COVER PAGE - PROTOCOL

Protocol Number:	812P311
Title:	An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
Protocol Version:	5.0
Date:	15Dec2020
NCT:	NCT04143217

TITLE PAGE

Protocol Number:	812P311
Title:	An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
IND number:	108,864
Investigational Medicinal Product:	Viloxazine extended-release capsule
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Contract Research Organization (CRO):	[redacted]
CRO Medical Monitor	[redacted]
Supernus Medical Advisor	[redacted]
Phase:	3
Protocol Version:	5.0
Date:	15Dec2020
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator's Signature	Date

Print Name

SUPERNUS PHARMACEUTICALS, INC. PROTOCOL APPROVAL PAGE

Authors: [redacted]

Reviewers: [redacted]

Approvers: [redacted]

CLINICAL PROTOCOL SYNOPSIS

Sponsor: Supernus Pharmaceuticals, Inc.	
Name of Product: SPN-812 (viloxazine extended-release capsule)	**Name of Active Ingredient:** Viloxazine hydrochloride
Protocol Number: 812P311	**Phase of Development:** 3
Full Title of Study: An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder	
Number of Study Sites: Up to 40 study sites in the US	
Number of Subjects: Up to 366 subjects	
Indication: Attention-deficit/hyperactivity disorder (ADHD)	

Objectives:

Primary Safety Objective: To monitor and collect long-term safety data on the use of SPN-812 as monotherapy for the treatment of ADHD in the adult population.

Secondary Efficacy Objective: To evaluate the efficacy of SPN-812 as monotherapy for the treatment of ADHD in the adult population.

Endpoints:

Primary Safety Endpoints:

The primary safety endpoints are adverse events (AEs), clinical safety laboratory tests' results, vital signs, weight, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are:

1) Change from baseline (CFB) in the AISRS total score by visit.
2) CFB in the CGI-S score by visit
3) Percentage of subjects with a CGI-S score of 1 or 2 by visit.
4) CGI-I score by visit.
5) Percentage of subjects with a CGI-I score of 1 or 2 by visit.
6) CFB in the GAD-7 total score by visit.
7) CFB in the AISRS Inattention subscale score and the Hyperactivity/Impulsivity subscale score by visit.
8) AISRS 50% Responder rate (defined as the percentage of subjects with a ≥ 50% reduction in the CFB AISRS total score) by visit.
9) AISRS 30% Responder rate (defined as the percentage of subjects with a ≥ 30% reduction in the CFB AISRS total score) by visit.
10) CFB in the BRIEF-A Global Executive Composite (GEC) T-score by visit.
11) CFB in the BRIEF-A T-score by each Summary Index Scale and subscale by visit.
12) CFB in SDQ total score by visit
13) CFB in SDQ subscale scores by visit
14) CFB in AAQoL total score by visit
15) CFB in AAQoL subscale scores by visit

Study Design:

This is an open-label, long-term, multicenter, flexible-dose study of SPN-812 in adults diagnosed with ADHD. Up to 366 subjects will be enrolled. Subjects who have completed Study 812P306 (a randomized, double-blind, placebo-controlled study of SPN-812 for the treatment of ADHD) will be eligible for enrollment into Study 812P311. Interest and suitability will be ascertained at the last 1 to 2 visits of 812P306 to allow immediate enrollment into Study 812P311 for subjects who complete Study 812P306.

For subjects who complete Study 812P306 and rollover into Study 812P311 on the same day as or ≤7 days after their 812P306 EOS visit, use **INCLUSION/EXCLUSION CRITERIA 'A'** (Section 3.3.2.) and follow **SCHEDULE 'A'** (Table 1; Figure 1). All efficacy and safety assessments collected at the subject's end of study (EOS) Visit (812P306) will serve as their efficacy and safety assessments for Visit 1 (812P311).

For subjects who complete Study 812P306, but who rollover into Study 812P311 more than 7 days after their EOS Visit (812P306), use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2). Efficacy and safety assessments will be collected at a screening visit (Visit 'S') to determine eligibility, and subjects will return to the clinical site for Visit 1 within 28 days of screening to make final eligibility determination and complete baseline efficacy and safety assessments at Visit 1.

De novo subjects (individuals who did not screen/enroll in Study 812P306) may screen and, if eligible, enroll in Study 812P311, **but only after a "Note To File" has been submitted by the Sponsor to the IRB and approved**. The clinical sites will be notified when the approval is granted. For these subjects, use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2).

On a case-by-case basis, a subject who did not complete Study 812P306 (e.g., randomized, dosed SM and had at least one post-baseline AISRS assessment and then early terminated) may be allowed to screen and, if eligible, enroll in Study 812P311, but only after receiving approval from the Site Investigator, Medical Monitor, and the Sponsor. For these subjects, use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2).

All subjects will initiate SPN-812 dosing at 200 mg once daily (QD) during the first 2 weeks of the study. At Visit 2 (Week 2) and all subsequent study visits, per the Investigator's discretion based on the subject's clinical response and tolerability, the dose of SPN-812 can be titrated up or tapered down in increments of 50 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day per week to a target dose within the ranges between 200 and 600 mg/day. Additionally, after the first 12 weeks of dosing (after Visit 4), at the discretion of the Investigator and based on the subject's clinical response, the optimized dose of SPN-812 may be supplemented with an adjunctive FDA-approved stimulant treatment (see Section 4.3.).

Following the day that the subject takes first dose of SPN-812 (Day 1), the subject will have a study visit every 2 weeks for the first 4 weeks of the study (Visit 2 and Visit 3). After Visit 3, study visits (Visits 4-22) will occur 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148 and 156 weeks after first dose of SPN-812 (approximately every 8 weeks). In addition, the site should conduct a follow-up phone call (FPC) to each subject 4 weeks after Study Visits 3-21 to assess adverse events, changes in concomitant medications, obtain results of home pregnancy test (FOCP only). The timing of each study visit (V2-V22) and each FPCs should occur per the Schedule of Events and Assessments (Table 1 [**SCHEDULE 'A'**] or Table 2 [**SCHEDULE 'B'**]) relative to the date of subject's first dose of SPN-812.

Subjects will be contacted for a final safety follow-up (FPC) approximately 1 week after the EOS visit. The clinical course of each AE should be followed for at least 30 days following the date of last dose of SM (due to either EOS or ET) or until resolution, or until, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

Duration of Subject's Participation:

For subjects who follow **SCHEDULE 'A'**, the total study duration per subject, from Visit 1 to Visit 22/EOS will be up to ~156 weeks (3 years) or until SPN-812 becomes approved and commercially available for Adults.

For subjects who follow **SCHEDULE 'B'**, the total study duration per subject is up to 160 weeks, including screening (up to 4 weeks) and from Visit 1 to Visit 22/EOS (up to ~156 weeks [3 years]), or until SPN-812 becomes approved and commercially available for Adults.

Investigational Medicinal Products, Reference Therapy, Doses and Mode of Administration

Study Medication: SPN-812: 100 mg, 150 mg and 200 mg capsules.

Reference Therapy: None

Dose levels: Daily target dose of SPN-812 should be between 200 and 600 mg/day (QD).

Mode of Administration: Orally as intact capsules

Statistical Methodology

All subjects who are enrolled and receive at least one dose of SPN-812 during the OLE study will be in the Safety Population.

All statistical analyses will be based on the Safety Population. Summary statistics for continuous variables will include sample size (N), mean, median, standard deviation, minimum, and maximum. Summary statistics for discrete variables will be presented in terms of frequencies and percentages.

Each efficacy endpoint will be listed and summarized by group of the optimized dose as applicable. Total and subscale scores/points for AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, SDQ and AAQoL will be summarized by dose and visit and will be examined for trends.

More details will be provided in the Statistical Analysis Plan (SAP).

INCLUSION/EXCLUSION CRITERIA 'A'

Inclusion Criteria 'A':

1. Is a male or female who completed Study 812P306 and opts/consents to participate in the study if approved by PI.
2. Continues to be medically healthy and with clinically normal laboratory profiles, vital signs, and electrocardiograms (ECGs), in the opinion of the Investigator, as assessed at Visit 1.
3. Is able to read and understand the Informed Consent Form (ICF).

4. Has signed the ICF.
5. Is willing and able to attend study appointments within specified time windows.
6. Is a female of childbearing potential (FOCP) who is either sexually inactive (abstinent) or, if sexually active, agrees to use one of the following acceptable birth control methods beginning 30 days prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first SM administration
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide
    d. Established hormonal contraceptive

    Females are considered not to be of childbearing potential if they are either post-menopausal (amenorrhea for at least 2 years and serum follicle stimulating hormone (FSH) level of >40 IU/L) or permanently sterilized (e.g., bilateral tubal ligation, hysterectomy, bilateral oophorectomy for 6 months minimum prior to their Visit 1).
7. Is a male who:
    a. Agrees to use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from Visit 1 to ≥ 1 month after the last dose of SM, OR
    b. Has been surgically sterilized prior to Visit 1.

Exclusion Criteria 'A':

1. Is currently participating in another clinical trial other than Study 812P306.
2. Has any current psychiatric disorder per Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5) criteria other than ADHD with the following exceptions: ADHD is primary diagnoses with comorbidity/secondary diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias.
3. Current diagnosis of significant systemic disease and/or of a major psychiatric or neurological disorder, including history or family history of seizures or seizure-like disorders.
4. Current evidence of suicidality (suicidal thoughts or behaviors).
5. Female subjects who are pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable birth control methods throughout the study.
6. Has a positive result on urine drug screen at Visit 1.
7. Use of prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) at the Visit 1 and for the duration of the study.

8. Has a clinical laboratory value, vital sign value or ECG result at Visit 1 that is considered to be clinically significant in the opinion of the Investigator.
9. Has one or more clinical laboratory test values outside the reference range at Visit 1 that, in the opinion of the Investigator, are clinically significant, or any of the following (see Note below):
   - Serum creatinine > 1.5 times the upper limit of normal (ULN);
   - Serum total bilirubin > 1.5 times ULN;
   - Serum alanine aminotransferase or aspartate aminotransferase > 2 times ULN.
10. Has any of the following cardiology findings at Visit 1 (see Note below):
   - Abnormal ECG that is, in the Investigator's opinion, clinically significant;
   - PR interval > 220 ms;
   - QRS interval > 130 ms;
   - QTcF interval > 450 ms (for men) or > 470 ms (for women) (QT corrected using Fridericia's method);
   - Second- or third-degree atrioventricular block;
   - Any rhythm, other than sinus rhythm, that is interpreted by the Investigator to be clinically significant.
11. Any reason that, in the opinion of the Investigator, would prevent the subject from participating in the study.

Note: For subjects who follow **SCHEDULE 'A'**, with the approval from the investigator, medical monitor and the sponsor, repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time within 1 week following Visit 1 prior to first dose for each test to determine eligibility.

INCLUSION/EXCLUSION CRITERIA 'B'

Inclusion Criteria 'B':

1. Is male or female, aged 18 to ≤ 65 years at screening.
2. Is able to read and understand the Informed Consent Form (ICF).
3. Written informed consent obtained from the subject (a signed ICF).
4. Weight within the normal or overweight ranges according to accepted values of the Body Mass Index (BMI) Chart (18.0 to 35.0 kg/m^2).
5. Is able to swallow capsules whole, without crushing, chewing or cutting.
6. Is willing and able to attend study appointments within the specified time windows.
7. Has a primary diagnosis of ADHD according to the DSM-5 classification, with diagnosis made at least 6 months prior to screening and confirmed with Structured Clinical Interview for DSM-5 Clinical Trials version (SCID-5-CT; *de novo* subjects).
8. Has an AISRS total score of ≥ 24 at the screening (Visit 'S').
9. Has a CGI-S score of ≥ 4 (mildly ill or worse) at the screening (Visit 'S').

10. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use one of the following acceptable birth control methods beginning at least 28 days prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first SM administration
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide
    d. Established hormonal contraceptive

    Females are considered not to be of childbearing potential if they are either post-menopausal (amenorrhea for at least 2 years and serum follicle stimulating hormone [FSH] level of >40 IU/L) or permanently sterilized (e.g., bilateral tubal ligation, hysterectomy, bilateral oophorectomy for 6 months minimum prior to screening).
11. Males must:
    a. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from Visit 1 (baseline) to ≥ 1 month after the last dose of SM; or
    b. Have been surgically sterilized prior to the Screening Visit.

Exclusion Criteria 'B'

1. Is currently participating in another clinical trial or has participated in a clinical trial within 60 days prior screening, with the exception of Study 812P306.
2. Is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
3. Female subjects who are pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable birth control methods throughout the study.
4. Has a history of severe drug allergy or hypersensitivity, or known hypersensitivity, to the study medication.
5. Has a history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include subjects with:
    a. A current diagnosis of a major neurological disorder; or
    b. Seizures, seizure disorder or seizure-like events; or a history of seizure disorder within the immediate family (siblings, parents); or Encephalopathy
6. Has any history of schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, autism, post-traumatic stress disorder or obsessive-compulsive disorder.

