Dose. Patients who do not have a change of 30% or greater in their ADHD symptoms will continue in the study and will be dispensed Azstarys to be taken the next morning.

Participants will return to the study site every 7 days during the Azstarys treatment phase. The following procedures and assessments may be performed at Visits 3-6: vital signs, AISRS expanded, CGI-S, TASS/AMES, Expanded ASRS, C-SSRS and BRIEF-A.

Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants must take 80% of the prescribed doses of study medication in order to be considered compliant.

The TASS/AMSES will be done three times on days of administration. The recommended dosing is at 7 am +/- 1 hour. The first TASS/AMSES is done at half hour to one-hour post dose (7:30 to 8 am +/- 1 hour), the second TASS/AMSES is done 4 hours post dose (11 am +/- 1 hour) and the third TASS is done 12 hours post dose (7pm+/- 1 hour). All TASS/AMSES administrations will be via telephone.

During Azstarys treatment, participants will receive re-supply of study medication at the end of each visit. Subjects will go to Turtle Bay Pharmacy to pick up their medication at V3, V4, and V5.

The dose is initiated at a dose of 39.2 mg serd-mph/7.8 mg d-mph/day at Visit 3, titrated up (in the judgment of the investigator) up to 52.3 mg serd-mph/10.4 mg d-mph/day based upon clinical response and tolerability for visit 4, locked at visit 4, and holding at the dose from visit 5 of up to up to 52.3 mg serd-mph/10.4 mg d-mph at V6. Participants will be instructed to bring medication bottle at each study visit.

**Visit 3-6 (Days+/-1)**

- Record adverse events and prior/con meds as reported by participant or observed by investigator.
- Record vital signs, results of Blood Pressure and Pulse.
- Research Staff to review medication compliance with subject- ensure 80% compliance.
- Clinician to conduct the AISRS-expanded, CGI and CSSRS
- Patient will complete the self-questionnaires ASRS-expanded, Brief -A
- Clinician to write order for IP Azstarys after assessing continued eligibility
- Turtle Bay Pharmacy to dispense Azstarys, in accordance with specify procedures, instructions provided to participants.
- Record participant's adherence to treatment program.
- Provide subject with instructions for dosing, the next morning at 7am +/- 1 hour and the need to answer questionnaires 30mins after dosing, 4 hours after dosing and 12 hours after dosing.
- If subject miss appointment by one day they can have their appointment the following day early in the morning and be dispensed to take meds that morning before 12 noon. This is only done in unavoidable circumstances with P.I. permission. The deviation would be documented.

### 6.4.3. Final Study Visit

**Withdrawal/End of Treatment (Visit 6)**

This hybrid visit will be conducted for subjects who have completed their treatment at Visit 6, subjects who wish early withdrawal or subjects whom the investigator deems participation is no longer effective or safe.

Participants will return to the study site for Visit 6 within 7 days of Visit 5. The following procedures and assessments will be performed at Visit 6: vital signs, AISRS-expanded, CGI-S, TASS, AMSES, Expanded ASRS, C-SSRS and BRIEF-A.

Concomitant medications and AEs, if any, will be noted and drug accountability and compliance will be performed. Participants should report taking at least 80% of the prescribed study medication in order to be considered compliant.

The TASS/AMES will be done three times this day. The recommended dosing is at 7 am +/- 1 hour. The first TASS is done at half hour to one-hour post dose (7:30 to 8 am +/- 1 hour), the second TASS is done 4 hours post dose (11am +/- 1 hour) and the third TASS is done 12 hours post dose (7pm+/- 1 hour).

Once all assessments and procedures for this visit are completed, participants will be given the Adult ADHD Referral list to help with the transitioning into treatment as usual.

They are given compensation for last time per ClinCard after the visit is completed.

Those that complete the study, and at the principal investigator's discretion, as a curtesy, can request and receive a letter stating their diagnosis and their participation in the study.

Good Clinical Practice phone call is conducted 7 days after Week 5 Visit 6. Research staff will call subject to ensure all adverse events have resolved and that they have transitioned into treatment as usual.

#### 6.4.4. Withdrawal/Early Termination Visit

Patients can withdraw or take back their permission to use and share his/her health information at any time. When the patient withdraws their permission, they will not be able to take back information that has already been used or shared with others. In order to withdraw their permission from the study, patients must send a written notice to the principal investigator for the study noted on page one of their consent form. If patient withdraws their permission, he/she will not be able to stay in this study.

