COVER PAGE – STATISTICAL ANALYSIS PLAN (SAP)

Protocol Number:	812P412
Title:	A Phase IV, Open-Label, Flexible-Dose Safety Trial Evaluating SPN-812 Administered with Psychostimulants in Children and Adolescents (6 to 17 years of age) with Attention-Deficit/Hyperactivity Disorder (ADHD)
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SAP Version:	2.0
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STATISTICAL ANALYSIS PLAN

Study 812P412

A Phase IV, Open-Label, Flexible-Dose Safety Trial Evaluating SPN-812 Administered with Psychostimulants in Children and Adolescents (6 to 17 years of age) with Attention-Deficit/Hyperactivity Disorder (ADHD)

Name of Test Drug:	SPN-812 (Viloxazine extended-release [ER] capsules)
Prepared by:	Supernus Pharmaceuticals, Inc.
Protocol Version:	3.0
Protocol Date:	01 Feb 2022
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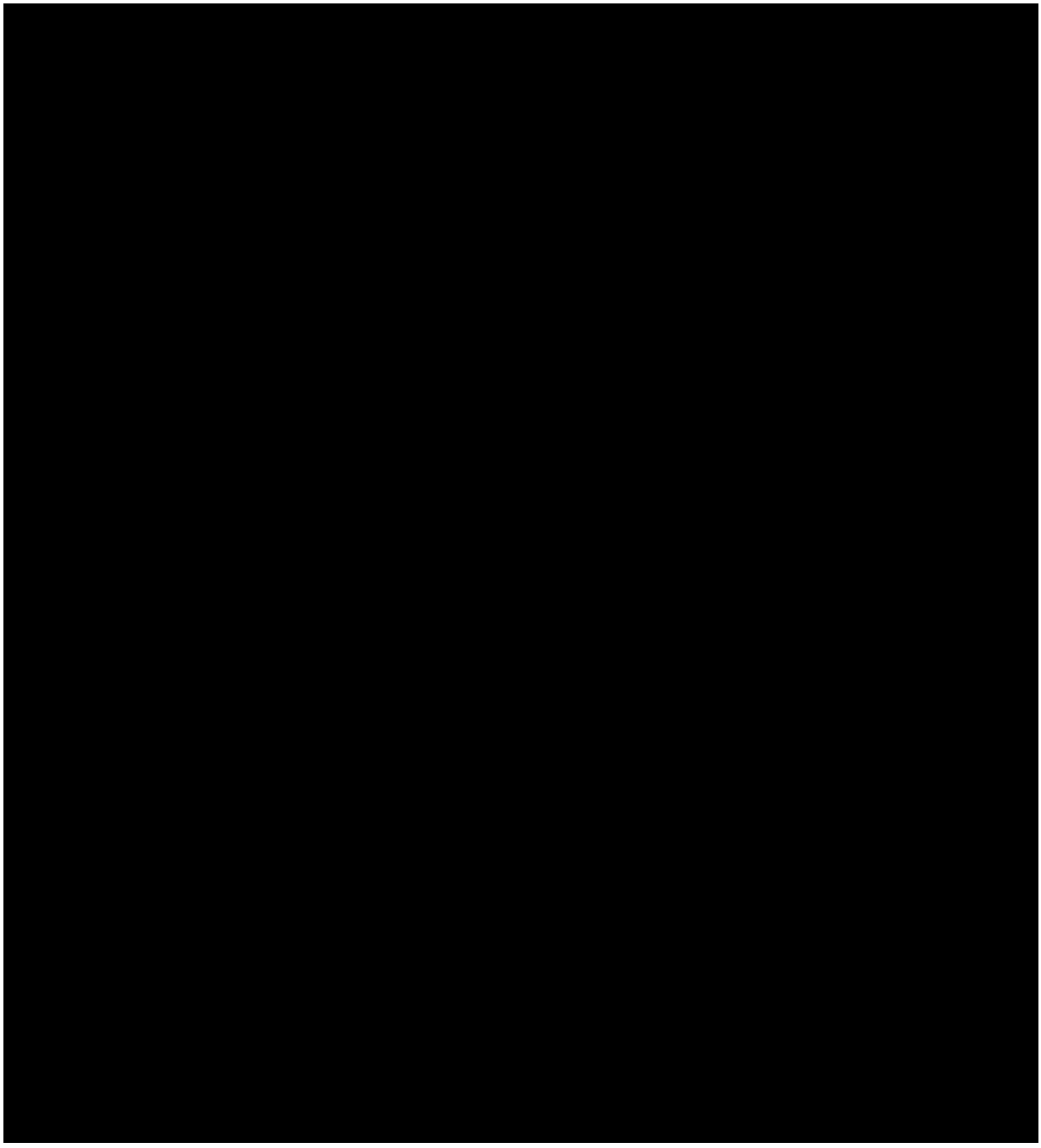
SIGNATURE PAGE



Document Version History

Version Number	Date	Section	Description of Change
1.0	14 June 2023	NA	First Approval
2.0	10 July 2023	Section 2.1: Study Objectives	Administrative changes, duplication of primary objective removed.
		Section 4.1: Definitions and derivations	Removal of AM and PM derivations since analysis will be performed using period weeks (Week 1-4 and Week 5-8)
		Section 6: Statistical Methods	Clarification that data will be summarized by week 1-4 and week 5-8 instead of AM/PM dosing.
		Section 7.2: Protocol Deviation	Protocol deviation as well as major protocol deviation definitions were inserted.
		Section 11: Changes of planned analyses from Protocol	Clarification on compliance derivations
		General	Administrative changes to correct typos, and other minor updates throughout the document.