7. Has any current psychiatric disorder (per DSM-5 criteria) other than ADHD with the following exceptions: ADHD is primary diagnoses with comorbidity/secondary diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias, and subject is not receiving pharmacological treatment for the comorbidity/secondary diagnoses (e.g., antidepressant for MDD) at time of screening nor for the duration of study.
8. Has organic mental disorders, or mental disorders due to a general medical condition (per DSM-5 criteria).
9. Has a current diagnosis or history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) (per DSM-5 criteria) within the 12 months prior to screening; or is assessed by the Investigator as having regularly consumed alcohol exceeding 21 units for males and 14 units for females per week (1 unit equals 340 mL of beer, 115 mL of wine, or 43 mL of spirits) within the 12 months prior to screening.
10. Is currently using, or has a positive result on the drug screening at the Screening Visit for drugs of abuse (alcohol, opiates, methadone, cocaine, methamphetamine [including ecstasy], phencyclidine, propoxyphene, methylphenidate, barbiturates, and benzodiazepines). If subject's serum drug screen for ethanol is positive at screening (Visit 'S') and the investigator determines subject does not have alcohol use disorder, then the subject may have a repeat serum drug screen for ethanol performed before Visit 1 within the allotted screening period (results must be received prior to Visit 1). If second serum drug screen for ethanol is positive, subject is excluded from participating in the study, however, if second serum drug screen for ethanol is negative, subject may proceed to Visit 1.
11. Is a (known or self-identified) current habitual/chronic cannabis user (medicinal or recreational); or
    - Has a positive urine drug screen for cannabis at screening (Visit 'S') and is considered, per the Investigator's judgement, to be a habitual/chronic cannabis user; or
    - Has a positive urine drug screen for cannabis at both the screening (Visit 'S') and follow-up drug screen (Visit 1), even though the subject is not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user.

    Note: Subjects who have a positive urine drug screen for cannabis at screening (Visit 'S') but who are not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user may, with Sponsor approval, undergo an additional urine drug screen at least 4 weeks after the initial urine drug screen at Visit 1 prior to randomization. Subjects must agree to refrain from cannabis use throughout study.
12. Has treatment-resistant ADHD based on a history of receipt of >2 approved ADHD medications that failed to adequately improve the subject's symptoms, with the

exception of subjects who completed Study 812P306. A subject who is naïve to ADHD treatment is not excluded from study participation.

13. Has any other disorder for which its treatment takes priority over treatment of ADHD or is likely to interfere with study treatment, impair treatment compliance, or interfere with interpretation of study results.
14. Has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin that has not been in remission for > 5 years prior to the first dose of SM.
15. Has or has had one or more of the following conditions considered clinically significant/relevant by the Investigator in the context of the study:
    - cardiovascular disease
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse < 50 bpm)
    - tachycardia (pulse > 100 bpm)
    - respiratory disease
    - hepatic impairment or renal insufficiency
    - metabolic disorder
    - endocrine disorder
    - gastrointestinal disorder
    - hematological disorder
    - infectious disorder
    - any clinically significant immunological condition
    - dermatological disorder
16. Exhibits clinically significant abnormal vital signs at screening (see Note below).
17. Has one or more screening clinical laboratory test values outside the reference range that, in the opinion of the Investigator, are clinically significant, or any of the following (see Note below):
    - Serum creatinine > 1.5 × the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 × ULN;
    - Serum alanine aminotransferase or aspartate aminotransferase > 2 × ULN.
18. Has any of the following cardiology findings at screening (see Note below):
    - Abnormal ECG that is, in the Investigator's opinion, clinically significant;
    - PR interval > 220 ms;
    - QRS interval > 130 ms;
    - QTcF interval > 450 ms (for men) or > 470 ms (for women) (QT corrected using Fridericia's method);
    - Second- or third-degree atrioventricular block;
    - Any rhythm, other than sinus rhythm, that is interpreted by the Investigator to be clinically significant.

19. Has any disease or medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
20. Evidence of infection with hepatitis B or C, or human immunodeficiency virus (HIV)-1 or HIV-2, as determined by results of testing at screening.
21. Lost or donated more than 450 mL of blood during the 30 days prior to screening.
22. Use of any investigational drug or prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) within 30 days or 5 half-lives prior to Visit 1 (baseline) (whichever is longer) during the screening period or anticipated for the duration of the study.
23. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations or near drowning with hospital admission.
24. Has attempted suicide within the 6 months prior to screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the 6 months prior to screening.
25. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

Note: For subjects who follow **SCHEDULE 'B'**, with the approval from the investigator, medical monitor and the sponsor, repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time for each test, at the discretion of the Investigator, as long as the repeat test result is available within the 28-day screening period (prior to first study dose) to determine eligibility.

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AAQoL	Adult ADHD Quality of Life scale
ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-IV/5	ADHD Rating Scale IV/5
ADR	Adverse drug reaction
AE	Adverse event
AISRS	ADHD Investigator Symptom Rating Scale
ANCOVA	Analysis of covariance
ATC	Anatomical-Therapeutic-Chemical (code)
BRIEF-A	Behavior Rating Inventory of Executive Function–Adult Version
BMI	Body mass index
CAARS	Conners Adult ADHD Rating Scale
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CI	Confidence interval
CL/F	Apparent clearance
CRA	Clinical research associate
CRO	Clinical research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders – 4^{th}/5^{th} Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
ER	Extended release
ET	Early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOCP	Females of childbearing potential
FSH	Follicle stimulating hormone
FPC	Follow-up phone call
GAD-7	Generalized Anxiety Disorder 7-Item scale
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
ICF	Informed consent form
ICH	International Conference on Harmonisation
IR	Immediate release
IRB	Institutional review board
IWRS	Interactive web response system
LS	Least square
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	Mixed model for repeated measures
MNAR	Missing not at random
OLE	Open-label extension
PFC	Prefrontal cortex
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred term
QD	Once daily
QTcF	QT corrected using Fridericia's method
REML	Restricted maximum likelihood
SADR	Suspected adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDQ	Symptoms of Depression Questionnaire
SM	Study medication
SNMA	Serotonin norepinephrine modulating agent
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
Vd/F	Apparent volume of distribution
WBC	White blood cell
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Background

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric condition characterized by inattention, hyperactivity and impulsivity. Epidemiological data suggest that ADHD affects up to 8% of children in the United States, while the estimated prevalence in the adult population is between 0.3% and 5% (**McCann and Roy-Byrne, 2004**). The standard pharmaceutical treatments for ADHD include psychostimulants, non-stimulants, and antidepressants. Stimulants (e.g., methylphenidate, amphetamine) are the first-line pharmacotherapies for the treatment of ADHD. However, 10% to 30% of patients do not adequately respond to stimulants or experience intolerable adverse events (AEs; e.g., decreased appetite, sleep problems, headaches) (**Briars and Todd, 2016**).

SPN-812 (extended-release viloxazine) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA). The active substance in SPN-812 is viloxazine, whose mechanism of action is multimodal with antagonistic activity observed at the 5-HT_{2B} receptor and agonistic activity at the 5-HT_{2C} receptor, as well as weaker antagonistic effects at $ADR_{\alpha 1B}$, $ADR_{\beta 2}$ and 5-H_{T7} receptors. Additionally, SPN-812 acts as a modulator with inhibitory effects at the norepinephrine reuptake transporter. Viloxazine was previously marketed in several European countries as an antidepressant as an immediate-release (IR) product. An extended-release (ER) formulation of viloxazine, SPN-812, has been developed by Supernus to prolong the release and absorption of viloxazine post-administration, thereby minimizing fluctuations in plasma drug levels and allowing longer dosing intervals for a drug with a relatively short half-life. SPN-812 was developed for potential use in the treatment of subjects with ADHD, based on the pharmacological properties and favorable safety profile and the current unmet medical need for effective long-acting, non-stimulant ADHD treatment in children and adolescents. SPN-812 is being evaluated in the current study for potential use in the treatment of ADHD in adults based on the pharmacological properties and favorable safety profile of viloxazine.

1.2. Clinical Information

The safety, pharmacokinetics (PK) and drug-drug interactions for the IR and ER formulations of SPN-812 have been evaluated in multiple Phase 1 studies in healthy adults. As of April 2019, a number of studies evaluating the efficacy and safety of SPN-812 treatment for ADHD in pediatric and adult populations have been completed, including one Phase 2 study in adults (18 to 65 years of age; 812P201), one pediatric Phase 2 in children (6 to 12 years of age; 812P202), and four pediatric Phase 3 studies, two in children (6 to 11 years of age; 812P301 and 812P303) and two in adolescents (12 to 17 years of age; 812P302 and 812P304). In addition, there is an ongoing pediatric open-label extension (OLE) safety study in children and adolescents (6 to 17 years of age; 812P310). Key findings from the completed Phase 1, Phase 2 and Phase 3 studies

are summarized below. Additional details are provided in the SPN-812 Investigator's Brochure.

1.2.1. Phase 1 Studies

Phase 1 studies include comparison of single and two-bead SPN-812 extended release (ER) formulations to an SPN-812 immediate release (IR) formulation at single and multiple doses (812P102 and 812P103, respectively), evaluation of food and sprinkling effects (812P105), drug-drug interactions (DDIs) on CYP1A2, 2D6, and 3A4 substrates with evaluation of SPN-812 ER metabolism in CYP2D6 poor metabolizers vs. CYP2D6 extensive metabolizers (812P113.1), DDI with d-amphetamine (812P113.2), DDI with methylphenidate (812P113.3), evaluation of the effect of alcohol on SPN-812 metabolism (812P115), evaluation of the effect of renal impairment on SPN-812 metabolism (812P112.1), evaluation of multiple dose SPN-812 on QT Interval (812P117), and evaluation of maximum tolerable doses and cardiac safety in a single and multiple-ascending dose study (812P120) have also been evaluated. In addition, a [14C]-labelled oral IR solution was used to examine human absorption, metabolism, and excretion (812P111).

Results from these studies demonstrated that 200 mg single dose of an extended release SPN-812 formulation resulted in a mean maximum plasma concentration (Cmax) of 1.33 µg/mL, area under the plasma concentration-time curve extrapolated to infinity (AUCinf) of 27.3 hr*µg/mL, median time to maximum concentration (Tmax) of 5 hours, and a half-life of approximately 7 hours (812P103). Lower mean Cmax was observed for SPN-812 as compared to SPN-812 IR and by 48 hours, overall viloxazine exposure was comparable between the two formulations. The rate of absorption of viloxazine was formulation dependent; SPN-812 exhibited a slower absorption rate than SPN-812 IR. Following multiple-dose administration of SPN-812 on consecutive days, steady-state was achieved by the second day of multiple dosing. Little systemic accumulation of viloxazine was observed as no major increase in pharmacokinetic (PK) parameters was observed following multiple administration of SPN-812 compared to single dose administration, during the same time interval.

The relative bioavailability of viloxazine was not affected when SPN-812 was administered via sprinkle over food. SPN-812 interacted as a strong inhibitor of CYP1A2, a weak inhibitor of CYP2D6, a weak inhibitor of CYP3A4; and displayed no significant differences in metabolism within CYP2D6 poor metabolizers and CYP2D6 extensive metabolizers (812P113.1). There was no DDI between SPN-812 and d-amphetamine (812P113.2) nor SPN-812 and methylphenidate (812P113.3). In addition, there was no dose dumping observed with co-administration of alcohol with SPN-812 (812P115). Renal impairment resulted in a 1.09-fold, 1.3-fold, and 1.9-fold increase in AUC for mild, moderate, and severe renal impairment subjects receiving 400 mg SPN-812 as compared to healthy subjects (812P112.1). Multiple doses of 1800 mg (supratherapeutic) SPN-812 did not affect cardiac repolarization as measured by QTcI and QTcF or other electrocardiographic parameters (812P117). In the single ascending/multiple ascending dose study, SPN-812 was well tolerated up to 2100

mg/day as a single dose and up to 1800 mg/day as multiple doses given once daily for 5 consecutive days. Intolerable adverse events (AEs) were not observed at doses of up to 1800 mg/day. SPN-812 at a single supra-therapeutic dose had no effect on cardiac repolarization or other electrocardiographic parameters, other than a slight increase in heart rate consistent with the known anticholinergic effect of viloxazine (812P120).

In the human absorption, metabolism, and excretion study, absorption of the isomers, R- and S-viloxazine, was rapid with a median Tmax of 1.0 hour and showed a 2:1 concentration ratio, respectively. Nearly 100% of the radioactive dose was recovered with approximately 90% being recovered within 24 hours of administration, demonstrating complete absorption of the drug followed by rapid elimination. The primary circulating form was SPN 812; the only metabolite found above 10% total radioactivity was de-activated hydroxylated glucuronide.

The most common AEs in the Phase 1 studies in healthy adults were somnolence and headache. Most AEs were mild; none were severe or serious. No clinically significant, study medication-related findings were observed for laboratory or electrocardiogram (ECG) tests in any study. In general, SPN 812 is considered to be well tolerated with no safety events observed that would be unexpected for viloxazine.

1.2.2. Phase 2 Studies

The randomized, blinded, proof-of-concept Phase 1/2 study 812P201 compared an IR formulation of SPN-812 and placebo administered three times a daily in a dose range of 150 to 300 mg/day in 52 adults (26 per treatment) with ADHD. In addition to assessing the safety and tolerability of SPN-812 IR, scores of both the Investigator-rated and patient-rated Conners Adult ADHD Rating Scale (CAARS) were collected at weekly intervals during the 6-week treatment period. Treatment with SPN-812 IR showed a statistically significant reduction in median CAARS total ADHD symptom score compared to placebo. Treatment-emergent AEs were reported in 23 (88.5%) subjects in the SPN-812 IR group and in 18 (72.0%) subjects in the placebo group. The most common AEs in SPN-812 IR group were nausea, decreased appetite, headache, and insomnia. There were no clinically significant ECGs, clinical laboratory test results, vital signs, or physical examination findings in either group during the study. No serious adverse events (SAEs) or deaths occurred during the study.