Patients will be withdrawn if, in the opinion of the study doctor, it is no longer safe for the patient to participate in the study. We can get verbal permission to follow-up with the patient in the event they suffer adverse events. We will document three attempts to contact the patient via phone. If unable to contact, we will send the patient a certified letter. (Attachment)

#### 6.4.5. Unscheduled Visit

Unscheduled Visits approved by the principal investigator will be documented in source documents. These visits would be for safety labs/EKGs, early withdrawal or missed visits.

### *6.5. Concomitant Medications, Treatments, and Procedures*

Prior and Concomitant Therapy will be followed throughout the study. Any medication or non-pharmacological therapy that is taken by or administered to the subject at any point during the

course of the study must be recorded in the case report form (CRF). Subjects will be encouraged to talk with the research team at each visit to document any new medicines, vitamins, and herbal supplements. Azstarys may affect the way other medicines work and other medicines may affect how Azstarys works. Taking Azstarys with other medicines or supplements can cause serious side effects.

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

### 6.5.1. Precautionary Medications, Treatments, and Procedures

Contraindications for participation in this study are:

1. Known hypersensitivity to serdexmethylphenidate, methylphenidate, or product components.
2. Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days.

## *6.6. Prohibited Medications, Treatments, and Procedures*

Subjects taking stimulant or non-stimulant medications for the treatment of ADHD during screening will be washed out for a period equivalent to 5 half-lives of the medication prior to baseline evaluations. This would be approximately 7-21 days per investigator's decision.

Use of any of the following medications is not permitted during the study; unless approved by investigator and documented in source.

1. Antidepressant prescription medication (e.g., paroxetine, sertraline, venlafaxine, monoamine oxidase [MAO] blocker, tricyclic, etc.) and St. John's Wort.
2. Anticonvulsant medications (e.g., phenytoin, carbamazepine, lamotrigine, valproic acid, etc.) and antipsychotic medication.
3. Sedating antihistamines (e.g., doxilamine succinate, diphenhydramine) for use in sedation or aiding with sleep. Subjects' routinely using sedating antihistamines for seasonal allergies will be required to switch to non-sedating alternatives for the duration of the study, unless otherwise contraindicated.
4. Other medications or supplements that may interfere with the assessment of cognitive function are not permitted during the study.

Treatment with any OTC or prescribed medication will not be permitted unless discussed with and approved by the study medical monitor/Corium LLC/investigator.

Subjects will be screened for drug and alcohol abuse during the prescreen phase. Subjects are instructed on the dangers of drinking alcohol or engaging in drug use during treatment with Azstarys. They will be warned not to use Azstarys for any other condition except the condition for this study: ADHD. Subjects will be instructed and reminded at each study visit not to share this medication with other people, even if they have ADHD. They will be reminded that the Azstarys may harm those for who it is not prescribed for and it is against the law. Subjects will be reminded to report any adverse events or concomitant medications they are taking at each visit.

Subjects will be reminded to take their medication at 7am each morning, as the study assessments are dependent on the consumption of Azstarys at 7:00 am.

### *6.7. Participant Access to Study Agent at Study Closure*

Azstarys is FDA approved. Subjects will be instructed about CoriumCares https://azstarys.com/savings-and-support, to access if eligible, coupon savings. Which are provided by Corium LLC.

## 8. Assessment of Safety

Throughout the study, we will monitor subjects for safety and possible pregnancy. During the screening and eligibility period, we will conduct and report, if applicable clinical laboratory results, to include pregnancy testing, ECG readings and the C-SSRS (conducted as needed per clinician discretion) if there are significant clinical findings. We will monitor subjects weekly for abnormal vital signs, adverse events, and concomitant medications. All adverse events results will be tabulated in manuscripts along with significance testing using the appropriate general linear model.

Subjects will be given a pregnancy contact sheet in the event there is a pregnancy. The pregnant woman will be given a pregnancy inform consent to read and sign to allow us to follow-up with the pregnancy until terminated or full-term delivery.