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LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-5	ADHD Rating Scale, 5th Edition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
BPM	Beats per minute
CFB	Change from Baseline
CGI-S	Clinical Global Impression-Severity of Illness
CGI-I	Clinical Global Impression-Improvement
CRA	Clinical Research Associate
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5™	ADHD per Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ER	Extended-Release
ET	Early Termination
IR-ADHD-RS-5	Investigator Rated ADHD Rating Scale, 5th edition
MedDRA	Medical Dictionary for Regulatory Activities
MINI KID	Mini International Neuropsychiatric Interview for Children and Adolescents
PK	Pharmacokinetics
PR-ADHD-RS-5	Parent Rated ADHD Rating Scale, 5th edition
PT	Preferred Term
QD	Once a day
QTcF	QT interval corrected using Fridericia's method
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDSC	Sleep Disturbance Scale for Children
SOC	System Organ Class
SM	Study Medication
TEAE	Treatment-Emergent Adverse Event
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WPREMB-R	Weekly Parent Rating of Evening and Morning Behavior-Revised

1. Introduction

This document describes the statistical analyses and data presentations to be performed on safety and efficacy data collected during the conduct of Study 812P412, titled, "*A Phase IV, Open-Label, Flexible-Dose Safety Trial Evaluating SPN-812 Administered with Psychostimulants in Children and Adolescents (6 to 17 years of age) with Attention-Deficit/Hyperactivity Disorder (ADHD)*" (Protocol Version 3.0, 01Feb2022).

The purpose of this SAP is to ensure the credibility of the study findings by specifying detailed statistical approaches to the analysis of the data prior to database lock. This SAP covers the planned analyses of all data collected on the electronic case report forms (eCRFs) and electronic diary and will describe handling of data issues. It describes the efficacy and safety variables, anticipated data manipulations, and other details of the analyses not provided in the study protocol. The analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to evaluate the safety and tolerability of AM and PM dosing of SPN-812 administered with a psychostimulant (methylphenidate or amphetamine) for the treatment of ADHD in children and adolescents (6-17 years of age).

2.1.2. Secondary Objectives

The following are the secondary objectives:

1. Evaluate the safety and tolerability of AM versus PM dosing of SPN-812 administered with a psychostimulant (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age).
2. Evaluate the efficacy of AM and PM dosing of SPN 812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on:
    i. ADHD symptoms as measured by the Investigator-rated ADHD-RS-5 (IR-ADHD-RS-5).
    ii. the global assessment of severity for ADHD as measured by the Clinical Global Impression-Severity of Illness (CGI-S) scale.
    iii. the global assessment of improvement for ADHD as measured by the Clinical Global Impression-Improvement (CGI-I) scale.
    iv. sleep as measured by the Sleep Disturbance Scale for Children (SDSC).

v. home functioning in the morning and evening as measured by the Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R).

3. Evaluate the efficacy of AM versus PM dosing of SPN 812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age).
    i. ADHD symptoms as measured by the Investigator-rated ADHD-RS-5 (IR-ADHD-RS-5).
    ii. the global assessment of severity for ADHD as measured by the Clinical Global Impression-Severity of Illness (CGI-S) scale.
    iii. the global assessment of improvement for ADHD as measured by the Clinical Global Impression-Improvement (CGI-I) scale.
    iv. sleep as measured by the Sleep Disturbance Scale for Children (SDSC).
    v. home functioning in the morning and evening as measured by the Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R).
4. Evaluate efficacy in the morning for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Morning Parent-Rated-ADHD-RS-5 (PR-ADHD-RS-5).
5. Evaluate efficacy in the evening for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Evening PR-ADHD-RS-5.
6. Evaluate duration of efficacy within day (morning versus evening) for AM and PM dosing of SPN-812 administered with psychostimulants (methylphenidate or amphetamine) for ADHD in children and adolescents (6-17 years of age) on ADHD symptoms as measured by the Morning and Evening PR-ADHD-RS-5.

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Safety endpoints for Weeks 1-4 (AM dosing) and Weeks 5-8 (PM dosing) are adverse events (AEs), clinical safety laboratory tests results, vital signs, weight, height, body mass index (BMI), electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS) assessment.

2.2.2. Secondary Endpoints

- Safety endpoints for Weeks 1-4 (AM dosing) versus Weeks 5-8 (PM dosing) are AEs, clinical safety laboratory tests results, vital signs, weight, height, BMI, ECGs, physical examination, and the C-SSRS assessment.

7. Secondary endpoints for evaluating the efficacy of SPN-812 at Week 4 (AM dosing) and Week 8 (PM dosing) are:

i. Change from baseline (CFB) in the IR-ADHD-RS-5 Total Score at Week 4 and Week 8.
ii. CFB in CGI-S score at Week 4 and Week 8.
iii. CGI-I score at Week 4 and Week 8.
iv. CFB in SDSC total score and subscale scores at Week 4 and Week 8
v. CFB in WPREMB-R total score and subscale scores at Week 4 and Week 8.

8. Secondary endpoints for evaluating the efficacy of SPN-812 Week 4 (AM dosing) versus Week 8 (PM dosing) are:
   i. CFB in the IR-ADHD-RS-5 Total Score at Week 4 versus Week 8.
   ii. CFB in CGI-S score at Week 4 versus Week 8.
   iii. CGI-I score at Week 4 versus Week 8.
   iv. CFB in SDSC total score and subscale scores at Week 4 versus Week 8
   v. CFB in WPREMB-R total score and subscale scores at Week 4 versus Week 8.
9. The CFB in the Morning PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).
10. The CFB in the Evening PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).
11. The CFB in the Morning PR-ADHD-RS-5 Total Score versus the CFB in the Evening PR-ADHD-RS-5 Total Score at Week 4 (AM dosing) and Week 8 (PM dosing).

3. Study Description

3.1. Study Design

This is an open-label, flexible-dose, safety study of SPN-812 in pediatric patients diagnosed with ADHD per Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5™) criteria who are experiencing an inadequate efficacy response to psychostimulant therapy. Approximately 60 subjects will enroll, and approximately 50 subjects are expected to complete this study. During screening period (up to 4 weeks), subjects will continue their psychostimulant ADHD treatment. During Weeks 1-4 of the Treatment period, eligible subjects will take daily SPN-812 dose in the combination with their current psychostimulant therapy in the morning (AM) hours but during Weeks 5-8, subjects will take daily SPN-812 dose in the EVENING (PM) hours in combination with their current psychostimulant. The total duration of treatment period is 8 weeks. Total duration of the study between screening visit and end of study (EOS) visit is up to 12 weeks.