The 812P202 study in children with ADHD assessed the effect of SPN-812 in reducing the symptoms of ADHD as measured by the ADHD Rating Scale IV (ADHDRSIV). Subjects aged 6 to 12 years were randomized in a 1:2:2:2:2 ratio of placebo or active treatment (SPN-812 100, 200, 300, or 400 mg) and received 3 weeks of titration at 100 mg/week followed by 5 weeks of maintenance dosing for a total of 8 weeks of treatment. Mean ADHD-RS-IV Total Scores improved throughout treatment in all groups. Differences in change from baseline to end of study between SPN-812 and placebo were statistically significant at the three higher SPN-812 doses ($p \leq 0.0310$) but not at the 100-mg dose. The treatment effect compared to placebo increased with the dose; however, pairwise comparisons among the four active treatment groups showed no statistically significant differences among the SPN-812 doses. All doses of SPN-812

were well tolerated with no serious or severe AEs and no clinically significant effect on laboratory values of common hematology and chemistry tests. The most common AEs were somnolence, decreased appetite, and headache.

1.2.3. Phase 3 Studies

Four pivotal Phase 3 studies of SPN-812 for the treatment of ADHD have been completed in the pediatric population: two studies in children 6 to 11 years of age (evaluating 100 mg, 200 mg, and 400 mg) and two studies in adolescents 12 to 17 years of age (evaluating 200 mg, 400 mg, and 600 mg). As of April 2019, results are available for all four studies.

Children (6 to 11 years of age)

Study 812P301 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 100 mg/day and 200 mg/day for the treatment of ADHD in children 6 to 11 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment for 6 weeks (1 week of titration followed by 5 weeks of maintenance at a fixed dose) with SPN-812 100 mg/day or 200 mg/day led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 47 (29.6%), 74 (48.1%), and 77 (47.8%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, decreased appetite, and headache. AEs were considered to be at least possibly treatment related in 16 (10.1%), 41 (26.6%), and 56 (34.8%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 2 (1.3%), 5 (3.2%), and 2 (1.2%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. SAEs were reported in 3 subjects: 2 in the SPN-812 100 mg/day treatment group and 1 in the SPN-812 200 mg/day treatment group. All SAEs were considered unlikely related or not related to study medication. No deaths occurred during the study.

Study 812P303 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 200 mg/day and 400 mg/day for the treatment of ADHD in children 6 to 11 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 200 mg/day or 400 mg/day for 8 weeks (3 weeks of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 47 (45.6%), 56 (52.3%), and 58 (58.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, headache, decreased appetite, and fatigue. AEs were considered to be at least possibly treatment related in 22 (21.4%), 42 (39.3%), and 51 (51.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. AEs

led to permanent study medication discontinuation (and study withdrawal) in 3 (2.9%), 6 (5.6%), and 4 (4.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. SAEs were reported in 3 subjects: 1 in the SPN-812 200 mg/day treatment group and 2 in the SPN-812 400 mg/day treatment group. No deaths occurred during the study.

Adolescents (12 to 17 years of age)

Study 812P302 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 200 mg/day and 400 mg/day for the treatment of ADHD in adolescents 12 to 17 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 200 mg/day or 400 mg/day for 6 weeks (1 week of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 38 (36.5%), 43 (43.4%), and 56 (53.3%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, decreased appetite, headache, fatigue and nausea. AEs were considered to be at least possibly treatment related in 20 (19.2%), 32 (32.3%), and 41 (39.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 0, 4 (4.0%), and 2 (1.9%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. SAEs were reported in 2 subjects, both in the SPN-812 200 mg/day treatment group. No deaths occurred during the study.

Study 812P304 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 400 mg/day and 600 mg/day for the treatment of ADHD in adolescents 12 to 17 years of age. The primary endpoint of the study was the change from baseline in ADHD--RS-5 Total Score at end of study. Treatment with SPN-812 400 mg/day for 7 weeks (2 weeks of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo; however, ADHD-RS-5 Total Score during treatment with SPN-812 600 mg/day did not showed a statistically significant improvement compared to placebo.

Throughout treatment, AEs were reported in 39 (40.2 %), 58 (58.0%), and 55 (55.6%) subjects in the placebo, SPN-812 400 mg/day, and SPN-812 600 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, fatigue, headache, decreased appetite, and nausea. AEs were considered to be at least possibly treatment related in 18 (18.6%), 44 (44.0 %), and 45 (45.5%) subjects in the placebo, SPN-812 400 mg/day, and SPN-812 600 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 1 (1.0%), 4 (4.0%), and 5 (5.1%) subjects in the placebo, SPN-812 400 mg/day, and SPN-812 600 mg/day treatment groups, respectively. SAEs were reported in 2 subjects, both in the SPN-812 400 mg/day treatment group. No deaths occurred during the study.

1.3. Study Rationale

The pharmacological similarity of viloxazine to other agents with proven efficacy in ADHD provides the rationale for a clinical trial to test its long-term effectiveness and safety in this indication. The effectiveness and safety of SPN-812 has been demonstrated in the 812P201 study, the change from baseline in CAARS total score at end of study (EOS) was significantly reduced with SPN-812 IR 150 to 300 mg/day compared to placebo in adults (ages ≥ 18 years of age) with ADHD. The efficacy and safety of SPN-812 showed positive results in three separate trials that assessed the effects of 200 mg/day and two separate trials assessing the effects of 400 mg/day. The proposed doses of 200 to 600 mg/day SPN-812 in the current open label extension study (812P311) and the previous randomized, double-blind, placebo-controlled study (812P306) are expected to provide similar exposure in adults compared to that provided by 200 to 400 mg/day in children and adolescents. This dose range was used in previous Phase I (single and multiple dose) studies where a low number of AEs were observed, and those AEs that were observed were mild to moderate in severity. This Open-Label Extension (OLE) study will determine the additional long-term safety and efficacy of SPN-812 in adult patients with ADHD among eligible subjects that have completed 812P306.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Safety Objective:

To monitor and collect long-term safety data on the use of SPN-812 as monotherapy for the treatment of ADHD in the adult population.

2.2. Secondary Efficacy Objective

To evaluate the efficacy of SPN-812 as monotherapy for the treatment of ADHD in the adult population.

2.3. Primary Safety Endpoints

The primary safety endpoints are adverse events (AEs), clinical safety laboratory test results, vital signs, weight, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS).

2.4. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1) Change from baseline (CFB) in the AISRS total score by visit.
2) CFB in the CGI-S score by visit.
3) Percentage of subjects with a CGI-S score of 1 or 2 by visit.
4) CGI-I score by visit.
5) Percentage of subjects with a CGI-I score of 1 or 2 by visit.
6) CFB in the GAD-7 total score by visit.
7) CFB in the AISRS Inattention subscale score and Hyperactivity/Impulsivity subscale scores by visit.
8) AISRS 50% Responder rate (defined as the percentage of subjects with a ≥ 50% reduction in the CFB AISRS total score) by visit.
9) AISRS 30% Responder rate (defined as the percentage of subjects with a ≥ 30% reduction in the CFB AISRS total score) by visit.
10) CFB in the BRIEF-A Global Executive Composite (GEC) T-score by visit.
11) CFB in the BRIEF-A T-score by each Summary Index Scale and subscale by visit.
12) CFB in the SDQ total score by visit.
13) CFB in the SDQ subscale scores by visit.
14) CFB in the AAQoL total score by visit.
15) CFB in the AAQoL subscale scores by visit.

3. INVESTIGATIONAL STUDY PLAN

3.1. Overall Study Design and Plan

This is an open-label, long-term, multicenter, flexible-dose study of SPN-812 in adults diagnosed with ADHD. Up to 366 subjects will be enrolled. Subjects who have completed Study 812P306 (a randomized, double-blind, placebo-controlled study of SPN-812 for the treatment of ADHD) will be eligible for enrollment into the Study 812P311. Interest and suitability will be ascertained at the last 1 to 2 visits of 812P306 to allow immediate enrollment into Study 812P311 for subjects who complete Study 812P306.

For subjects who complete Study 812P306 and rollover into Study 812P311 on the same day as or ≤7 days after 812P306 EOS visit, use **INCLUSION/EXCLUSION CRITERIA 'A'** (Section 3.3.2.) and follow **SCHEDULE 'A'** (Table 1; Figure 1). All efficacy and safety assessments collected at the subject's end of study (EOS) Visit (812P306) will serve as their efficacy and safety assessments for Visit 1 (812P311).

For subjects who complete Study 812P306, but who rollover into Study 812P311 more than 7 days after their EOS Visit (812P306), use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2). All efficacy and safety assessments will be collected at a screening visit (Visit 'S') to determine eligibility, and subjects will return to the clinical site for Visit 1 within 28 days of screening to make final eligibility determination and complete baseline efficacy and safety assessments.

De novo subjects (individuals who did not screen/enroll in Study 812P306) may screen and, if eligible, enroll in Study 812P311, **but only after a "Note To File" has been submitted by the Sponsor to the IRB and approved**. The clinical sites will be notified when the approval is granted. For these subjects, use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2). Subjects who follow **SCHEDULE 'B'** and are taking any prohibited medications at screening (e.g., ADHD medications) should discontinue use (washout) at least 7-days prior to first dose of OLE SM.

On a case-by-case basis, a subject who did not complete Study 812P306 (e.g., randomized, dosed SM and had at least one post-baseline AISRS assessment and then early terminated) may be allowed to screen and, if eligible, enroll in Study 812P311, but only after receiving approval from the Site Investigator, Medical Monitor, and the Sponsor. For these subjects, use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2).

All subjects will initiate SPN-812 dosing at 200 mg/day once daily (QD) during the first 2 weeks of the study. At Visit 2 and all subsequent study visits, per the Investigator's discretion and based on Investigator's assessment of the subject's clinical response and tolerability, the dose of SPN-812 can be titrated up or tapered down in increments of 50 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day per week to a target dose within the ranges between 200 and 600 mg/day. Additionally, after the first 12 weeks of dosing (after Visit 4), at the discretion of the Investigator and based on the subject's clinical

response, the optimized dose of SPN-812 may be supplemented with an adjunctive FDA-approved stimulant treatment (see Section 4.3.).

Following the day that the subject takes first dose of SPN-812 (Day 1), the subject will have a study visit every 2 weeks for the first 4 weeks of the study (Visit 2 and Visit 3). After Visit 3, study visits (Visits 4-22) will occur 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148 and 156 weeks after first dose of SPN-812 (approximately every 8 weeks). A Point of Care (POC) urine drug screen (Test 1 and 2) will be completed at Visits 1, 6, 8, 10, 12, 14, 16, 18, and 20 (Table 3). In addition, the site should conduct a follow-up phone call (FPC) with each subject 4 weeks after Study Visits 3 thru Visit 21 to assess adverse events, changes in concomitant medications and obtain results of home pregnancy test (FOCP only). Subjects will also be contacted for final safety follow-up (FPC) approximately 1 week after the End of Study (EOS) visit.

The timing of Study Visits 2-22 and FPCs should occur per the Schedule of Events and Assessments (**SCHEDULE 'A'** [Table 1] or **SCHEDULE 'B'** [Table 2]) by day of study relative to the date of subject's first dose of SPN-812.

Note: The same assessments/procedures are performed at Study Visits 2-22 between **SCHEDULE 'A'** and **SCHEDULE 'B'**.

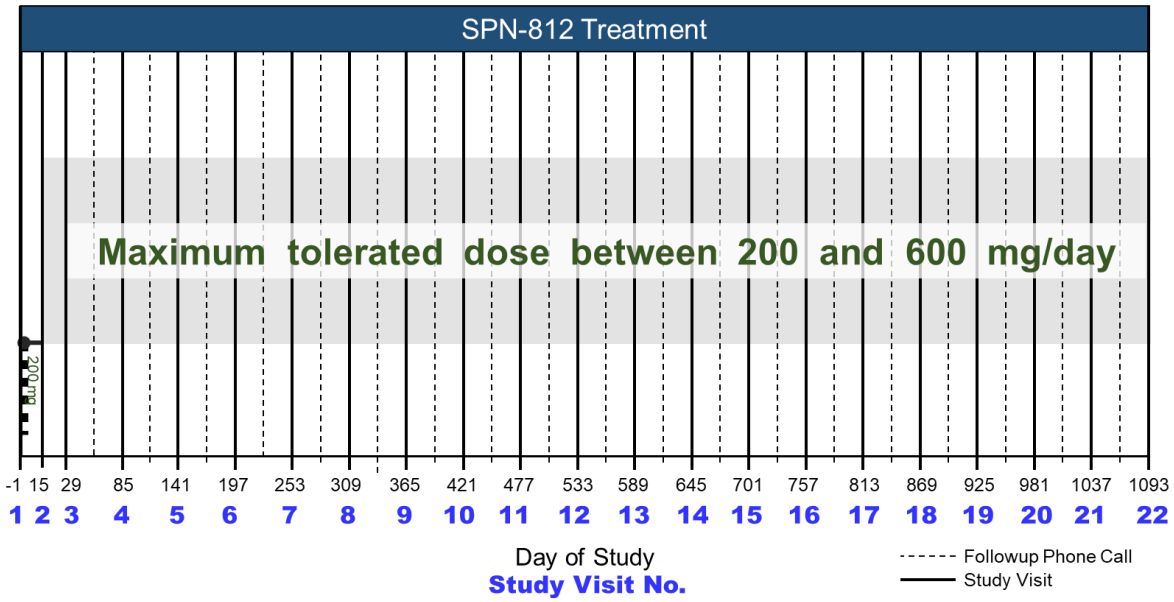
For subjects who follow **SCHEDULE 'A'**, the total study duration per subject from Visit 1 to Visit 22/EOS will be ~156 weeks (3 years) or until SPN-812 becomes approved and commercially available for Adults.