Good clinical practices; we will call subjects one week after their last dose of study medication to ensure they are not experiencing any adverse events and have connected to treatment as usual in the community

### 8.1.1. Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

### 8.1.2. Definition of Serious Adverse Events (SAE)

**Serious Adverse Event**

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent

one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

### 8.1.3. Definition of Unanticipated Problems (UP)

**Unanticipated Problems Involving Risk to Subjects or Others**
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

## *8.2. Classification of an Adverse Event*

### 8.2.1. Severity of Event

All AEs will be assessed by the study clinician. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

### 8.2.2. Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (Azstarys) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

#### 8.2.3. Expectedness

Dr. Adler and Medical Monitor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

### *8.3. Time Period and Frequency for Event Assessment and Follow-Up*

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify Corium LLC any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. Corium LLC should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

### *8.4. Reporting Procedures – Notifying the IRB*

We will report any instances of unanticipated adverse events or problems with this study to the IRB immediately.

**Adverse Event**

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of a study. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significant

***Serious Adverse Event***

Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event
- All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

#### 8.4.1. Adverse Event Reporting

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document (though should be grouped under one diagnosis). All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the outcome. Any serious adverse event

that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

**For Narrative Reports of Safety Events**
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

**Investigator Reporting: Notifying the Study Sponsor:** Corium LLC
The following describes events that must be reported to Corium LLC in an expedited fashion.

**Initial Report: within 24 hours:**

- The following events must be reported to Corium LLC or designee by email to dlsspvdrugsafety@eversana.com, or by eFax: (510) 903-4260: with copy to PVOperations@coirumintil.com and coh@coriumintl.com, within 24 hours of awareness of the event:
- Unanticipated problems related to study participation.
- Serious adverse events, regardless of whether they are unexpected.

Additionally, for initial SAE notification, an FDA Form 3500A (MEDWATCH Form) must be completed by the investigator with all of the known information about the subject and event and emailed or faxed to Corium LLC, within 24 hours to CORIUM LLC Or designee.at: dlsspvdrugsafety@eversana.com, with copy to PVOperations@coirumintil.com, and:

Charles Oh MD
Chief Medical Officer at Corium, LLC
coh@coriumintl.com

11 Farnsworth Street
4th Floor
Boston, MA 02210

The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

**Follow-up report: within 48 hours:**
As a follow-up to the initial report, within the 48 hours following the awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the IRB

reporting and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse events shall be provided promptly to the study sponsor; Corium LLC or designee within 48 hours of receipt, using the same contact information as above."

**Adverse Event Reporting Period**
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 7 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any at the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

### 8.4.2. Serious Adverse Event Reporting
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Generally, any AE considered serious by the PI or Sub-investigator, or which meets the definition of an SAE included in Section 8.1.2, Definition of Serious Adverse Event must be submitted on an SAE form to the Data and Safety Monitor, who may request to receive real-time notification of all SAEs.

### 8.4.3. Unanticipated Problem Reporting
Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and Corium LLC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to Corium LLC within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the Corium LLC within 5 working days if meeting reporting criteria for RNI days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP if needed within 5 days' timeline in accordance with policy of the IR's receipt of the report of the problem from the investigator.

### 8.4.4. Reporting of Pregnancy

Throughout this study, we will monitor safety and possible pregnancy by conducting safety clinical tests during screening and eligibility period. We will collect urine pregnancy test to ensure safe participation in the study. We will report to Corium LLC and our IRB within the necessary times. See section on adverse events. In addition, we will provide pregnant women with a pregnant woman contact sheet and pregnant woman ICF requesting permission to follow pregnant women to pregnancy outcome.

## *8.5. Reporting Procedures – Notifying the Study Corium LLC*

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the Corium LLC within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study Corium LLC within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by Corium LLC and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to Corium LLC.

## *8.6. Data Safety Monitoring*

The Principal Investigator (Lenard Adler, MD) and the independent medical monitor (Donald Goff, MD) are responsible for data safety monitoring reviews.

Dr Goff is Director at Nathan Kline Institute, Marvin Stern Professor and Vice Chair for Research Department of Psychiatry NYU Langone Medical Center. Dr. Goff. Dr. Goff is board certified in psychiatry and licensed to practice medicine in the state of New York.

He and Dr Adler will review all the AEs, including those AES listed in section 2.4 of the protocol on a quarterly basis throughout the trial. Drs Adler and Goff will also be responsible to address trial-related medical questions or problems, and evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. . The summary of the outcomes of the safety reviews along with accumulated adverse events and deviations will be promptly submitted to Corium LLC as well.