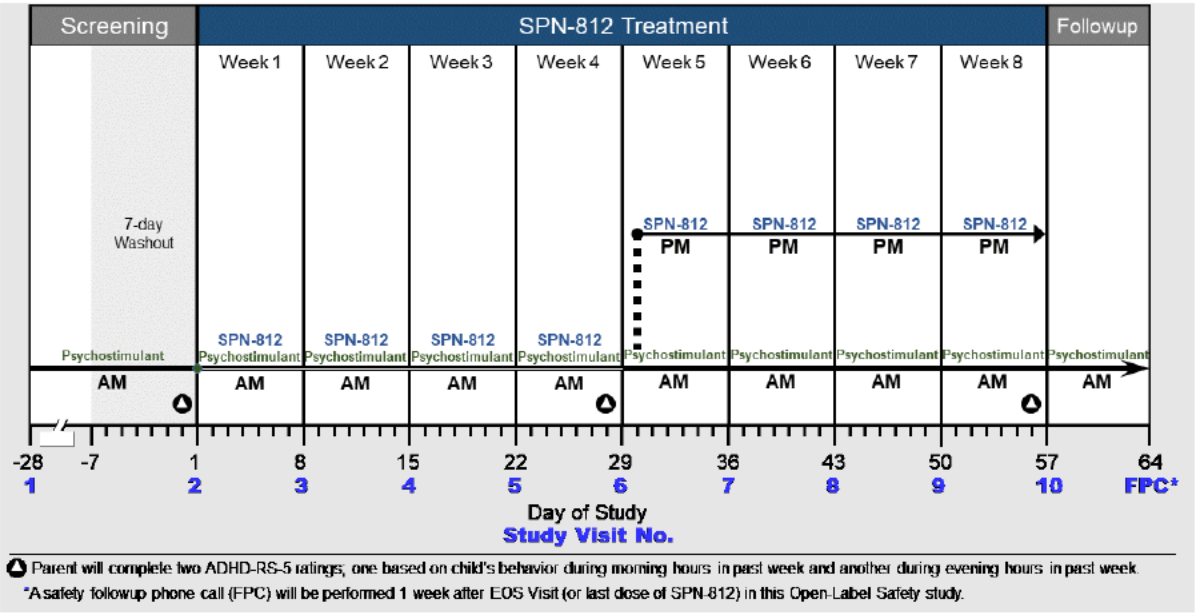
During the Treatment period, subjects will complete weekly study visits (Visits 3-10) during the Treatment Period (Days 2-57). At each post-baseline study visit, safety evaluations will be conducted, efficacy assessments (IR-ADHD-RS-5, CGI-S, CGI-I) will be administered, drug compliance will be evaluated, and subject will return bottle of study medication and receive next bottle of study medication, if required. SDSC and WPREMB-R will only be administered at Visits 6 and 10 during Treatment Period. In addition, parent/guardian must complete a 'Morning' PR-ADHD-RS-5 and 'Evening' PR-ADHD-RS-5 one or two days prior to Study Visits 2, 6, and 10. Parent will rate their child's behavior based upon interactions with their child during the morning hours in the past week and then rate their child's behavior based upon interactions with

their child during the evening hours in the past week.

Subjects who discontinue early from the study will undergo safety evaluations. Subjects will receive a telephone call approximately 1 week after EOS (or last dose of SPN-812) for final safety assessments.

A study schematic is provided in Figure 1 below.

Figure 1: Study Schematic



3.2. Schedule of Study Visits and Procedures

All subjects who are eligible, enroll and take the initial dose of SPN-812 will be followed according to the protocol regardless of the number of doses of SPN-812 taken, unless consent for follow-up is withdrawn. Table 1 below presents the Schedule of Visits and Procedures for the study.

Table 1: Schedule of Events and Assessments

Study Period	Screening	Baseline	Treatment							EOS/ET	Follow-up phone call
Visit Number	1	2	3	4	5	6	7	8	9	10	FPC
Day of Study	-28 to -1	1	8	15	22	29	36	43	50	57	64
Week of Study	-4 to -1	–	1	2	3	4	5	6	7	8	–
Study Visit Window	–	–	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2
Signed informed consent/assent	√ [a]										
MINI KID	√										
Relevant histories (social, medical, psychiatric, family psychiatric, neurological)	√										
Demographics	√										
Smoking, alcohol consumption use/history	√										
Physical examination	√ [b]									√ [b, c]	
Review eligibility criteria	√	√									
Blood sample for clinical safety laboratory tests	√	√	√	√	√	√	√	√	√	√	
Blood sample for Confirmatory analysis	√ [d]	√ [d]	√ [d]	√ [d]	√ [d]	√ [d]	√ [d]	√ [d]	√ [d]	√ [d]	
Urine sample for urinalysis	√									√	
Standard Urine drug screen	√										
Point of Care urine drug screen (Test 1) [e]		√	√	√	√	√	√	√	√	√	
Point of Care urine drug screen (Test 2 and 3) [e]	√	√	√	√	√	√	√	√	√	√	
Serum pregnancy test (FOCP only)	√										
Urine pregnancy test (FOCP only)		√	√	√	√	√	√	√	√	√	
Vital signs [f]	√ [f]	√ [f]	√ [f]	√ [f]	√ [f]	√ [f]	√ [f]	√ [f]	√ [f]	√ [f]	
Weight	√	√	√	√	√	√	√	√	√	√	
ECG	√	√	√	√	√	√	√	√	√	√	
Provide diary instructions to parent/guardian	√	√									
Reminder call		√ [g]				√ [g]				√ [g]	
Review/collect PR-ADHD-RS-5		√ [h]				√ [h]				√ [h]	
Review/Collect Dosing Diary		√ [i]	√ [i]	√ [i]	√ [i]	√ [i]	√ [i]	√ [i]	√ [i]	√ [i]	
IR-ADHD-RS-5	√ [j]	√ [j]	√ [j]	√ [j]	√ [j]	√ [j]	√ [j]	√ [j]	√ [j]	√ [j]	