For subjects who follow **SCHEDULE 'B'**, the total study duration per subject is up to 160 weeks, including screening (up to 4 weeks) and from Visit 1 to Visit 22/EOS (up to ~156 weeks [3 years]), or until SPN-812 becomes approved and commercially available for Adults.

Details of each study visit are provided in Section 5.

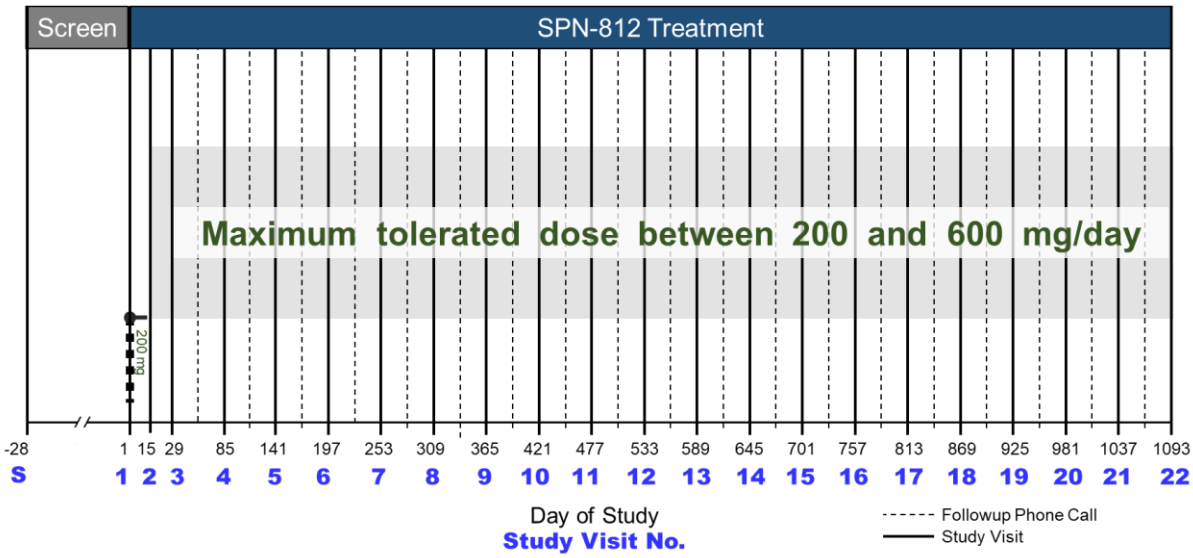
Unscheduled visits may be conducted at the discretion of the Investigator for safety reasons or to dispense additional SM throughout the study. AEs, concomitant medications and caffeine use will be assessed at all scheduled and unscheduled visits.

Figure 1 SCHEDULE 'A' Study Schematic



Note: Subjects who complete Study 812P306 and rollover into Study 812P311 on the same day as or ≤ 7 days after their 812P306 EOS visit will follow **SCHEDULE 'A.** The assessments collected during 812P306 EOS Visit will serve as assessments for 812P311 Visit 1 (Day -1). All subsequent study visits (2-22) will occur relative to the day/date of subject's first dose of SPN-812 (Day 1). Subjects who follow **SCHEDULE 'A'** will take first dose of OLE SM the morning after Visit 1. All subjects will initiate SPN-812 dosing at 200 mg once daily (QD) during the first 2 weeks of the study. At and after Visit 2, per the Investigator's discretion based on the subject's clinical response and tolerability, the dose of SPN-812 can be titrated up or tapered down in increments of 50 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day per week to a target dose within the range between 200 and 600 mg/day. Subjects who complete the OLE Safety study should receive a follow-up phone call for safety 1 week after EOS.

Figure 2 SCHEDULE 'B' Study Schematic



Note: Subjects who complete Study 812P306, but who rollover into Study 812P311 more than 7 days after their EOS Visit (812P306), subjects who were early terminated during Study 812P306, and *de novo* subjects will follow **SCHEDULE 'B'.** Screening is up to 28 days after obtaining informed consent at Visit 'S'. Subject taking any prohibited medications at screening (e.g., ADHD medications) should discontinue use (washout) at least 7-days prior to first dose of OLE SM. All subsequent study visits (2-22) will occur relative to the day/date of subject's first dose of SPN-812 (Day 1). Subjects who follow **SCHEDULE 'B'** will take first dose of OLE SM the morning of Visit. All subjects will initiate SPN-812 dosing at 200 mg once daily (QD) during the first 2 weeks of the study. At and after Visit 2, per the Investigator's discretion based on the subject's clinical response and tolerability, the dose of SPN-812 can be titrated up or tapered down in increments of 50 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day per week to a target dose within the range between 200 and 600 mg/day. Subjects who complete the OLE Safety study should receive a follow-up phone call for safety 1 week after EOS.

3.2. Rationale for Study Design

An open-label uncontrolled study with safety as the primary endpoint is a standard design for evaluating the long-term safety of an investigational product in a clinical trial setting. The secondary efficacy endpoints for this study were selected to align with the efficacy endpoints used in the Phase 3 adult ADHD study 812P306 from which subjects would be enrolled.

A dose level range of 200 to 600 mg/day SPN-812 was selected based on the efficacy results from the Phase 2 adult and child phase 2 and Phase 3 pediatric studies, with flexible dosing permitted to align with real-world prescribing and treatment practices for ADHD.

3.3. Study Population

3.3.1. Number of Subjects

Up to 366 subjects will be enrolled. Subjects who completed Study 812P306 (a randomized, double-blind, placebo-controlled study of SPN-812 for the treatment of ADHD) will be eligible for enrollment into Study 812P311.

On a case-by-case basis, a subject who did not complete Study 812P306 (e.g., randomized, dosed SM and had at least one post-baseline AISRS assessment and then early terminated) may be allowed to screen and, if eligible, enroll in Study 812P311, **but only after receiving approval from the Site Investigator, Medical Monitor, and the Sponsor**.

De novo subjects (individuals who did not screen/enroll in Study 812P306) may screen and, if eligible, enroll in Study 812P311, **but only after a "Note To File" has been submitted by the Sponsor to the IRB and approved**. The clinical sites will be notified when the approval is granted.

3.3.2. INCLUSION/EXCLUSION CRITERIA 'A'

Use only for subjects who completed Study 812P306 and rolled over into Study 812P311 on **same day** as or **≤ 7 days after** their 812P306 EOS visit.

3.3.2.1. Inclusion Criteria 'A'

1. Is a male or female who completed Study 812P306 and opts/consents to participate in the study if approved by PI.
2. Continues to be medically healthy and with clinically normal laboratory profiles, vital signs, and electrocardiograms (ECGs), in the opinion of the Investigator, assessed at Visit 1.
3. Is able to read and understand the Informed Consent Form (ICF).
4. Has signed the ICF.

5. Is willing and able to attend study appointments within specified time windows.
6. Is a female of childbearing potential (FOCP) who is either sexually inactive (abstinent) or, if sexually active, agrees to use one of the following acceptable birth control methods beginning at least 30 days prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first SM administration
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide
    d. Established hormonal contraceptive

    Females are considered not to be of childbearing potential if they are either post-menopausal (amenorrhea for at least 2 years and serum follicle stimulating hormone [FSH] level of >40 IU/L) or permanently sterilized (e.g., bilateral tubal ligation, hysterectomy, bilateral oophorectomy for 6 months minimum prior to their Visit 1).
7. Is a male who:
    a. Agrees to use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from Visit 1 to ≥ 1 month after the last dose of SM,
    OR
    b. Has been surgically sterilized prior to Visit 1.

3.3.2.2. Exclusion Criteria 'A'

1. Is currently participating in another clinical trial other than Study 812P306.
2. Has any current psychiatric disorder per Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5) criteria other than ADHD with the following exceptions: ADHD is primary diagnoses with comorbidity/secondary diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias.
3. Current diagnosis of significant systemic disease and/or of a major psychiatric or neurological disorder, including history or family history of seizures or seizure-like disorders.
4. Current evidence of suicidality (suicidal thoughts or behaviors).
5. Female subjects who are pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable birth control methods throughout the study.
6. Has a positive result on urine drug screen at Visit 1.
7. Use of prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) at the Visit 1 for the duration of the study.
8. Has a clinical laboratory value, vital sign value or ECG result at Visit 1 that is considered to be clinically significant in the opinion of the Investigator.

9. Has one or more clinical laboratory test values outside the reference range at Visit 1 that, in the opinion of the Investigator, are clinically significant, or any of the following (see Note below):
   - Serum creatinine > 1.5 times the upper limit of normal (ULN);
   - Serum total bilirubin > 1.5 times ULN;
   - Serum alanine aminotransferase or aspartate aminotransferase > 2 times ULN.
10. Has any of the following cardiology findings at Visit 1 (see Note below):
   - Abnormal ECG that is, in the Investigator's opinion, clinically significant;
   - PR interval > 220 ms;
   - QRS interval > 130 ms;
   - QTcF interval > 450 ms (for men) or > 470 ms (for women) (QT corrected using Fridericia's method);
   - Second- or third-degree atrioventricular block;
   - Any rhythm, other than sinus rhythm, that is interpreted by the Investigator to be clinically significant.
11. Any reason that, in the opinion of the Investigator, would prevent the subject from participating in the study.

Note: For subjects who follow **SCHEDULE 'A'**, with the approval from the investigator and the sponsor, repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time within 1 week following Visit 1 prior to first dose for each test to determine eligibility.

3.3.3. INCLUSION/EXCLUSION CRITERIA 'B'

Use only for delayed rollover subjects (rolled over into Study 812P311 more than 7 days after their 812P306 EOS Visit), subjects who were early terminated during Study 812P306, and *de novo* subjects.

3.3.3.1. Inclusion Criteria 'B':

1. Is male or female, aged 18 to ≤ 65 years at screening.
2. Is able to read and understand the Informed Consent Form (ICF).
3. Written informed consent obtained from the subject (a signed ICF).
4. Weight within the normal or overweight ranges according to accepted values of the Body Mass Index (BMI) Chart (18.0 to 35.0 kg/m^2).
5. Is able to swallow capsules whole, without crushing, chewing or cutting.
6. Is willing and able to attend study appointments within the specified time windows.
7. Has a primary diagnosis of ADHD according to the DSM-5 classification, with diagnosis made at least 6 months prior to screening and confirmed with Structured Clinical Interview for DSM-5 Clinical Trials version (SCID-5-CT; *de novo* subjects).
8. Has an AISRS total score of ≥ 24 at the screening (Visit 'S').
9. Has a CGI-S score of ≥ 4 (mildly ill or worse) at the screening (Visit 'S').

10. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use one of the following acceptable birth control methods beginning at least 28 days prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first SM administration
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide
    d. Established hormonal contraceptive

    Females are considered not to be of childbearing potential if they are either post-menopausal (amenorrhea for at least 2 years and serum follicle stimulating hormone [FSH] level of >40 IU/L) or permanently sterilized (e.g., bilateral tubal ligation, hysterectomy, bilateral oophorectomy for 6 months minimum prior to screening).
11. Males must:
    a. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from Visit 1 (baseline) to ≥ 1 month after the last dose of SM; or
    b. Have been surgically sterilized prior to the Screening Visit.

3.3.3.2. Exclusion Criteria 'B'

1. Is currently participating in another clinical trial or has participated in a clinical trial within 60 days prior to screening, with the exception of Study 812P306.
2. Is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
3. Female subjects who are pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable birth control methods throughout the study.
4. Has a history of severe drug allergy or hypersensitivity, or known hypersensitivity, to the study medication.
5. Has a history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include subjects with:
    a. A current diagnosis of a major neurological disorder; or
    b. Seizures, seizure disorder or seizure-like events; or a history of seizure disorder within the immediate family (siblings, parents); or Encephalopathy
6. Has any history of schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, autism, post-traumatic stress disorder or obsessive-compulsive disorder.
7. Has any current psychiatric disorder (per DSM-5 criteria) other than ADHD with the following exceptions: ADHD is primary diagnoses with comorbidity/secondary

diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias, and subject is not receiving pharmacological treatment for the comorbidity/secondary diagnoses (e.g., antidepressant for MDD) at time of screening nor for the duration of study.