A summary of the outcomes of these safety reviews along with accumulated adverse events and deviations will be submitted to the IRB as part of an annual progress report at the time of the Continuing Review submission.

### *8.7. Study Halting Rules*

The medical monitor and Principal Investigator will determine whether the study should be halted after three severe AEs with probable relationship to the study procedures are discovered. The PI or qualified designee will inform the medical monitor within 24 hours of this occurrence, cease screening and enrollment of new participants, and will provide the medical monitor with a list of AEs. The medical monitor will convene an ad hoc meeting by teleconference or in writing as soon as possible and will provide recommendations for proceeding with the study to the PI. If the medical monitor finds it is likely that the study procedures contributed to negative outcomes, they will consider solutions including protocol modifications or potentially terminating the study.

## 9. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Medical Monitor Donald Goff MD will perform monitoring for this study.
- The onsite monitoring will include all Study flow data of all enrolled subjects, adverse events, and protocol deviations. The monitoring is done yearly and throughout the study when needed.
- Memo of report is generated for Principal Investigator and is shared with the IRB.
- NYU IRB will be provided copies of monitoring reports within 7 days of visit.
- Details of clinical site monitoring may be documented in a CMP. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

## 10. Statistical Considerations

### *10.1. Statistical and Analytical Plans (SAP)*

Statistical Analysis Plan: Our primary outcome is effects on overall adult ADHD symptoms via total AISRS expanded (18 item total) Score. In secondary analyses, we will also analyze the following variables: Evaluation of ADHD subset IA and HI symptoms on AISRS-expanded, TASS 0.5 to 1 hour, 4 hours and 12 hours post dose: (total, inattentive and hyperactive-impulsive subsets) (for effects of AZSTARYS over time at different points of the day and into early evening ); expanded Adult ADHD Self Report Scale (ASRS) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets); symptoms of executive function (BRIEF-A: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor)

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the open-label as the independent variable. All analyses will use the ITT sample. For our design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for subjects who have experienced a greater than a 30% change in their total AISRS-expanded (18-item) scores during baseline in the analyses. These patients who experience ≥30% change in their total AISRS –expanded (18 items) scores during two weeks observation stabilization period will be discontinued from the protocol. We anticipate that, based on the literature, 10% or fewer of patients will have the 30% change in their AISRS-expanded (18-item only) scores from screening to end of observation stabilization period and that the overall discontinuation rate in the trial will be 20%. Changes within the day in TASS/AMES ratings 0.5 to 1-hour post dose vs. 4-hour post dose vs. 12 hours post dose will also be analyzed via the general linear regression model. Correlations between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

Exploratory Objectives: We will explore correlations of TASS/AMES ratings with AISRS-expanded ratings to examine overall ADHD ratings vs. ADHD ratings throughout the day. We will look at changes in BRIEF-A measures throughout the study. Furthermore, we will examine potential differential effects of Azstarys in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF- A >= 65 at baseline). We will also examine correlations in self-report of ADHD symptoms on the ASRS) versus clinician report of ADHD symptoms on the AISRS, and also changes in self-report measures of executive function and emotional dyscontrol on the ASRS expanded versus these measures on the BRIEF-A.

### *10.2. Description of Statistical Methods*

Our primary outcome is effects on overall adult ADHD symptoms via total Expanded AISRS (18-item only) Score, assessing executive function deficits (EFDs; nine items) and emotional dyscontrol (EC; four items). EFDs are deficiencies of high order cognitive processes, such as self-control, self-regulation, and ability to prioritize and to plan multiple tasks. EC includes symptoms of mood lability, irritability, and emotional overreactivity. These prompts have been written for the AISRS-expanded to help guide the rater to explore the full manifestations of symptoms in an adult with ADHD. (Silverstein et al 2018).

In secondary analyses, we will also analyze the following variables: Evaluation of ADHD subset IA and HI symptoms on AISRS, and TASS/AMES 0.5 to 1 hour, 4 hours and 12 hours post dose: (total, inattentive and hyperactive-impulsive subsets) (for effects of Azstarys over time at different points of the day and within the day), expanded Adult ADHD Self Report Symptom Rating Scale (ASRS) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets), symptoms of executive function (BRIEF: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), executive dysfunction and emotional dyscontrol by using the ADHD symptoms scale validated for DSM-5 (AISRS- expanded) and the (BRIEF-A).