Study Period	Screening	Baseline	Treatment							EOS/ET	Follow-up phone call
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**FPC**
Day of Study	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**
Week of Study	**-4 to -1**	**–**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**–**
Study Visit Window	**–**	**–**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
CGI-S	√	√	√	√	√	√	√	√	√	√	
CGI-I			√	√	√	√	√	√	√	√	
SDSC		√				√				√	
WPREMB-R		√				√				√	
C-SSRS (Baseline)	√[k]										
C-SSRS (Since Last Visit)		√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	√[l]	
Review adverse events		√[m]	√	√	√	√	√	√	√	√	√
Review concomitant medications/caffeine use	√[n]	√	√	√	√	√	√	√	√	√	√
SM dispensed		√	√	√	√	√	√	√	√		
SM returned/accountability			√	√	√	√	√	√	√	√	

ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD-RS-5 = ADHD Rating Scale 5th Edition; CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression – Severity of Illness scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; FOCP = females of childbearing potential; FPC = follow-up phone call; IR-ADHD-RS-5 = investigator-rated ADHD-RS-5; MINI KID = Mini International Neuropsychiatric Interview for Children & Adolescents; PR-ADHD-RS-5 = Parent-rated ADHD-RS-5; WPREMB-R = Weekly Parent Rating of Evening and Morning Behavior-Revised; SDSC = Sleep Disturbance Scale for Children; SM = study medication.

a. To be obtained prior to performing any study procedures.
b. Includes height, excludes genitourinary system
c. Changes from Screening only
d. A confirmatory blood sample will be collected to determine psychostimulant and viloxazine/metabolite concentrations. Collect and process sample in the same manner as a Pharmacokinetic (PK) sample.
e. See Table 3 from Protocol to determine which substance is being tested by Point of Care Urine Drug Screen Test 1, 2 or 3.
f. Includes orthostatic blood pressure and pulse rate, respiratory rate and oral temp. Orthostatic blood pressure and pulse rate should be assessed 5 minutes after subject has been sitting and again within 3 minutes of standing.
g. If paper version of diary is being used, a phone call should be made to parent/guardian 2-3 days prior to Study Visits 2, 6, and 10 to remind he/she to complete a "Morning" and "Evening" PR-ADHD-RS-5 prior to study visit.
h. Parent/guardian must complete a PR-ADHD-RS-5 one to two days prior to Study Visits 2, 6, and 10 to rate their child's behavior in past week, one based on interactions with their child during the morning hours and another based on interactions with their child during the evening hours.
i. If electronic diary is completed, please review data at each visit. If paper version of diary is completed, collected and enter data. Note: Only the psychostimulant dosing diary is performed during screening period prior to V2.
j. Use age-appropriate IR-ADHD-RS-5 (Protocol Appendix 11.1.1.1 [6-11yrs] or 11.1.1.2 [12-17 yrs])
k. Use C-SSRS Baseline version per subject's age at screening (Protocol Appendix 11.6.1 [6-11 yrs] or 11.7.1 [12-17 yrs]).
l. Use C-SSRS SLV version per subject's age at screening (Protocol Appendix 11.6.2 [6-11 yrs] or 11.7.2 [12-17 yrs]).
m. Events prior to first dose of SPN-812 are Medical Hx; events after the first dose are Adverse Event.

n. Review subject's prior lifetime history of concomitant medication(s) and current concomitant medication(s).

3.3. Study Population

The study population will comprise children and adolescent who are 6 to ≤17 years and 9 months of age diagnosed with ADHD and on a stable psychostimulant regimen for treatment of ADHD with a partial but inadequate efficacy response (IR-ADHD-RS-5 total score of ≥24 and a CGI-S score of ≥3 at Screening and Baseline) to psychostimulant therapy.

3.4. Completion and Discontinuation of Subjects

Subjects will be considered to have completed the study if they complete all visits up to and including Visit 10 or complete 8 weeks (56 days ±2 days) of treatment. Subjects who dose SPN-812 but withdraw or are withdrawn from participation in the study by the Investigator before he/she finishes the study (i.e., after Visit 2 but prior to Visit 10 or less than 54 days of treatment exposure), should complete an early termination (ET) visit. Procedures listed for Visit 10 should be completed at the ET visit.

All reasons for screening failure will be recorded. If the subject passes screening but fails eligibility at Visit 2 (Baseline), the reason(s) will also be recorded.

The Investigator(s) or subjects themselves may stop SPN-812 treatment at any time for safety or personal reasons. A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Sponsor may also withdraw the subject at any time in the interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor and/or Clinical Research Associate (CRA) before the subject stops SPN-812 treatment. Subjects removed from the study for any reason will not be replaced.

Reasons for subject's early discontinuation/termination may include:

- Withdrawal of consent (parent/guardian)
- Withdrawal of assent (subject)
- Inclusion/Exclusion criteria
- Noncompliance
- Lack of Efficacy
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

3.5. Study Treatments

3.5.1. Study Medication Identity, Packaging, and Labeling

Study medication (SPN-812) are capsules supplied in labeled bottles by the Sponsor. Each bottle of SM will include capsules that contain either 100 mg or 200 mg of SPN-812 in 90-count bottles. Each bottle will be labeled with the protocol number, at a minimum.

3.5.2. Study Medication Administration

Study medication (SPN-812) will be administered orally once daily (QD), with or without food, as an intact capsule or by sprinkling the content of the capsule on one tablespoon of applesauce followed by drinking water after having ingested the SM/applesauce mix. A daily diary (e.g., paper or electronic source) will capture daily SPN-812 dose information, including total daily dose (mg), dosing date/time (MM/DD/YYYY, 00:00 AM/PM), administration method [e.g., subject swallowed total daily dose as intact capsule(s) or subject swallowed total daily dose as a SM/applesauce mix], and reason why no SPN-812 dose was taken or why a partial SPN-812 dose was taken, if applicable.

See Table 2 below for the SM administration schedule. Each SPN-812 capsule contains either 100 mg or 200 mg SPN-812.

Table 2: Study Medication Administration

Age Group	Starting Dose	Dose Range	Dose Increments for Titrating Up or Tapering Down (per week)
6-11 years	100 mg/day	100-400 mg/day	100 mg/day
12-17 years	200 mg/day	100-600 mg/day	100 or 200 mg/day

3.5.3. Method of Assigning Subjects to Treatment Groups

This is an open-label study. All eligible subjects will receive active treatment (SPN-812).