8. Has organic mental disorders, or mental disorders due to a general medical condition (per DSM-5 criteria).
9. Has a current diagnosis or history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) (per DSM-5 criteria) within the 12 months prior to screening; or is assessed by the Investigator as having regularly consumed alcohol exceeding 21 units for males and 14 units for females per week (1 unit equals 340 mL of beer, 115 mL of wine, or 43 mL of spirits) within the 12 months prior to screening.
10. Is currently using, or has a positive result on the drug screening at the Screening Visit for drugs of abuse (alcohol, opiates, methadone, cocaine, methamphetamine [including ecstasy], phencyclidine, propoxyphene, methylphenidate, barbiturates, and benzodiazepines). If subject's serum drug screen for ethanol is positive at screening (Visit 'S') and the investigator determines subject does not have alcohol use disorder, then the subject may have a repeat serum drug screen for ethanol performed before Visit 1 within the allotted screening period (results must be received prior to Visit 1). If second serum drug screen for ethanol is positive, subject is excluded from participating in the study, however, if second serum drug screen for ethanol is negative, subject may proceed to Visit 1.
11. Is a (known or self-identified) current habitual/chronic cannabis user (medicinal or recreational); or
    - Has a positive urine drug screen for cannabis at screening (Visit 'S') and is considered, per the Investigator's judgement, to be a habitual/chronic cannabis user; or
    - Has a positive urine drug screen for cannabis at both the screening (Visit 'S') and follow-up drug screen (Visit 1), even though the subject is not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user.

    Note: Subjects who have a positive urine drug screen for cannabis at screening (Visit 'S') but who are not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user may, with Sponsor approval, undergo an additional urine drug screen at least 4 weeks after the initial urine drug screen at Visit 1 prior to randomization. Subjects must agree to refrain from cannabis use throughout study.
12. Has treatment-resistant ADHD based on a history of receipt of >2 approved ADHD medications that failed to adequately improve the subject's symptoms, with the

exception of subjects who completed Study 812P306. A subject who is naïve to ADHD treatment is not excluded from study participation.

13. Has any other disorder for which its treatment takes priority over treatment of ADHD or is likely to interfere with study treatment, impair treatment compliance, or interfere with interpretation of study results.
14. Has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin that has not been in remission for > 5 years prior to the first dose of SM.
15. Has or has had one or more of the following conditions considered clinically significant/relevant by the Investigator in the context of the study:
    - cardiovascular disease
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse < 50 bpm)
    - tachycardia (pulse > 100 bpm)
    - respiratory disease
    - hepatic impairment or renal insufficiency
    - metabolic disorder
    - endocrine disorder
    - gastrointestinal disorder
    - hematological disorder
    - infectious disorder
    - any clinically significant immunological condition
    - dermatological disorder
16. Exhibits clinically significant abnormal vital signs at screening (see Note below).
17. Has one or more screening clinical laboratory test values outside the reference range that, in the opinion of the Investigator, are clinically significant, or any of the following (see Note below):
    - Serum creatinine > 1.5 × the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 × ULN;
    - Serum alanine aminotransferase or aspartate aminotransferase > 2 × ULN.
18. Has any of the following cardiology findings at screening (see Note below):
    - Abnormal ECG that is, in the Investigator's opinion, clinically significant;
    - PR interval > 220 ms;
    - QRS interval > 130 ms;
    - QTcF interval > 450 ms (for men) or > 470 ms (for women) (QT corrected using Fridericia’s method);
    - Second- or third-degree atrioventricular block;
    - Any rhythm, other than sinus rhythm, that is interpreted by the Investigator to be clinically significant.

19. Has any disease or medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
20. Evidence of infection with hepatitis B or C, or human immunodeficiency virus (HIV)-1 or HIV-2, as determined by results of testing at screening.
21. Lost or donated more than 450 mL of blood during the 30 days prior to screening.
22. Use of any investigational drug or prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) within 30 days or 5 half-lives prior to Visit 1 (baseline) (whichever is longer) during the screening period or anticipated for the duration of the study.
23. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations or near drowning with hospital admission.
24. Has attempted suicide within the 6 months prior to screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the 6 months prior to screening.
25. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

Note: For subjects who follow **SCHEDULE 'B'**, with the approval from the investigator, medical monitor and the sponsor, repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time for each test, at the discretion of the Investigator, as long as the repeat test result is available within the 28-day screening period (prior to first study dose) to determine eligibility.

3.4. Completion of Study and Discontinuation of Subjects

Subjects will be considered to have completed the study if they complete all visits up to and including Visit 22 (EOS).

If SPN-812 is not approved for Adults at the time of Visit 22, subjects may choose to continue in the study; repeating Visit 21 procedures every 8 weeks (including FPC in 4 weeks after each subsequent study visit) until SPN-812 becomes approved and commercially available for Adults.

Subjects who are enrolled and dosed with SM, but who withdraw or are withdrawn from participation in the study by the Investigator before he/she finishes the study (i.e., prior to Visit 22), should complete an early termination (ET) Visit. Procedures listed for the EOS visit should be completed at the ET Visit.

All reasons for screen failure will be recorded.

The Investigator(s) or subjects themselves may stop SM 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 subject participation in the study without consent for any reason, but is in the best interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor and Clinical Research Associate (CRA) before the subject stops SM. Subjects removed from the study for any reason will not be replaced.

Reasons for a subject's early discontinuation may include:

- Subject lost to follow-up
- Subject's withdrawal of consent
- Investigator ended subject's participation in study
- Other

The primary reason for the subject's early discontinuation must be recorded in the subject's medical record and on the electronic case report form (eCRF). If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF.

4. Study Treatment

4.1. Study Medication Identity, Packaging and Labeling

Study medication is supplied as capsules that contain 100 mg, 150 mg and 200 mg of SPN-812, packaged in bottles. Each bottle will be labeled with the protocol number and subject ID, at a minimum.

4.2. Study Medication Administration

Study medication will be administered orally once daily (QD) as intact capsules, with or without food. The daily dose should be taken in the morning. Splitting the daily dose (e.g., taking part of the daily dose in the morning and the remainder of the daily dose in the evening) is not permitted. Confirm that subject is taking daily dose in the morning; if subject reports that he/she is taking daily dose later in the day (e.g., evening) without prior Site Investigator or Sponsor approval, the medical monitor must be informed immediately. The medical monitor must then inform the Sponsor.

Subjects who follow:

- **SCHEDULE 'A'** will take first dose of OLE SM the morning after Visit 1 at home.
- **SCHEDULE 'B'** will take first dose of OLE SM the day of Visit 1 at clinic.

All subjects will initiate SPN-812 dosing at 200 mg/day during first 2 weeks of the study. At and after Visit 2, per the Investigator's discretion based on the subject's clinical response and tolerability, the dose of SPN-812 can be titrated up or tapered down in increments of 50 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day per week to a target dose within the range between 200 and 600 mg/day.

Doses:

- 200 mg/day = (200 mg capsule × 1) [once daily]
- 250 mg/day = (100 mg capsule × 1) + (150 mg capsule × 1) [once daily]
- 300 mg/day = (200 mg capsule × 1) + (100 mg capsule × 1) [once daily]
- 350 mg/day = (200 mg capsule × 1) + (150 mg capsule × 1) [once daily])
- 400 mg/day = (200 mg capsule × 2) [once daily]
- 450 mg/day = (150 mg capsule × 3) [once daily]
- 500 mg/day = (200 mg capsule × 2) + (100 mg capsule × 1) [once daily]
- 550 mg/day = (200 mg capsule × 2) + (150 mg capsule × 1) [once daily]
- 600 mg/day = (200 mg capsule × 3) [once daily]

4.3. Adjunctive Stimulant Therapy

If after 12 weeks of dosing SPN-812 (Visit 4) the Site Investigator determines that administration of the optimized dose of SPN-812 is not eliciting an adequate clinical response, the Site Investigator may consider supplementing SPN-812 therapy with an adjunctive FDA -approved stimulant for use in ADHD [e.g., Vyvanse® (lisdexamfetamine dimesylate), Concerta® (methylphenidate)]. Adjunctive stimulant therapy should be initiated at the lowest recommended daily dose, and the dosing and safety management guidelines provided in the prescribing information for the stimulant must be followed.

Dose adjustment for the stimulant as well as evaluation of clinical response will be at the Investigator's discretion. Regardless of the dose of stimulant administered, the subject must continue to receive SPN-812 at the optimized dose determined per the study protocol. Subjects with known previous allergic reactions to either methylphenidate or amphetamine or other ingredients found in those dosage forms are not eligible for concomitant stimulant therapy. Adjunctive stimulant therapy should be carefully documented.

4.4. Method of Assigning Subjects to Treatment Arm

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

4.5. Blinding

This is an open-label study.

4.6. Study Medication Handling and Accountability

All SM will be supplied by the Sponsor to the Investigator. SM supplies must be stored in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM label.

Following Sponsor instructions and in compliance with International Conference on Harmonisation (ICH) E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log, a copy of which will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject; collection of unused supplies; and subsequent return of unused SM to the Depot must be maintained with dates. This SM accountability log includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or a representative of the Food and Drug Administration (FDA). The assigned CRA will review these documents along with all other study conduct documents at specified intervals once SM has been received by the study site. All used, partly used, and unused clinical supplies, including empty containers, are to be returned to the Depot at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the study site. Upon completion of SM accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Depot with a copy of the completed SM disposition form to the Sponsor.

4.7. Concomitant Medications

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).

Subjects who follow **SCHEDULE 'B'** and are taking any prohibited medications at screening (e.g., ADHD medications) should discontinue use (washout) at least 7 days prior to first dose of OLE SM.

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

- Nutritional supplements (e.g., multivitamins, fish oil) (herbal supplements are prohibited)
- EMLA® or other numbing cream for venipuncture
- Common over-the-counter therapies for minor transient ailments (e.g., acetaminophen for headache, ibuprofen for fever).
- Following the first 12 Weeks of dosing OLE SM, subjects may supplement SPN-812 with an adjunctive FDA approved stimulant for use in ADHD [e.g., Vyvanse® (lisdexamfetamine dimesylate), Concerta® (methylphenidate)] (See Section 4.3.).

All concomitant medications will be recorded in the eCRF, including Adjunctive Stimulant Therapy (carefully document reason for use).

Caffeine use is permitted during the study and will be recorded in the eCRF.

5. STUDY METHODS

5.1. Study Visits and Procedures

All subjects who are enrolled 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. The Sponsor or Sponsor's designee must be notified of all deviations from the protocol visit or procedures, except as noted, and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule. Subjects will be instructed to call study personnel to report any abnormalities during the intervals in between study visits and to come to the study site if medical evaluation is needed and as the urgency of the situation indicates. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator or qualified designee as source data for study follow-up.

For subjects who complete Study 812P306 and rollover into Study 812P311 on the same day as or ≤7 days after their 812P306 EOS visit, use **INCLUSION/EXCLUSION CRITERIA 'A'** (Section 3.3.2.) and follow **SCHEDULE 'A'** (Table 1; Figure 1). All efficacy and safety assessments collected at the subject's end of study (EOS) Visit (812P306) will serve as their efficacy and safety assessments for Visit 1 (812P311).

For subjects who complete Study 812P306, but who rollover into Study 812P311 more than 7 days after their EOS Visit (812P306), use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2). All efficacy and safety assessments will be collected at a screening visit (Visit 'S') to determine eligibility, and subject will return to the clinical site for Visit 1 within 28 days of screening to make final eligibility determination and complete baseline efficacy and safety assessments.

On a case-by-case basis, a subject who did not complete Study 812P306 (e.g., randomized, dosed SM and had at least one post-baseline AISRS assessment and then early terminated) may be allowed to screen and, if eligible, enroll in Study 812P311, but only after receiving approval from the Site Investigator, Medical Monitor, and the Sponsor. For these subjects, use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2).

De novo subjects (individuals who did not screen/enroll in Study 812P306) may screen and, if eligible, enroll in Study 812P311, **but only after a "Note To File" has been submitted by the Sponsor to the IRB and approved**. The clinical sites will be notified when the approval is granted. For these subjects, use **INCLUSION/EXCLUSION CRITERIA 'B'** (Section 3.3.3.) and follow **SCHEDULE 'B'** (Table 2; Figure 2).

The timing of each study visit (Visit 2-Visit 22) and each FPC should occur per the Schedule of Events and Assessments relative to the date of subject's first dose of SPN-812 (Day 1) [e.g., Visit 4 occurs on Day 85 (± 7 days) or 85 days (± 7 days) after the date of subject's first dose of SPN-812].