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the open-label as the independent variable. All analyses will use the ITT sample. For our

design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for Subjects who experience a 30% change in AISRS-expanded (18-item only in the analyses. We have chosen to exclude those patients that experience greater than a 30% change in their total AISRS-expanded (18-item only) scores during open-label treatment and will discontinue them from the protocol. We anticipate that based on the literature that 10% or fewer of patients will have the 30% change in AISRS-expanded (18-item only) and that the overall discontinuation rate in the trial will be 20%. Changes within the day in TASS/AMES ratings 0.5 to 1-hour post dose vs. 4-hour post dose vs. 12 hours post dose will also be analyzed via the general linear regression model. Correlations between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

### 10.2.1. Analysis of the Primary Efficacy Endpoint(s)

Our primary outcome is effects on overall adult ADHD symptoms via total Expanded AISRS (18-item) Score, assessing executive function deficits (EFDs; nine items) and emotional dyscontrol (EC; four items). EFDs are deficiencies of high order cognitive processes, such as self-control, self-regulation, and ability to prioritize and to plan multiple tasks. EC includes symptoms of mood lability, irritability, and emotional overreactivity. These prompts have been written for the AISRS-expanded to help guide the rater to explore the full manifestations of symptoms in an adult with ADHD. (Silverstein et al 2018)

Missing outcome data will be handled in regards to analysis in the following way: last observation will be carried forward.

### 10.2.2. Analysis of the Secondary Endpoint(s)

In secondary analyses, we will also analyze the following variables: Evaluation of ADHD subset IA and HI symptoms on AISRS-expanded, and TASS/AMES 0.5 to 1 hour, 4 hours and 12 hours post dose: (total, inattentive and hyperactive-impulsive subsets) (for effects of Azstarys over time at different points of the day and within the day), expanded Adult ADHD Self Report Symptom Rating Scale (ASRS) Symptom Checklist (total, inattentive and hyperactive-impulsive, executive function and emotional control subsets) , symptoms of executive function (BRIEF: GEC, metacognition, behavioral regulation scales and subscales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), executive dysfunction and emotional dyscontrol by using the ADHD symptoms scale validated for DSM-5 (AISRS- expanded)(ASRS-expanded) and the (BRIEF-A).

Our statistical analysis framework will be the general linear regression model. We will choose the distributional family and link function based on the distribution of the outcome variables. Each regression model will predict the outcome as the dependent variable with weeks in trial after the end of the open-label as the independent variable. All analyses will use the ITT sample. For our design, a significant effect of week assesses the significance of the drug effect. We have chosen an IIT analyses as we can include all patients except for Subjects who experience a 30% change in AISRS-expanded (18-items) in the analyses. We have chosen an open-label and will not include in the open- label treatment subjects who experience greater than a 30% change in their total AISRS-expanded(18-item)scores during two-week observation period. We anticipate that based on the literature that 10% or fewer of patients will be excluded. for having the 30% change in AISRS-expanded(18-item) at baseline prior to open-label treatment and the overall discontinuation rate in the trial will be 20%. Changes within the day in TASS ratings 0.5 -1-hour post dose vs. 4-hour post dose vs. 12 hours post dose will also be analyzed via the general linear regression model. Correlations

between ADHD and executive function ratings will be examined via Spearman's correlation coefficients.

### 10.2.3. Safety Analyses

Primary Objective: The primary objective of this proposal is to examine the efficacy of Azstarys on ADHD symptoms and Executive Function. The primary measure of ADHD symptoms will be the total score on the AISRS-expanded (18-items).

Secondary Objective(s): To examine changes after Azstarys treatment in: 2) overall inattentive (IA) and hyperactive-impulsive (HI) ADHD symptom subsets on the AISRS- expanded and overall impairment via the clinical global impression-severity (CGI-S) scale.; 3) total ADHD symptoms about twelve hours after AM dosing as measured via total scores on the Time Sensitive Adult ADHD Symptom Scale (TASS)and Smoothness of Effect Scale (AMSES) (Three times daily on assessment visit day) ; and 4) in clinical symptoms of Executive Function and emotional dyscontrol, as measured by the BRIEF-A and AISRS-expanded.