3.5.4. Blinding and Unblinding

This is an open-label study, non-randomized, therefore treatment blinding is not applicable.

3.5.5. Concomitant Medications

Subjects must continue taking stable daily dose of psychostimulant medication at least 5 days per week in the morning throughout study, including the screening period and 8-week SPN-812 treatment period. A Diary (e.g., paper or electronic) will be used to confirm daily psychostimulant medication dose in the morning each day during the study. The total daily dose of subject's psychostimulant medication cannot be increased during 8-week SPN-812 treatment, but it may be decreased once.

Subjects may not be on any prohibited medication as indicated in the inclusion/exclusion criteria. SPN-812 is a strong CYP1A2 inhibitor. Substrates with a narrow therapeutic window are prohibited during the study. Specific prohibited concomitant medications for this study include

known CYP1A2 substrates (e.g., theophylline, melatonin, etc.). Subjects will undergo a washout period of prohibited medication for at least 1 week (or 5 half-lives of the medication, whichever is longer) before the Baseline Visit (Day 1).

No concomitant medications are allowed during the study, with the following exceptions:

- Nutritional supplements (e.g., multivitamins, fish oil) (however, herbal supplements are prohibited)
- EMLA® or other numbing cream for venipuncture
- Common over-the-counter (OTC) therapies for minor transient ailments (e.g., acetaminophen for headache, ibuprofen for fever).
- Over-the-counter, non-sedating allergy medications and antibiotics.

All concomitant medications will be recorded in the eCRF.

Caffeine use is not prohibited during the study, however, caffeine intake will be assessed at screening, baseline and at all post-baseline study visits and recorded in the eCRF.

3.6. Sample Size and Power

There is no consideration for power or sample size determination in this open-label study. There are approximately 50 subjects expected to complete this study. Based on an early discontinuation rate of 20%, approximately 60 subjects would need to be enrolled. Based on a screen failure rate of 40%, approximately 100 subjects will be screened to enroll approximately 60 subjects.

4. Definitions and Derivations

4.1. General study level definitions

- **Baseline** is the last non-missing assessment recorded before receiving the first dose of study medication and will be used as the baseline observation for all calculations of change from baseline.
- **Change from Baseline** = value at current time point – value at baseline.
- **Percent Change from Baseline** = (change from baseline / value at baseline) * 100.
- **Body Mass Index (BMI) kg/m^2** =

$$\left(\frac{weight\ (kg)}{\frac{height(cm)}{100} * \frac{height(cm)}{100}}\right)$$

- **Treatment Emergent Adverse Event (TEAE)** = an AE with a start date on or after the first dose of study medication is taken, or that worsened following first administration of study medication (SPN-812).
- **Duration of Adverse Event** = AE end date – AE start date + 1
- **Duration of Treatment Exposure** = date of last dose – date of first dose + 1 (overall and by dose timing [Section 4.2.1])

- **Total Dose (mg) Taken Based on Drug Accountability=** total dispensed dosage – total returned dosage.
- **Average Daily Dose Based on Drug Accountability**= (total dispensed dosage – total returned dosage)/duration of exposure
- **Total planned Dose Based on Drug Accountability=** total planned dose for each day shown in the dispensed section for the subject.
- **SM Compliance Based on Drug Accountability**= [(total dispensed dosage – total returned dosage)/total planned dose based on drug accountability]×100%.
- **Total Dose (mg) Taken Based on Drug Administration=** total dispensed dosage – total missed dosage.
- **Average Daily Dose Based on Drug Administration=**(total dispensed dosage – total missed dosage)/duration of exposure.
- **Total Expected Dosed based on Drug Administration**= Total dose expected based on the number of days for each administration record.
- **SM Compliance Based on Drug Administration**= [(total dispensed dosage – total missed dosage)/total expected dose based on drug administration] ×100%.

5. Study Variables

5.1. Safety Variables

The safety endpoints of this study include the following:

- Adverse events (AEs)
- Clinical safety laboratory tests results
- Vital signs (orthostatic blood pressure and pulse rate, respiratory rate, temperature)
- Weight/Height/BMI
- 12-Lead Electrocardiogram (ECG)
- Physical examination
- Suicidality (C-SSRS)

5.2. Efficacy Variables

The efficacy endpoints of this study include the following:

- Investigator-rated (IR) ADHD-RS-5
- Morning Parent-rated (PR) ADHD-RS-5
- Evening Parent-rated (PR) ADHD-RS-5

- CGI-S scale
- CGI-I scale
- SDSC and subscales
- WPREMB-R and subscales

5.3. Confirmatory Blood Sample

A confirmatory blood sample will be collected at each study visit (1-10) to assess concentrations of psychostimulant, viloxazine, and viloxazine's metabolite.

6. Statistical Methods

6.1. General Principles

All statistical analysis, data processing, tabulation of descriptive statistics and graphical representations will be performed using SAS version 9.4 or higher.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non--missing values, mean, standard deviation (SD), median, interquartile (Q1 and Q3), minimum, and maximum. If warranted, standard error (SE) will be displayed for some efficacy figures.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the safety population, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each study visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean, Q1, Q3, and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified and with the following exceptions: a percentage of 0% will not be displayed (i.e., only the count of 0 will be displayed), and a percentage of 100% will be displayed with 0 decimal places.

Data collected at unscheduled time points will not be summarized but will be presented in subject listings.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Data will be summarized by periods for weeks 1-4 and weeks 5-8 and overall depending on the endpoint. In the case that the data supporting the endpoint is collected only at study visits, summary will be presented by scheduled visits. In the case that the data supporting the endpoint is collected at times other than study visits (e.g., Adverse Events), the data will be presented with

the columns of Weeks 1-4 and Weeks 5-8 in addition to the overall participation in the trial.

6.2. Analysis Populations

The following analysis populations are planned for this study:

The **Safety Population** consists of all subjects who enrolled in the study and receive at least one dose of SM. The Safety population will be used for all analyses including both safety and efficacy analyses.