Table 1 SCHEDULE 'A': Schedule of Events and Assessments

Study Period	**Initial Visit**	**Treatment**					**EOS/ ET**	**Safety follow-up phone call**
Visit Number	**1**	**-**	**2**	**3**	**FPC[a]**	**4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21**	**22**	**FPC**
Day of Study (days since first dose of SM)	**-1**	**1**	**15**	**29**	**57, 113, 169, 225, 281, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065**	**85, 141, 197, 253, 309, 365, 421, 477, 533, 589, 645, 701, 757, 813, 869, 925, 981, 1037**	**1093**	**1100**
Week of Study (week since first dose of SM)	**--**	**--**	**2**	**4**	**8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, 104, 112,120, 128, 136, 144, 152**	**12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148**	**156**	**157**
Study Visit Window (days relative to nominal visit)	**--**	**--**	**± 3**	**±3**	**±3**	**±7**	**±7**	**±2**
Signed informed consent	√							
Relevant histories (social, medical, psychiatric, neurological, family psychiatric)	√							
Demographics	√							
Smoking, alcohol consumption	√							
Physical examination	√						√	
Blood sample for FSH (post-menopausal females only)	√							
Inclusion/exclusion criteria	√							
POC Urine drug screen	√ [f]					√ [f]		
Urine pregnancy test (FOCP only)	√		√	√		√	√	
Urinalysis	√			√		√	√	
Blood sample for chemistry	√			√		√	√	
Blood sample for hematology	√			√		√	√	
ECG	√			√		√	√	
Orthostatic blood pressure [c]	√		√	√		√	√	
Vital signs [b], weight	√		√	√		√	√	
Dispensed home pregnancy test kit (FOCP only)				√		√		
C-SSRS (SLV)	√		√	√		√	√	
AISRS [d]	√		√	√		√	√ [e]	
CGI-S [d]	√		√	√		√	√ [e]	

Study Period	**Initial Visit**	**Treatment**					**EOS/ ET**	**Safety follow-up phone call**
Visit Number	**1**	**-**	**2**	**3**	**FPC[a]**	**4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21**	**22**	**FPC**
Day of Study (days since first dose of SM)	**-1**	**1**	**15**	**29**	**57, 113, 169, 225, 281, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065**	**85, 141, 197, 253, 309, 365, 421, 477, 533, 589, 645, 701, 757, 813, 869, 925, 981, 1037**	**1093**	**1100**
Week of Study (week since first dose of SM)	**--**	**--**	**2**	**4**	**8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, 104, 112,120, 128, 136, 144, 152**	**12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148**	**156**	**157**
Study Visit Window (days relative to nominal visit)	**--**	**--**	**± 3**	**±3**	**±3**	**±7**	**±7**	**±2**
CGI-I [d]	√		√	√		√	√ [e]	
GAD-7	√		√	√		√	√ [e]	
BRIEF-A	√			√		√	√ [e]	
SDQ	√			√		√	√ [e]	
AAQoL	√			√		√	√ [e]	
Review concomitant medications and caffeine use	√		√	√	√	√	√	√
Review adverse events	√		√	√	√	√	√	√
Confirm home pregnancy test results (FOCP only) [g]					√			
SM dispensed	√		√	√		√		
SM return and accountability			√	√		√	√	
Subject take 1st dose		√						

AAQoL = Adult ADHD Quality of Life scale; ADHD = Attention-Deficit/Hyperactivity Disorder; AISRS = Adult ADHD Investigator Symptom Rating Scale; BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version (Self); CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity of Illness scale; C-SSRS (SLV) = Columbia Suicide Severity Rating Scale Since Last Visit Version; ECG = electrocardiogram; EOS = end of study; ET = early termination; FOCP = females of childbearing potential; FPC = Follow-up Phone Call; FSH = follicle stimulating hormone; GAD-7 = Generalized Anxiety Disorder 7-item scale; POC = Point of Care UDS; SDQ = Symptoms of Depression Questionnaire; SM = study medication.

a. After Visit 3, a follow-up phone call should be conducted 4 weeks after each study visit.
b. This includes orthostatic blood pressure/heart rate, as well as respiratory rate and oral temperature.
c. Orthostatic blood pressure/heart rate should be measured after the subject has been seated for at least 5 minutes and again within 3 minutes of subject standing
d. Investigator-rated efficacy assessments should be performed/conducted/collected prior to administering any self-reported efficacy assessments to the subject.
e. If the subject's ET Visit is conducted >7 days after the date of the subject's last dose of SM, do not perform efficacy assessments at the ET Visit.
f. Point of Care urine drug screen (Test 1 and 2) at Visits 1, 6, 8, 10, 12, 14, 16, 18, and 20 (see Table 3).
g. FOCPs should perform the home pregnancy test within 3 days prior to the monthly FPC.

Table 2 SCHEDULE 'B': Schedule of Events and Assessments

Study Period	**Screen**	**Treatment**					**EOS/ET**	**Safety follow-up phone call**
Visit Number	**S**	**1**	**2**	**3**	**FPC[a]**	**4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21**	**22**	**FPC**
Day of Study (days since first dose of SM)	**-28 to -1**	**1**	**15**	**29**	**57, 113, 169, 225, 281, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065**	**85, 141, 197, 253, 309, 365, 421, 477, 533, 589, 645, 701, 757, 813, 869, 925, 981, 1037**	**1093**	**1100**
Week of Study (week since first dose of SM)	**--**	**--**	**2**	**4**	**8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152**	**12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148**	**156**	**157**
Study Visit Window (days relative to nominal visit)	**--**	**--**	**±3**	**±3**	**±3**	**±7**	**±7**	**±2**
Signed informed consent	√							
Relevant histories (social, medical, psychiatric, neurological, family psychiatric)	√							
Demographics	√							
Smoking, alcohol consumption	√							
Physical examination	√						√	
Blood sample for FSH (post-menopausal females only)	√							
SCID-5-CT[i]	√[h]							
Serology	√							
Inclusion/exclusion criteria	√	√						
Serum ethanol	√							
Standard urine drug screen	√							
POC urine drug screen	√[g]	√[f]				√[f]		
Serum pregnancy test (FOCP only)	√							
Urine pregnancy test (FOCP only)		√	√	√		√	√	
Urinalysis	√	√		√		√	√	
Blood sample for chemistry	√	√		√		√	√	
Blood sample for hematology	√	√		√		√	√	
ECG	√	√		√		√	√	

Study Period	**Screen**	**Treatment**					**EOS/ET**	**Safety follow-up phone call**
Visit Number	**S**	**1**	**2**	**3**	**FPC[a]**	**4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21**	**22**	**FPC**
Day of Study (days since first dose of SM)	**-28 to -1**	**1**	**15**	**29**	**57, 113, 169, 225, 281, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065**	**85, 141, 197, 253, 309, 365, 421, 477, 533, 589, 645, 701, 757, 813, 869, 925, 981, 1037**	**1093**	**1100**
Week of Study (week since first dose of SM)	**--**	**--**	**2**	**4**	**8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152**	**12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148**	**156**	**157**
Study Visit Window (days relative to nominal visit)	**--**	**--**	**±3**	**±3**	**±3**	**±7**	**±7**	**±2**
Orthostatic blood pressure [c]	√	√	√	√		√	√	
Vital signs [b] and weight	√	√	√	√		√	√	
C-SSRS (B/S)	√							
C-SSRS (SLV)		√	√	√		√	√	
AISRS [d]	√	√	√	√		√	√ [e]	
CGI-S [d]	√	√	√	√		√	√ [e]	
CGI-I [d]			√	√		√	√ [e]	
GAD-7		√	√	√		√	√ [e]	
BRIEF-A		√		√		√	√ [e]	
SDQ		√		√		√	√ [e]	
AAQoL		√		√		√	√ [e]	
Review concomitant medications and caffeine use	√	√	√	√	√	√	√	√
Review adverse events		√ [j]	√	√	√	√	√	√
Dispensed home pregnancy test kit (FOCP only)				√		√		
Confirm home pregnancy test results (FOCP only)[h]					√			
SM dispensed		√	√	√		√		
SM return and accountability			√	√		√	√	
Subject take 1st dose		√						

AAQoL = Adult ADHD Quality of Life scale; ADHD = Attention-Deficit/Hyperactivity Disorder; AISRS = Adult ADHD Investigator Symptom Rating Scale; BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version (Self); CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity of Illness scale; C-SSRS (B/S) = Columbia Suicide Severity Rating Scale Baseline/Screening Version; C-SSRS (SLV) = Columbia Suicide Severity Rating Scale Since Last Visit Version; ECG = electrocardiogram; EOS = end of study; ET = early termination; FOCP = females of childbearing potential;

FPC = Follow-up Phone Call; FSH = follicle stimulating hormone; GAD-7 = Generalized Anxiety Disorder 7-item scale; POC = Point of Care UDS; SCID-5-CT = Structured Clinical Interview for DSM-5 Clinical Trials version; SDQ = Symptoms of Depression Questionnaire; SM = study medication; UDS = urine drug screen.

a. After Visit 3, a follow-up phone call should be conducted 4 weeks after each study visit.
b. This includes orthostatic blood pressure/heart rate, as well as respiratory rate and oral temperature.
c. Orthostatic blood pressure and heart rate should be measured after the subject has been seated for at least 5 minutes and again within 3 minutes of subject standing
d. Investigator-rated efficacy assessments should be performed/conducted/collected prior to administering any self-reported efficacy assessments to the subject.
e. If the subject's ET Visit is conducted >7 days after the date of the subject's last dose of SM, do not perform efficacy assessments at the ET Visit.
f. Point of Care urine drug screen (Test 1 and 2; see Table 3) at Visit 1 and only at Visits 6, 8, 10, 12, 14, 16, 18, and 20.
g. Point of Care urine drug screen Test 2 only (see Table 3) at Visit 'S'.
h. FOCPs should perform the home pregnancy test within 3 days prior to the monthly FPC.
i. The SCID-5-CT is performed at Visit 'S' for *de novo* subjects only.
j. Event(s) occurring after first dose of OLE SM should be captured as an adverse event; event(s) occurring prior to first dose of OLE SM should be captured as medical history.

5.1.1. Study Initiation

5.1.1.1. SCHEDULE 'A' ['Same day/Short Delayed (≤7 day)' Rollover Subjects]:

5.1.1.1.1. Visit 1 – Initial Study Visit

The following assessments will be conducted:

- Review Inclusion/exclusion criteria
- ICF signed
- Social, medical, psychiatric, family psychiatric, and neurological histories
- Demographics
- Smoking and alcohol consumption use/history
- Physical examination
- Blood sample for:
  - FSH (post-menopausal females only)
  - Chemistry and hematology
- Urine sample for:
  - Urinalysis
  - Urine pregnancy test (FOCP only)
  - Point of Care Urine Drug Screen Test 1/Test 2 (see Table 3)
- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Perform ECG
- C-SSRS ('Since Last Visit' version)
- AISRS, CGI-I, CGI-S, GAD-7, BRIEF-A, SDQ and AAQoL
- Review concomitant medications and Caffeine use
- Review adverse events (events occurring before first dose of SPN-812 should be recorded as medical history; events occurring after first dose of SPN-812 should be recorded as an AE)
- Dispense Study Medication; subject should take first dose of SPN-812 at home in the morning the next day after Visit 1.

5.1.1.2. SCHEDULE 'B' ['Long Delayed' (>7days) Rollover & *De Novo* Subjects]

5.1.1.2.1. Visit 'S' – Screening Visit **[SCHEDULE 'B']**

The following assessments will be conducted:

- ICF signed
- SCID-5-CT
- Social, medical, psychiatric, family psychiatric, and neurological histories
- Demographics
- Smoking and alcohol consumption use/history
- Physical examination and height
- Blood sample for:
  - FSH (post-menopausal females only)
  - Serum pregnancy test (FOCP only)
  - Hematology and serum chemistry (non-fasted sample allowed)
  - Serology (HIV, Hepatitis B and Hepatitis C)
  - Serum drug screen (ethanol)
- Urine sample for:
  - Urinalysis
  - Drug Screen: Standard UDS & Point of Care UDS Test 2 only (Table 3)
- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Perform ECG
- C-SSRS ('Baseline/Screening' version)
- AISRS and CGI-S
- Review Inclusion/Exclusion criteria
- Concomitant medications and caffeine use

Note: Remind subject to discontinue any prohibited medications ≥7 days prior to Visit 1

5.1.1.2.2. Visit 1 – Baseline **[SCHEDULE 'B']**

The following assessments will be conducted:

- Blood sample for hematology/serum chemistry (non-fasted allowed)
- Urine sample for:
  - Urinalysis
  - Urine pregnancy test (FOCP only)
  - Point of Care Urine Drug Screen, Test 1 and Test 2 (Table 3)
- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Perform ECG
- C-SSRS ('Since Last Visit' version)
- AISRS, CGI-S, GAD-7, BRIEF-A, SDQ and AAQoL
- Review adverse events (events occurring before first dose of SPN-812 should be recorded as medical history; events occurring after first dose of SPN-812 should be recorded as an AE)
- Review Concomitant medications and caffeine use
- Review Inclusion/Exclusion criteria
- Dispense Study Medication; subject should take first dose of SPN-812 at clinic day of Visit 1

5.1.2. Visit 2 – Treatment Period

The following assessments will be conducted:

- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Urine sample for urine pregnancy test (FOCP only)
- C-SSRS ('Since Last Visit' version)
- AISRS, CGI-S, CGI-I, and GAD-7
- Review concomitant medications and Caffeine use
- Review adverse events
- SM dispensed
- SM return and accountability

5.1.3. Visit 3 – Treatment Period

The following assessments will be conducted:

- Blood sample for chemistry and hematology
  - Chemistry
  - Hematology
- Urine sample for:
  - Urinalysis
  - Urine pregnancy test (FOCP only)
- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Perform ECG
- C-SSRS ('Since Last Visit' version)
- AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, SDQ and AAQoL
- Review concomitant medications and Caffeine use
- Review adverse events
- Dispense Home Pregnancy Test kit with instructions (FOCPs only) **
- SM dispensed
- SM return and accountability

5.1.4. Visit 4 to Visit 21 – Treatment Period

The following assessments will be conducted:

- Blood sample for
  - Chemistry
  - Hematology
- Urine sample for:
  - Urinalysis
  - Urine pregnancy test (FOCP only)
  - Point of Care Urine Drug Screen, Test 1 and Test 2 (Table 3)
    - **Only at Visits 6, 8, 10, 12, 14, 16, 18, and 20**
- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Perform ECG
- C-SSRS ('Since Last Visit' version)
- AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, SDQ, and AAQoL
- Review concomitant medications and Caffeine use
- Review adverse events
- Dispense Home Pregnancy Test kit with instructions (FOCPs only) **
- SM dispensed
- SM return and accountability

5.1.5. Visit 22 – End of Study / Early Termination

The following assessments will be conducted at EOS/ET* visit:

- Blood sample for:
  - Chemistry
  - Hematology
- Physical examination
- Urine sample for:
  - Urinalysis
  - Urine pregnancy test (FOCP only)
- Vital signs (includes orthostatic blood pressure/heart rate) and weight
- Perform ECG
- C-SSRS ('Since Last Visit' version)
- AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, SDQ, and AAQoL *
- Review concomitant medications and Caffeine use
- Review adverse events
- SM return and accountability

* For subjects who discontinue/terminate early (ET Visit), the EOS assessments will be performed at that visit. If the subject's ET Visit is conducted >7 days after the date of the subject's last dose of SM, efficacy assessments should not be performed at the ET Visit.