Exploratory Objectives: We will examine potential differential effects of Azstarys in the sample of patients who have defined executive dysfunctions (GEC score on BRIEF-A >= 65 at baseline). We will also examine self-report of ADHD symptoms (on ASRS) versus clinician report (AISRS) and also changes in self-report measures of executive function and emotional dyscontrol on the ASRS versus these measures on the BRIEF-A.

### 10.2.4. Adherence and Retention Analyses

Research staff will ensure subject adhere to the study visit schedule by confirming appointments at each visit. Subjects will adhere to the medication schedule by conducting compliance check at each visit. Subjects are asked to have at least 80% compliance. Subjects will be contacted three times via telephone/email if subject misses a visit. If no response there will be an approved IRB certified letter sent to the subject. All will be documented in subject source document folder. If subject misses visit and are non-compliant their participation will be assessed by study doctor. Principal investigator can discontinue subject per his discretion.

### 10.2.5. Planned Interim Analysis

Not applicable, interim analysis not planned at this time

## *10.3. Sample Size*

Up to 30 patients will be screened, 20 enrolled (two-week observation stabilization period), approximately 20 patients to be Enrolled (Azstarys), to be sure that 15 evaluable patients reach the end of treatment at week five. The graph shows power at different values of the Cohen's d effect size for estimating the difference between baseline and endpoint values. For our primary analysis, which uses a two-sided test with a type I error of 0.05, it shows that 15 evaluable patients will give power of 90% or more for effect sizes of 0.6 or greater. 0.6 is a reasonable expectation for an effect size it is half of the 1.2 effect size reported by Spencer et al. 2008 and thus is at the lower end of what we should expect to see in this study. We believe that the power will be slightly higher in direct comparison vs. Spencer as that study was parallel group placebo controlled. The use of eliminating subject with a change of 30% or greater in their AISRS-expanded between screening to end of two week prior to open label treatment period should increase the power somewhat in this trial in terms of direct comparison.

## 11. Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects 'diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the Corium LLC, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

## 12. Quality Assurance and Quality Control

The principal investigator has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. The investigator will ensure all research staff working on this protocol meet the acceptance of the IRB. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this clinical trial. The training will be documented on training logs.

Either institution or senior research staff may conduct quality assurance audits. Audits will include, but are not limited to IMP supply, presence of required documents, the informed consent process, and comparison of the data in REDCap against the paper source documents. The senior research staff, investigator or co-investigator will also spot check charts, REDCap, and sign off on completed subjects.

During each subject's visit to the clinic, research staff will record progress notes to document all significant observations. The investigator or co-investigator will sign these notes at each visit.

At a minimum, these notes will contain documentation of the informed consent process, any revised consents, eligibility (inclusion/exclusion criteria prior to study medication administration), date of the visit and the corresponding visit in the trial schedule. The note will also include the presence or absence of adverse events (severity, frequency, duration, action taken, outcome and relationship to study medication as assessed by the investigator/co-investigator). Notes will also include changes in concomitant medications or dosages. Included in the progress note will be all telephone numbers or other means of contact that provide any significant clinical information. Source documents and source data will meet the same fundamental elements of data quality (e.g. attributable, legible, and accurate)

This study will use urine Pregnancy test and Urine Toxicology from Nobel Medical, these tests have CLIA waiver and will be conducted prior to dosing. Tests will be conducted using a urine dipstick or urine cup.

Noble Medical 19525 Janacek Court, Suite 104 Brookfield, WI 53045 877-836-5713 info@noblemedical.com John Hlavachek john@noblemedical.com)

1. NMCup-12-01-BT12PanelCup, CLIA Waived, AMP500/BAR300/BUP10/BZO300/COC150/MET500/MDMA500/MTD300/OPI300/OXY100/ TCA1000/THC50
2. hCG Women Pregnancy Strip, 25mIU/ml, Sample: urine. 50 strips each box CLIA Waived

Note: Urine Drug Screen and Pregnancy tests are required within 24 hours of study intervention and results available prior to administration of study product Azstarys

We will rely on their list of normal and abnormal values and will maintain all laboratory information in regulatory binder. We will use an NYU cardiologist to read all EKGs and respond with clinical judgement to the investigator regarding inclusion or exclusion of subjects in accordance with Good Clinical Practices. We will retain all standard operating procedures in the essential documents folder and will also circulate among the staff at start of the project and at each amended change.