6.3. Interim Analysis and Data Monitoring

No interim analyses are planned.

6.4. Handling of Dropouts or Missing Data

6.4.1. Missing Efficacy variables

Missing efficacy variables will be handled using the following rules:

- **ADHD-RS-5 Total Score** = sum of the 18 individual items. Each individual item is scored on a scale of 0 to 3, where 0 = none and 3 = severe, so the total score ranges from 0 to 54. Higher scores indicate more severe symptoms. If more than 3 items of ADHD-RS-5 are missing, then the total score will be set to missing. If ≤3 items are missing, then the values for the missing items will be imputed using the mean of the non-missing items rounded to the nearest integer. It will be applied for both the investigator-rated ADHD-RS-5 and the parent-rated ADHD-RS-5.
- **ADHD-RS-5 Inattention Subscale Score** = sum of the first 9 individual items. Each individual item is scored on a scale of 0 to 3, where 0 = none and 3 = severe, so the total score ranges from 0 to 27. Higher scores indicate more severe symptoms. If the total score is missing, then both subscales (inattention or Hyperactivity/ Impulsivity) will be set to missing. It will be applied for both the investigator-rated ADHD-RS-5 and the parent-rated ADHD-RS-5.
- **ADHD-RS-5 Hyperactivity/Impulsivity Subscale Score** = sum of 16 to 24 individual items. Each individual item is scored on a scale of 0 to 3, where 0 = none and 3 = severe, so the total score ranges from 0 to 27. Higher scores indicate more severe symptoms. If the total score is missing, then both subscales (inattention or Hyperactivity/ Impulsivity) will be set to missing. It will be applied for both the investigator-rated ADHD-RS-5 and the parent-rated ADHD-RS-5.
- **SDSC Total Score** = sum of the 26 individual items. Each individual item is scored on a scale of 1 to 5, so the total score ranges from 26 to 130. Raw scores can be converted to T-scores, where a T-score >70 (>95th percentile) is indicative of a clinically significant sleep problem. The parent will rate their child for each item based on the past week (7 days). Higher scores indicate worse sleep disturbances. If one item has no rating/score (missing), the total score will be set to missing.
- **SDSC Disorders of Initiating and Maintaining Sleep (DIMS) Scale Score** = sum the score of the items 1, 2, 3, 4, 5, 10, and 11. If one item has no rating/score (missing), the

scale score will be set to missing.

- **SDSC Sleep Breathing Disorders (SBD) Scale Score** = sum the score of the items 13,14,15. If one item has no rating/score (missing), the scale score will be set to missing.
- **SDSC Disorders of Arousal Scale (DA) Score** = sum the score of the items 17, 20, 21. If one item has no rating/score (missing), the scale score will be set to missing.
- **SDSC Sleep-wake Transition Disorders (STD) Scale Score** = sum the score of the items 6,7,8,12,18,19. If one item has no rating/score (missing), the scale score will be set to missing.
- **SDSC Disorders of Excessive Somnolence (DES) Scale Score** = sum the score of the items 22,23,24,25,26. If one item has no rating/score (missing), the scale score will be set to missing.
- **SDSC Sleep Hyperhidrosis (SH) Scale Score** = sum the score of the items 9,16. If one item has no rating/score (missing), the scale score will be set to missing.
- **WPREMB-R Total Score** = sum of the 11 individual items. Each individual item is scored on a scale of 0 (no difficulty) to 3 (a lot of difficulty), so the total score ranges from 0 to 33. If one item has no rating/score (missing), the total score will be set to missing.
- **WPREMB-R Morning Subscale Score** = sum of items 1, 2 and 3 1. Each individual item is scored on a scale of 0 to 3, so the subscale score ranges from 0 to 9. If one item has no rating/score (missing), the subscale score will be set to missing.
- **WPREMB-R Evening Subscale Score** = sum of items 4, 5, 6, 7, 8 9, 10 and 11. Each individual item is scored on a scale of 0 to 3, so the subscale score ranges from 0 to 24. If one item has no rating/score (missing), the subscale score will be set to missing.

6.4.2. Missing Safety Variables

Missing dates for AEs and non-study concomitant medications will be imputed using the following rules:

If partial AE or medication dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows.

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or month and day is/are unknown, then:
  - If the year matches the year of first dose date and the end date (if present) is after first dose date, then impute as the month and day of the first dose date.
  - Otherwise, assign 01 January.
- If the year and month are known, but the day is unknown, then:
  - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
  - Otherwise, assign 01.

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date, but assign as missing value.
- If the year is known, but the month or month and day is/are unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
    - Otherwise, assign the last day of the month.

Missing data for all other safety endpoints will not be imputed.

6.5. Analysis Visit Windows

Data from scheduled visits will be analyzed. Visits will be analyzed as scheduled. Unscheduled measurements will be excluded from the descriptive statistics and statistical analyses (except if the unscheduled visit used for baseline) but will be included in listings.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations of the number and percentage of subjects in each of the following categories:

- Screened Subjects
- Subjects in the Safety Population

The number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation will be summarized. The reason for early discontinuation may include any of the following:

- Withdrawal of consent (parent)
- Withdrawal of assent (subject)
- Inclusion/Exclusion criteria
- Noncompliance
- Occurrence of unmanageable AEs
- Lack of Efficacy
- Lost to follow-up
- Other

All disposition information as well as inclusion and exclusion criteria met/not met and reasons for screen failures will be listed.

7.2. Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. A major protocol deviation is defined as a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Protocol deviations will be listed, and major protocol deviations will be summarized.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, age group, sex, ethnicity, race (White vs Non-white which including other races besides White), smoking, alcohol consumption use/history, height/ weight/BMI at screening and IR-ADHD-RS-5 Total score and subscale scores, CGI-S score at baseline will be presented.

Age will be broken up into two age groups (children: 6-11, adolescent: 12-17).

The number and percent of subjects reporting various medical histories, grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), will be tabulated. This analysis will be conducted for the Safety Population.