** FOCPs should perform the home pregnancy test within 3 days prior to the monthly FPC.

5.1.6. Safety Follow-up Phone Call (FPC)

After Visit 3 until EOS, the site should conduct a follow-up phone call with each subject 4 weeks after each study visit to assess adverse events, changes in concomitant medications, caffeine use, and confirm results of Home Pregnancy Test (FOCPs only). Subjects who are FOCPs should perform the home pregnancy test within 3 days prior to the monthly FPC.

In addition, the site should also conduct a follow-up phone call with each subject approximately 1 week after the EOS/ET Visit:

- AEs
- Concomitant medications and Caffeine use

5.1.7. Unscheduled Visits

At the discretion of the investigator throughout the study, unscheduled visits may be conducted to perform or repeat assessments, including ECG, measure vital signs and weight, draw blood sample for hematology and/or serum chemistry or serum pregnancy test (FOCP), obtain urine sample for urine pregnancy test and/or urine drug screen (POC [if applicable]; see Table 3), administer C-SSRS ('Since Last Visit' version), perform physical examination. AEs, concomitant medications and 'caffeine use' should also be assessed at all unscheduled visits. SM may also be dispensed and/or returned at unscheduled visits, if needed.

6. STUDY VARIABLES AND ASSESSMENTS

6.1. Efficacy Assessments

6.1.1. Adult ADHD Investigator Symptom Rating Scale (AISRS)

The adult ADHD Investigator Symptom Rating Scale (AISRS) was developed to better measure the presence and severity of ADHD symptoms based on DSM-IV diagnostic criteria in adult patients ([redacted]**Spencer et al., 2010**). It is a semi-structured clinical interview with suggested prompts for each item to improve interrater reliability. The scale consists of 18 items that directly correspond to the 18 symptoms of ADHD and are further subdivided into two subscales: Inattention (9 items) and Hyperactivity/Impulsivity (9 items). During the interview with the subject, the clinician/investigator rates the frequency and severity of each symptom on a 4-point Likert-type scale, where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe, with a maximum total score of 54 points and maximum subscale score of 27 points. The scale allows the assessment of functional impairments linked to each symptom dimension. The AISRS total score is the sum of the Inattention and Hyperactivity/Impulsivity subscale scores.

6.1.2. Clinical Global Impression – Severity of Illness (CGI-S)

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (**Guy, 1976**). The Clinical Global Impression – Severity of Illness scale (CGI-S[redacted]) is a single item clinician rating of the clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The CGI-S is evaluated on a 7-point scale, where 1 = Normal, not at all ill, asymptomatic, 2 = Borderline Ill, 3 = Mildly Ill, 4 = Moderately Ill, 5 = Markedly Ill, 6 = Severely Ill, and 7 = Extremely Ill. Successful therapy is indicated by a lower overall score in subsequent testing.

6.1.3. Generalized Anxiety Disorder 7-item Scale (GAD-7)

Generalized Anxiety Disorder 7-item scale (GAD-7) is a self-reported 7-item questionnaire for measuring the severity of generalized anxiety disorder ([redacted] **Spitzer et al., 2006**). The GAD-7 measures the severity of various symptoms of generalized anxiety disorder over the past 2 weeks according to reported response categories with assigned points. The patient scores each GAD-7 item on 4-point Likert scale, where 0 = Not at all, 1 = Several days, 2 = Over half the days, and 3 = Nearly every day. The clinician/investigator can obtain the total score by summating all 7 items. GAD-7 total scores range from 0 to 21, where a total score of 1 to 4 = None/Minimal anxiety, 5 to 9 = Mild anxiety, 10 to 14 = Moderate anxiety, and ≥ 15 = Severe anxiety. It takes less than 5 minutes to complete the GAD-7.

6.1.4. Clinical Global Impression – Improvement (CGI-I)

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (**Guy, 1976**). The Clinical Global Impression – Improvement scale (CGI-I; [redacted]) is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. The Investigator/rater should consider their total clinical experience with the subject who has ADHD and rate improvement in the subject's condition compared to his/her's baseline assessment at the beginning of the subject's randomized, double-blind, placebo-controlled study.
The CGI-S score obtained at the baseline serves as a good basis for making this assessment. The CGI-I is evaluated on a 7-point scale with 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, and 7 = Very much worse. Successful therapy is indicated by a lower overall score in subsequent testing.

Please note the following before assessing CGI-I:

- For subjects who follow **SCHEDULE 'A'**, Baseline = Visit 2 (812P306)
- For subjects who follow **SCHEDULE 'B**', Baseline = Visit 1 (812P311)

6.1.5. Behavior Rating Inventory of Executive Function–Adult (BRIEF-A)

The Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A; Self report) is a standardized rating scale that captures views of an individual's executive functions into everyday behaviors in adults ages 18 to 90 years ([redacted] **Roth et al., 2005**; **Roth et al., 2013**). It has been utilized in clinical trials to assess changes in executive function with treatment for neurological and psychiatric disorders, including ADHD (**Adler et al., 2014**). The BRIEF-A is 75-item in nine non overlapping scales and two summary index scales that assesses aspects of executive function and problems with self-regulation from the perspective of the individual. The subject rates each item on a 3-point Likert scale (Never, Sometimes, or Often) based on their experienced within the last month. Higher scores indicate poorer executive function. The BRIEF-A takes 15-20 minutes to complete. The self-report provides the insight of the individual's viewpoint of their own difficulties in self-regulation.

Description of the nine BRIEF-A scales (**Roth et al., 2013**) by summary index scale:

1. The **Behavioral Regulation Index (BRI)** captures the ability to maintain appropriate regulatory control of one's own behavior and emotional responses. The BRI is broken down into the following four scales within the BRIEF-A:

   - Inhibit: Control impulses; appropriately stop verbal, attentional, physical behavior at the proper time
   - Shift: Move freely from one situation, activity, or aspect of a problem to another as the situation demands; think flexibly to aid problem-solving
   - Emotional control: Modulate one's emotional responses appropriately
   - Self-Monitor: Recognize the effect of one's own behavior on others

2. The **Metacognitive Index (MI)** reflects the individual's ability to initiate activity and generate problem-solving ideas, to sustain working memory, to plan and organize problem-solving approaches, to monitor success and failure in problem solving, and to organize one's materials and environment. The MI is broken down into the following four scales within the BRIEF-A:

   - Initiate: Begin a task or activity without external prompting; independently generate ideas
   - Working memory: Hold information in mind in order to complete a task; stay with, or stick to, an activity
   - Plan/organize: Anticipate future events; set goals; develop steps ahead of time to carry out a task; organize information and behavior to achieve and objective; carry out tasks in a systematic manner
   - Task Monitor: Assess performance during or after finishing a task for mistakes
   - Organization of Materials: Keep workspace and living areas in an orderly manner; keep track of materials needed for tasks

6.1.6. Symptoms of Depression Questionnaire (SDQ)

The Symptoms of Depression Questionnaire (SDQ) is designed to measure the severity of symptoms across several subtypes of depression and was developed (items chosen) on the basis of the most current knowledge of depressive symptoms and Major Depressive Disorder (MDD) subtypes ([redacted]. ; **Pedrelli et al., 2014**). The SDQ is a 44-item self-report depression scale that inquires about an extensive number of depressive symptoms. Items reflect a broad and heterogeneous collection of depression related symptom features, and it includes several items that inquire about anxiety symptoms. The SDQ has been utilized in clinical trials along with other commonly used scales like the Montogmery Asberg Depression Rating Scale (MADRS) assessing potential treatments in patients with depression (**Fava et al., 2016**; **Papakostas et al., 2019**). The subject self-rates/scores each item on a 6-point scale (1-6) as it pertains to the past month. Each item is rated based on a subject's perception of what is normal for the individual (score = 2), what is better than normal (score = 1), and what is worse than normal (scores = 3–6). A SDQ average (mean) score greater than 3.5, which is equivalent to a Montgomery-Asberg Depression Rating Scale (MADRS) score of 25, is consistent with severe depression (**Fava et al., 2016**). The clinician/investigator generates a total score (SDQ-T) by summated all 44 scores. SDQ total scores can range from 44-264. SDQ-T refers to the total score of the SDQ. SDQ-1 subscale includes items related to lassitude, mood, and cognitive functioning; SDQ-2 subscale includes items related to anxiety, agitation, irritability, and anger; SDQ-3 subscale includes items related to suicidal ideation. SDQ-4 subscale assesses disruptions in sleep quality. SDQ-5 subscale includes items on changes in appetite and weight. The SDQ takes less than 10 minutes to complete.

6.1.7. Adult ADHD Quality of Life Scale (AAQoL)

The AAQoL is a self-report rating scale designed to assess health-related quality of life (HRQL) that has been validated in adult patients with ADHD ([redacted] **Brod et al., 2006**; **Brod et al., 2015**). Development of the scale followed the industry guidance ‘‘Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims’’ set by the Food and Drug Administration (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf). The AAQoL is a 29-item questionnaire that measures how ADHD has impacted the subject’s quality of life over the past 2 weeks. The AAQoL includes 4 domains:

1) Life Productivity: 11 items, including “getting things done on time,” “completing projects or tasks,” “remembering important things,” and “balancing multiple projects”;
2) Psychological Health: 6 items, including “feeling anxious,” “overwhelmed,” and “fatigued”;
3) Relationships: 5 items, including “tension,” “annoyance,” and “frustration in relationships”; and
4) Life Outlook: 7 items, including “perceptions that energy is well spent,” “people enjoy spending time with you,” “you can successfully manage your life,” and “you are as productive as you would like to be”.

The subject rates/scores each item on a 5-point Likert scale, where 1 = Not at all/Never, 2 = A little, 3 = Somewhat, 4 = A lot, and 5 = Extremely/Very often. To derive overall and subscale scores, item scores are transformed to a 0 to 100-point scale, and higher scores indicate better HRQL. It takes approximately 5 to 10 minutes to complete the AAQoL.

6.2. Safety Variables and Assessments

Safety assessments include monitoring, evaluation, and recording of all concomitant medications, and the evaluation of AEs, clinical laboratory test results, vital signs and 12-lead ECGs, C-SSRS, and the performance of physical examinations as detailed in the Schedule of Events and Assessments.

Site Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Supernus or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subjects.

6.3. Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (GCP), an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

Examples of AE include but are not limited to:

- Any new disease, inter-current injuries, or exacerbation of an existing disease.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period.

6.3.1. Adverse Events of Special Interest (AESI)

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.

6.3.2. Causality

Adverse events may be categorized as either Adverse Drug Reactions or Suspected Adverse Drug Reactions based on their relationship to SM and the degree of certainty about causality.

Suspected adverse drug reactions (SADRs) are a subset of adverse events for which there is evidence to suggest a causal relationship between the drug and the AE, i.e., there is a reasonable possibility that the drug caused the adverse event.

Adverse drug reactions (ADRs) are a subset of all SADRs for which there is reason to conclude that the drug caused the event.

6.3.3. Recording and Evaluation of Adverse Events

All subjects who enter the study (Visit 1 under **SCHEDULE 'A'**; or Visit 'S' under **SCHEDULE 'B'**) will be questioned regarding any current and prior medical health status or diagnoses, which will be documented as medical history. At each contact with the subject following first dose of OLE SM, the Site Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate adverse event module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though they may be grouped under one diagnosis. For example, fever, elevated WBC, cough, abnormal chest X-ray, etc., can all be reported as "pneumonia".

All AEs occurring after first dose and throughout the study period must be recorded. A treatment-emergent adverse event (TEAE) is defined as 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. All AEs in this study will be recorded after administration of OLE SM, therefore all will be treatment-emergent. The clinical course of each AE should be followed for at least 30 days following the date of last dose of SM

(either due to EOS or ET) or until resolution, or until, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

The Investigator is responsible for evaluating AEs and determining the following:

- Serious vs. Non-serious: Is the event a Serious Adverse Event (SAE)?
- Causality: Was AE related or possibly related to the SM?
- Severity: How pronounced is the incapacity/discomfort caused by an AE?

6.3.4. Criteria for Assessing Severity

The Site Investigator will evaluate the comments of the subject and the response to treatment in order that he or she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

The criteria for assessing severity are different from those used for seriousness.