QC procedures will be implemented beginning with the data entry system. Data will be double entered by two different study team members. Missing data will be logged as a period.

Study staff will follow all written SOPs, the study principal investigator will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities. *If required.*

## 13. Ethics/Protection of Human Subjects

### *13.1. Ethical Standard*

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

### *13.2. Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

### *13.3. Posting of Clinical Trial Consent Form*

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

### *13.4. Participant and Data Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Possible loss of confidentiality related to urine screens and clinical data obtained during this study is recognized. As a guard against the loss of confidentiality, all information will be stored in locked files, which can be accessed only by members of the research staff for this project.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and Corium LLC(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of Corium LLC.

The study monitor, other authorized representatives of the Corium LLC, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records

required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

We will not store any human samples. We will store the study data. The source documents will be all the clinical findings and observations collected either on the actual scale or on the specific source documents for each study visit. This will include all urine pregnancy and drug toxicology laboratory and EKG results. The results of the documents will be entered into REDCap and rechecked for accuracy. The REDCap form will have a check off at the bottom of the page indicating completion of entry into REDCap

REDCap is a secure web application used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments). REDCap supports online or offline data capture for research studies and operations. Deidentified data from REDCap may be exported into Excel spreadsheets for analysis.

Subjects are called three times a day from an NYU mobile device. TASS/AMES information will be entered directly into REDCap.

Dr. Adler will handle statistical analysis of this study.

## 14. Data Handling and Record Keeping

### *14.1. Data Collection and Management Responsibilities*

In this study, data will be collected, stored (digital, hard copy, etc.) and maintained in a secure manner (encryption, password protection, etc.). Only minimal information will be collected from the prescreens. Prescreens will be destroyed after all necessary information is collected. The prescreens of those who have passed to screening will be added to a source chart and stored in a locked cabinet in a locked room until eligibility is determined. Once eligible, the subject is baselined and all source documents are stored in the same manner in a locked room in a locked cabinet. Data will be entered into the secure data capture system REDCap. Unidentified data will also be stored in our shared drive for writing purposes.

The documentation into the source documents for research visits should occur in real time and no later than 4 business days from the date of the visit. in the case of vacation or holiday. If the documentation is later than four business days, this should be considered a late entry with an

explanation. Documentation of the data should occur within 7 business days of the visit. If not entered within that time period, we will document in the source documents the reason for the delay.

**Source Documents**
Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

**Case Report Forms**
The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

### *14.2. Study Records Retention*

**Records Retention**
It is the investigators responsibility to retain study records. Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last

approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of Corium LLC, if applicable. It is the responsibility of Corium LLC to inform the investigator when these documents no longer need to be retained.

### *14.3. Protocol Deviations*

**Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:

- One or more participants were placed at increased risk of harm
- The event has the potential to occur again
- The deviation was necessary to protect a subject from immediate harm

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (e.g., violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact Corium LLC or designee at the earliest possible time by telephone. The investigator, medical monitor and Corium LLC will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and Corium LLC, and reviewed with the Data Safety Monitor

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to Corium LLC and IRB

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

### *14.4. Publication and Data Sharing Policy*

The investigator at NYU will have the primary responsibility for publishing the study results. The data will be analyzed and discussed prior to submission of the study results for publication.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by Corium LLC for the purposes of performing the study, will be published or passed on to any third party without the consent of the study investigator of this study.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is Corium LLCed by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., tCorium LLC or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

## 15. Study Finances

### *15.1. Funding Source*

Corium LLC will provide the study with funding to purchase Azstarys in this study.