Prior medications and psychostimulant (methylphenidate or amphetamine) will be summarized by the number and percentage of subjects taking each medication, classified using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) Anatomical –Therapeutic Chemical Classification (ATC) Class Level 4 and preferred name (ATC Class Level 5). This analysis will be conducted for the Safety Population.

7.4. Exposure and Compliance

Duration of treatment exposure will be summarized using descriptive statistics. Additionally, duration of treatment exposure will be summarized by duration category.

Duration of treatment exposure will be categorized as follows: 1-7 days, 8-14 days, 15-21 days, 22-28 days, 39-35 days, 36-42 days, 43-49 days, and >=50 days.

Subject exposure for planned daily dose will be summarized by study visit, dose (100 mg, 200 mg, 300 mg, 400 mg, 500 mg and 600 mg).

For each treatment, SM compliance based on drug accountability and administration will be summarized by compliance category (<80%, 80 to 120%, and >120%) and number of subjects in each compliance category. Study medication compliance based on drug accountability and administration will also be summarized as a continuous variable using descriptive statistics.

Average daily dosing based on drug accountability and administration for each subject will be summarized using descriptive statistics (N, Mean(SD), Median, Q1, Q3, Min and Max) for weeks 1- 4 and Weeks 5-8. Distribution of SPN-812 doses at Week 4 and Week 8 will be summarized using descriptive statistics.

8. Efficacy Analysis

All efficacy endpoints will be summarized descriptively using the safety population. All efficacy data will be presented in data listings.

The descriptive statistics including N, mean, standard deviation, median, Q1, Q3, minimum and maximum of observed value and change from baseline will be presented by visit.

For IR-ADHD-RS-5 Total Score and subscale scores, CGI-S, SDSC (total and subscale scores) and WPREMB (total and subscale scores), the following CFB analyses will be provided:

- A comparison of week 4 vs week 8 difference in CFB a nominal p-value from paired t-test will be presented.
- Change from baseline by visit.

For CGI-I:

- A comparison of week 4 vs week 8 difference in CGI-I score will be provided: nominal p-value from paired t-test will be presented.
- CGI-I score by visit will be provided.

For Morning PR-ADHD-RS-5 Total Score and Evening PR-ADHD-RS-5 Total Score:

- A comparison of week 4 vs week 8 difference in CFB will be provided.

The following will be provided for PR-ADHD-RS-5 Total Score and subscale scores:

- CFB in the Morning PR-ADHD-RS-5 versus the Evening PR-ADHD-RS-5 at Week 4.
- CFB in the Morning PR-ADHD-RS-5 versus the Evening PR-ADHD-RS-5 at Week 8.

Analysis of 30% and 50% IR-ADHD-RS-5 Total score responder rates, defined as having at least a 30% and 50% reduction respectively from baseline IR-ADHD-RS-5 Total score will be presented.

For each subject, the percent reduction will be calculated as 100*(IR-ADHD-RS-5 Total Score at week Y-Baseline IR-ADHD-RS-5 Total Score)/ Baseline ADHD-RS-5 Total Score.

- The number and percentage of IR-ADHD-RS-5 responders will be summarized and presented, the odds ratio between week 4 and week 8 will be presented along with the associated 95% CI.
- The responder 30% and 50% rates for IR-ADHD-RS-5 will be presented by visit.

A CGI-S and CGI-I “responder” is defined as having a CGI-S score of 1 or 2.

- The number and percentage of CGI-S/I responders will be summarized and presented. The odds ratio between week 4 and week 8 will be presented along with the associated 95% CI.
- The responder rates for CGI-S/I will be presented at by visit.

9. Safety and Tolerability Analysis

Safety assessments include monitoring, evaluation, and recording of all concomitant medications, and the evaluation of AEs, clinical laboratory test results, vital signs, weight, height, BMI, 12-lead ECGs, C-SSRS, and physical examinations.

All safety analyses will be performed on the Safety population. No inferential statistics will be performed.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA Version 23.1.

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the date of the first dose of study medication, or that worsened in severity following the first dose of study medication. All AEs in this study will be recorded after administration of study medication, therefore all will be considered treatment-emergent.

The causal relationship of the AE to the study medication is determined by the investigator as "Not Related", "Unlikely Related", "Possibly Related", and "Definitely Related". These will be mapped to "Unrelated (Not Related or Unlikely Related)" and "Related (Possibly Related or Definitely Related)".

Adverse event severity grades are reported as "mild", "moderate", or "severe".

Summaries of incidence rates (frequencies and percentages) of individual TEAEs will be presented by SOC, PT, and (Week 1 - 4, Week 5 - 8 and overall duration [i.e., Week1-Week8]). Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by relationship.

Each subject will be counted only once within each summation level (SOC and PT). If a subject experiences more than 1 TEAE within each summation level, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity. If a particular event is missing severity and/or causal relationship to study medication, then the strongest possible severity or causal relationship will be assumed for analysis (severity = severe, relationship = definitely related).

Incidences will be presented by descending frequency of SOC and PT within SOC, and then alphabetically within PT where the incidence is the same; this is based on overall subjects then alphabetically in case of a tie.

In addition, number and percent of patients reporting common AEs (≥5% in any treatment group) will be presented by SOC and PT.

Missing and partially missing AE start and/or stop dates will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.4.2.

In the AE data listings, all AEs will be displayed. AEs that are treatment emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study medication, SOC, and PT will be prepared for the Safety Population.

A data listing of AEs leading to withdrawal of study medication will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths, Adverse Events of Special Interest, and Serious Adverse Events

Any deaths, adverse events of special interest, and serious adverse events that occur during the study will be listed.

Adverse events of special interest (AESI) are defined as seizure or AEs that might represent a seizure. This includes, but is not limited to syncope/syncopal episode, pseudoseizure, myoclonus, and severe muscle spasms.

9.2. Laboratory Data

Laboratory tests (clinical chemistry, hematology) will be performed at all study visits and results will be summarized descriptively by study visit (week 1 to 4 with AM dosing, week 5 to 8 with PM dosing) as both observed values and change from baseline values. Urinalysis will be performed at screening and EOS. Number and percentage of subjects with abnormal qualitative urinalysis results will be provided by study visit.

Laboratory values for clinical chemistry and hematology will be presented at each visit using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for the actual and change from baseline values will be presented in Tables. Laboratory assessment values of the form of "< x" or "<= x" (i.e., below or at/below the lower limit of quantification) or "> x" or ">= x" (i.e., above or at/above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics. For listings however, the original ranges (e.g., "< x", "<= x", "> x", ">= x") as stated in the database will be presented.

Laboratory values for clinical chemistry and hematology will be flagged as abnormally low (L) if the value < lower limit of the normal range, normal (N) if the value is within normal range or abnormally high (H) if the value > upper limit of the normal range. In addition, shift tables for the change from baseline by study visit will be presented.

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged and presented along with corresponding normal ranges (if available). A separate listing of abnormal laboratory values will be provided. All study visits within a parameter for a subject will be presented if at least 1 study visit within that parameter has an abnormal result.

Standard urine drug screen results, and pregnancy test results will be listed separately.

9.3. Vital Signs

Vital signs will be collected at all study visits. Descriptive summaries of actual values and changes from baseline will be calculated for height (cm), weight (kg), BMI (kg/m^2), oral body temperature (ºC), respiration rate (breaths per minute), sitting pulse rate (beats per minute [bpm]), standing pulse rate (bpm), sitting systolic blood pressure (mmHg), standing systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), and standing diastolic blood pressure (mmHg). These summaries will be presented by study visit.

The number of subjects with vital signs below, within, or above normal ranges, by study visit will be tabulated (shift tables) for each parameter.

The number of subjects with vital signs values below, within, or above normal ranges, by study visit will be tabulated (shift tables) for each vital sign parameter by treatment group. Normal ranges are presented in Table 3.

Table 3: Vital Sign Normal Ranges

Parameter	Low		High	
	Children (6-11)	Adolescents (12-17)	Children (6-11)	Adolescents (12-17)
Systolic Blood Pressure (mmHg)	90	90	120	135
Diastolic Blood Pressure (mmHg)	50	64	80	90
Pulse Rate (beats/min)	70	60	120	100
Temperature (C)	35.5	35.5	37.5	37.8
Respiratory Rate (breaths/min)	18	12	25	20
Body Mass Index	18.5	18.5	<95 percentile	<95 percentile
Height	106cm	136cm	161.8cm	187.8cm
Weight	20kg	35kg	59kg	88.8kg

9.4. Electrocardiograms

12-Lead ECGs will be collected at all study visits. Descriptive summaries will be presented for heart rate (bpm), PR interval (msec), QRS duration (msec), uncorrected QT interval (msec), and QTcF (msec). These summaries will be presented by study visit.

The number of subjects with ECG results below, within, or above normal ranges, by study visit will be tabulated (shift tables) for each parameter.

Normal, abnormal but not clinically significant, and abnormal and clinically significant ECG investigator interpretation results will be flagged in the listings.

Additionally, the number and percentage of subjects with actual QTcF values ≤450 msec, 450 msec to ≤480 msec, 480 to ≤ 500 msec, >500 msec and with changes from baseline <= 30 msec, 30 msec to ≤ 60 msec, and >60 msec will be presented. Normal ranges are presented in Table 4.

Table 4. Electrocardiograms Normal Ranges

Parameter	Low		High	
	Children (6-11)	Adolescents (12-17)	Children (6-11)	Adolescents (12-17)
HR	60	50	140	130
PR	90	90	170	200
QRS duration	40	40	90	100
QT interval	350	350	440	440
QTcF	350	350	440	440

9.5. Physical Examination

The physical examination conducted at screening will include assessments of all body systems except genitourinary. Any findings during screening will be recorded as medical history and any clinically significant abnormal findings during treatment will be recorded as an AE. At the EOS physical examination, only changes from the screening visit will be noted.

All physical examination results will be listed.

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

Assessment of suicidal ideation and behavior will be conducted using the Columbia-Suicide Severity Rating Scale (C-SSRS) which classifies suicidal ideation and behavior events into 11 preferred categories including 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category of self-injurious behaviors with no suicidal intent. The C-SSRS will be performed at all study visits. At the Screening visit, the "baseline" version of the C-SSRS will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during the past 6 months. At the subsequent study visits, the "since last visit" version will be administered.

The number and percentages of subjects with a response of "Yes" at any point on the suicidal ideation only, suicidal behavior only, and suicidality (ideation and behavior combined) items will be summarized by study visit.

9.7. Concomitant Medications

Prior and concomitant medications coded using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) (version Sep, 2020), will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and PN (i.e., ATC classification Level 5), if applicable, using counts and percentages for the Safety Population.

If a medication starts prior to the first dose and continues after the first dose, it will be considered both prior and concomitant. Prior and concomitant medications will also be listed.

9.8. Other Safety Assessments

Follow-up phone call data will be listed.

10. Confirmatory Blood Sample

Concentration for viloxazine and Psychostimulant will be summarized using descriptive statistics (N, Mean/SD, Median, Q1, Q3, Min/Max) by visit.

11. Changes of planned analyses from the Protocol

For SM compliance, the derivation based on retuned capsules as defined in the study protocol could not be used because of the following:

- Subjects did not consistently return bottles on the visit following the visit on which they were dispensed. As such, the derivation of the number of capsules intended to be taken cannot be completely followed.

• Dosage requires capsules of multiple dose levels to be taken. In those cases, the number of capsules missed may reflect greater or lesser compliance with the intended dose depending upon the dose level of capsule that was missing. In the case where capsules of multiple dosage strength were taken, the average dose/capsule was assumed for the capsules (e.g., 300 mg dosage for Adolescents was 1 capsule of 100 mg and 1 capsule of 200 mg, each capsule is calculated to be 150 mg).

Hence the derivations provided in Section 4.1 will be used to derive SM compliance, that is:

- **SM Compliance Based on Drug Accountability**= [(total dispensed dosage – total returned dosage)/total planned dose based on drug accountability] ×100%.

In addition, compliance based on drug administration will be added to provide a full compliance based on both drug accountability and drug administration.

- **SM Compliance Based on Drug Administration**= [(total dispensed dosage – total missed dosage)/total expected dose based on drug administration] ×100%.