**Charles Oh, MD**
Chief Medical Officer at Corium, LLC
coh@coriumintl.com
11 Farnsworth Street 4th Floor
Boston, MA 02210

| Visit 1 | | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | ClinCard Patient Reimbursement |
|---|---|---|---|---|---|---|---|---|
| Week -3-0 Screening/Baseline | Week -3-0 Screening/Baseline | Week1<br><br>Two-week Observation Stabilization period)-telephone check | Week 2<br><br>Initiation Dose | Week3<br><br>Flexible-Dose] | Week 4<br><br>Dose locked] | Week 5<br><br>EOS | Week 6<br><br>GCP Telephone check | After completed visits |
| | | Observation stabilization | Pharmacy Dispensation cost 120.00 | Pharmacy Dispensation cost 120.00 | Pharmacy Dispensation cost 120.00 | No dispensation | No dispensation | 360.00 for (3) pharmacy dispensations |
| This visit is not completed and done remote (no compensation) | 40.0 (completion of both parts of visits) | 10.00 | 40.00 | 40.00 | 40.00 | 40.00 | 10.00 | Total: 220.00 |

### *15.2. Costs to the Participant*

Participants will not incur any costs as a result of participating in the study. All research activities are paid by the Azstarys study.

### *15.3. Participant Reimbursements or Payments*

Participants will receive payments for the time, effort, and inconvenience of study participation. ClinCards will make payments for completed visits as indicated below. Participants will be given reimbursement after each completed visit on their ClinCard. Their selection will be documented on the consent form, the subject binder, and the administrative binder. Pharmacy dispensation cost to Turtle Bay Pharmacy will be added at each visit for three visits to ClinCards.

## 16. Conflict of Interest Policy

All study members will complete the NYU financial disclosure forms. Dr. Adler, who may have conflict of interest with studies (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.), will have any conflict reviewed by a properly constituted Conflict of Interest Committee. A Committee sanctioned conflict management plan that has been reviewed and approved by Corium LLC prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study

leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by Corium LLC prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

## 17. References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## 18. Schedule of Events

| **Study team procedures** | **Week -3-0 Visit 1**<br><br>**Screening / Baseline** | **Week -3-0 Visit 1**<br><br>**Screening / Baseline** | **Week 1 Visit 2 Two-week Observation Stabilization period-** *telephone check* | **Week 2 Visit 3 Initiation Dose** | **Week 3 Visit 4 Flexible-Dose** | **Week 4 Visit 5 Dose locked** | **Week 5 Visit 6 *EOS* Dose hold** | **Week 6 Visit 7** *GCP Telephone check* |
|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 1 | Visit 2(TC) | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 (TC) |
| OPEN-LABEL AZSTARYS Dispensed @ visit *Dispensation dose starts the morning after visit to clinic. The next morning subject will take first dose* | Screening | Screening | Zero | 39.2 mg serd-mph/7.8 mg d-mph | up to 52.3 mg serd-mph/10.4 mg d-mph | up to 52.3 mg serd-mph/10.4 mg d-mph/hold dose | EOS no dispensation | 0 |
| Dose patient is on that day.<br><br>*Subject on this dose for 7 days* | Screening | Screening | Zero | 0 | 39.2 mg serd-mph/7.8 mg d-mph | up to 52.3 mg serd-mph/10.4 mg d-mph | up to 52.3 mg serd-mph/10.4 mg d-mph | 0 |
| Consent | X | | | | | | | |
| Demographics | X | | | | | | | |
| MINI | X | | | | | | | |
| ACDS v1.2 | X | | | | | | | |
| AISRS | X | | | X | X | X | X | |
| CGI S | X | | | X | X | X | X | |
| Psychiatric History | X | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CSSRS | X | | X | X | X | X | X | |
| Medical History/Prior Meds | X | | | | | | | |
| Physical Exam | X | | | | | | | |
| Height | X | | | | | | | |
| Weight | X | | | X | X | X | X | |
| Vitals signs | X | | | X | X | | | |
| Study drug / dispensation | | | | X | X | X | | |
| Subject IP compliance check | | | | X | X | X | X | |
| Clinician RX / Dose Adjustment | | | | X | X | X | X | |
| Expanded ASRS | X | X (if not done at first part of screening) | | X | X | X | X | |
| Brief A | X | | | X | X | X | X | |
| Adverse Events | | X | X | X | X | X | X | X |
| Con Meds | | X | X | X | X | X | X | X |
| TASS (3x on assessment visit day) | | X(instruction ) | | X | X | X | X | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Smoothness of Effect Scale (AMSES) (3x day on assessment visit day) | | X(instruction) | | X | X | X | X | |
| Electrocardiogram | X | | | | | | | |
| Urine Pregnancy dipstick | Ask LMP/Birth control | | | X | | | | |
| Urine Toxicology cup | | X | | X | | | | |