6.3.5. Criteria for Assessing Causality

The site Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or as a suspected reaction to SM. These are defined as follows:

Not suspected: The temporal relationship of the AE to SM administration makes a causal relationship unlikely, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- Not related: Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.

- Unlikely related: Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease or other drugs or chemicals could also explain event. Information on drug withdrawal may be lacking or unclear. This will be reported as a **Suspected Adverse Drug Reaction (SADR)**.

- **Definitely related**: Temporal relationship to SM administration is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The

response to withdrawal of the medication (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. This will be reported as an **Adverse Drug Reaction (ADR)**.

6.3.6. Serious Adverse Events

Adverse events are classified as serious or non-serious. An AE or ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization, 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, blood dyscrasias, a seizure that did not result in in-patient hospitalization or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

6.3.7. Investigator Responsibilities for Reporting SAEs

The site Investigator must immediately report to the Sponsor all SAEs, regardless of whether the Investigator believes they are drug related.

All SAEs must be reported to the Drug Safety Contact within 24 hours of first becoming aware of the SAE. The Investigator must complete an SAE Form and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports and other relevant documents). The Investigator will keep a copy of this SAE Report form on file at the study site.

The Site Investigator and/or study/safety physician, after thorough consideration of all facts that are available, must include an assessment of causality of an AE to SM in the report to the Sponsor.

Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor, as it becomes available, using the SAE Report Form.

The Drug Safety Contact for SAE reporting is:

6.3.8. Other Events Requiring Immediate Reporting

The Site Investigator must report a pregnancy that occurs in a subject during a clinical study to the Drug Safety Contact within 24 hours of first becoming aware of the event. Subjects who become pregnant during the study should be discontinued from study medication immediately. Pregnancy should be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor; the Site Investigator must follow any pregnant subject for 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor.

Acute suicidal crisis or clinically significant suicidal behavior or ideation should be reported to the Drug Safety Contact within 24 hours of first becoming aware of the event.

6.3.9. Sponsor Responsibilities for Reporting SAEs

The Sponsor will inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that study sites submit SAE information to the Sponsor in the manner described above.

Investigators must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB). Investigators must also submit the safety information provided by the Sponsor to the IRB unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB.

It is the responsibility of the Sponsor to notify all participating Investigators, in a written IND safety report, of any SADR that is both serious and unexpected. The Sponsor will also notify participating Investigators of any findings from other sources (other studies, animal and in vitro testing, etc.) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure.

6.4. Treatment-Emergent Suicidal Ideation

Prospective assessment of suicidal ideation and suicidal behavior is a mandatory part of the safety evaluations for any drug developed for a psychiatric indication (FDA, 2012). In this study, the initial evaluation of subjects will be conducted prior to enrollment to assess lifetime suicidal ideation and to identify subjects who must not participate in the trial due to pre-existing suicidality risk. The assessment will then be repeated at each subsequent study visit to monitor the occurrence of new suicidal and self-injurious tendencies.

6.4.1. 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) (Posner et al., 2011). The C-SSRS is an FDA-recommended prospective assessment instrument that directly 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 "Baseline/Screening" version should only be administered at Visit 'S' to subjects who follow **SCHEDULE 'B'** [redacted]. The C-SSRS "Since Last Visit" version should be administered at every study visit, including Visit 1 [redacted] for all subjects.

The instrument has been validated used successfully in adult patients with various psychiatric disorders that do not involve cognitive impairment. The C-SSRS outcomes that can be used for clinical management and safety monitoring are suicidal lethality rating, suicidal ideation score, and suicidal ideation intensity rating.

6.4.2. Suicide Risk Management Plan

The protocol procedures related to clinical care of patients with treatment-emergent suicidal ideation and behavior must be implemented to ensure proper management of the event and protection of subject's safety. If a disclosure of suicidal ideation is revealed as part of the C-SSRS questionnaire or when a subject spontaneously expresses that he/she may be a threat to him/herself, the study team should be prepared to quickly evaluate the event and to determine the appropriate course of action.

6.4.2.1. Assessment of Suicide Risk

Any indication of suicidal ideation should be evaluated as soon as possible by appropriately trained staff. The Investigator is responsible for making the final judgment regarding potential suicide risk and need subsequent action.

6.4.2.2. Acute Suicidal Crisis

A person evaluated as being at high risk should be transferred to an immediate care facility. The Investigator will guide intervention as clinically indicated and follow up with the subject within 1 week and/or refer him/her to a qualified mental health professional.

6.4.2.3. Non-acute Suicidal Risk

The Investigator will conduct safety planning with the subject and will follow up within 1 week.

Reference materials for subjects and caregivers should include lists of mental health organizations and professionals, outpatient behavioral services, local crisis and peer support groups and Suicide/Crisis Hotlines.

6.5. Clinical Measurements

6.5.1. Clinical Safety Laboratory Assessments

With the exception of urine pregnancy tests and urine drug screen tests, clinical laboratory tests are performed by a central laboratory as specified in the reference binder.

Details for collecting, handling, and shipping samples (including shipment addresses) are detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 1 [**SCHEDULE 'A'**] or Table 2 [**SCHEDULE 'B'**]) shows the time points at which blood and urine samples are collected. Table 3 presents the clinical laboratory tests to be performed.

Table 3 Clinical Laboratory Tests

Category	Parameters
Serology	Human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B, hepatitis C; **Visit 'S', SCHEDULE 'B' only**
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, and WBC count with differential
Chemistry	**Electrolytes**: Chloride, phosphate, potassium, sodium
	Liver function tests: Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin
	Renal function parameters: Blood urea nitrogen, creatinine
	Other: Glucose, Ca^{+2}, albumin, total protein, bicarbonate
	FSH: Post-menopausal females only
Urinalysis	Macroscopic examination[a], pH, specific gravity, protein, glucose, ketone, occult blood, WBC, nitrites, bilirubin, urobilinogen
Serum Drug Screen	Ethanol; **Visit 'S', SCHEDULE 'B' only**
'Standard' Urine Drug Screen (UDS)	amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy, methadone, methamphetamine, opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressant, THC (cannabinoids); **Visit 'S', SCHEDULE 'B' only**
Point of Care Urine Drug Screen	Test 1: amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy, methadone, methamphetamine, opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressant, THC (cannabinoids). Test 2: methylphenidate
On site Urine Pregnancy Test (at all study visits)	FOCP only
Home Urine Pregnancy Test (in between study visits following study visit 3)	FOCP only (dispense home pregnancy kit at Study Visits 3 thru 21)

FOCP = females of childbearing potential; FSH = follicle stimulating hormone; WBC = white blood cell
[a] A microscopic examination will be performed on abnormal findings unless otherwise specified.

6.5.2. Vital Signs and Weight

Vital signs measurements (e.g., orthostatic blood pressure/heart rate, oral temperature, and respiratory rate) and body weight is obtained at the time points shown in Schedule of Events and Assessments (Table 1 [**SCHEDULE 'A'**] or Table 2 [**SCHEDULE 'B'**]). Orthostatic blood pressure/heart rate are measured after the subject has been sitting for at least 5 minutes and again within 3 minutes of subject standing. Vital signs may be taken at any other time, as deemed necessary by the Investigator.

6.5.3. Physical Examinations and Height

Physical examinations are obtained at the time points shown in the Schedule of Events and Assessments (Table 1 [**SCHEDULE 'A'**] or Table 2 [**SCHEDULE 'B'**]). The physical examination conducted at the initial study visit will include assessments of all body systems except genitourinary. Any findings during initial study visit in this study (prior to first dose of OLE SM) will be recorded as medical history and any clinically significant abnormal findings during treatment period (after the first dose of OLE SM until the end of the study) will be recorded as an AE. For the physical examination at EOS, only changes from the initial study visit of this study (812P311) will be noted.

6.5.4. Electrocardiograms (ECGs)

A 12-lead ECG will be obtained at the time points shown in the Schedule of Events and Assessments (Table 1 [**SCHEDULE 'A'**] or Table 2 [**SCHEDULE 'B'**]). Additional ECGs may be performed at other times if deemed necessary by the Investigator.

The ECG will be recorded while the subject is resting in a supine position for at least 10 minutes. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate. All ECG tracings will be reviewed within 24 hours by the Investigator or qualified Sub-investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

6.6. Screening Scales and Assessment Tools

6.6.1. Structured Clinical Interview for DSM-5, Clinical Trials (SCID-5-CT)

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making the major DSM-5 diagnoses (Spitzer et al., 1992; First et al., 2015[redacted]). It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. The Clinical Trials version (SCID-5-CT) is an adaptation of the Research version (SCID-5-RV) that has been reformatted, streamlined, and optimized for use in clinical trials that incorporate typical inclusion and exclusion criteria. The SCID is broken down into separate modules corresponding to categories of diagnoses, including ADHD. Most sections begin with an entry question that would allow the interviewer to "skip" the associated questions if not met. For all diagnoses, symptoms are coded as present, subthreshold, or absent. A diagnosis of ADHD is made following the post-traumatic stress disorder diagnostic algorithm. Only administered SCID-5-CT to *de novo* subjects (Visit 'S' [**SCHEDULE 'B'**]).

7. STATISTICAL METHODS

7.1. General Considerations

In general, continuous variables will be summarized with standard descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized with frequencies and percentages.

The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, sorted by unique subject identifier. All data available from the eCRFs will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings.

Additional details of the statistical analysis will be provided in a separate statistical analysis plan (SAP). The statistical analysis methods described in the SAP will supersede the statistical methods described in this protocol.

7.2. Handling of Missing Data

If applicable, missing efficacy data will be imputed using multiple imputation.

Missing dates for occurrence of adverse events and non-study medication use will be imputed using the following rules:

1. Start dates with both missing day and month will be set to the 1st of January of that year, except as noted in rule 4 below. End dates with both missing day and month will be set to the 31st of December of that year.
2. Start dates with missing day only will be imputed with the first day of the month, except as noted in rule 4 below. End dates with missing day only will be imputed with the last day of the month.
3. Start dates with missing month only will be imputed by setting the month to January of the year. End dates with missing month only will be imputed to December of the year.
4. If a start date has missing day only with month and year the same as the month and year of the first dose date, then the start date will be set to the first dose date. If a start date has missing day and month with the year the same as the year of the first dose date, then the start date will be set to the first dose date.

7.3. Analysis Populations

The **Safety Population** is all subjects who are enrolled and receive at least one dose of SM. All statistical analyses will be based on the Safety Population.

7.4. Demographics and Baseline Analysis

Demographic/baseline variables including age, age group, sex, ethnicity, race, height and weight at Visit 1, and BMI will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables. The descriptive summary will be presented by optimized dose group and overall for the Safety Population.

7.5. Subject Disposition

A disposition of subjects will include the number and percentage of 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
- Noncompliance
- Occurrence of unmanageable AEs
- Lost to follow-up
- Related to COVID-19
- Other

7.6. Study Medication Exposure and Compliance

Duration of exposure is defined as the total number of days a subject is exposed to any SM. This will be calculated for each subject by taking the difference between the date of last dose minus the date of the first dose, plus 1 (date of last dose minus date of first dose +1).

Duration of treatment exposure will be summarized by duration category and will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Percent of SM compliance is defined as {(number of capsules dispensed minus number of capsules returned) / X × (date of last dose minus date of first dose + 1)}* 100%, where 'X' is equal to the number of capsules that the subject was instructed to take daily during the treatment period (i.e., between visits).

$$\%\, SM\ compliance = \left[\frac{(no.\ of\ capsules\ dispensed) - (no.\ of\ capsules\ returned)}{X\ \times [(date\ of\ last\ dose) - (date\ of\ first\ dose) + 1]}\right] \times 100$$

For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment.

7.7. Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the Safety Population.

7.8. Efficacy Analysis

The efficacy analysis will be based on the safety population. Each efficacy endpoint will be listed and summarized descriptively by group of the optimized dose, if applicable. In addition, if applicable, subjects who received adjunctive stimulant therapy will be identified by flagging for categorical summary. Total and subscale scores/points for AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, SDQ, and AAQoL will be summarized by optimized dose (if applicable) and visit and will be examined. Baseline will be defined for all subjects as the last non-missing value prior to SPN-812 dosing in Study 812P311.

7.9. Safety Analysis

Safety analyses will be performed by optimized dose group and overall based on the Safety Population.

The incidence rate of AEs will be calculated for each system organ class (SOC) and preferred term (PT). The severity of the AEs and the relationship to SM will be summarized for each SOC and PT.

AEs will be summarized using discrete summaries at the subject and event level by SOC and PT, and by severity and relationship separately. Verbatim description and Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for all AEs will be contained in the subject data listings.

Clinical laboratory values will be summarized by visit by optimized dose group and overall using descriptive statistics. For quantitative laboratory parameters, both actual values and change from baseline values will be summarized.

Vital signs will be summarized by visit by optimized dose group and overall using descriptive statistics. Both actual values and change from baseline will be summarized.

ECG results will be summarized by visit by optimized dose group and overall using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding).

C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only and suicidality (ideation and behavior combined). The summary will be presented by optimized dose group and overall.

7.10. Sample Size and Power Considerations

There is no consideration for power or sample size determination in this open label study. The present study is an extension of the blinded 812P306 study in patients with ADHD.

8. DOCUMENTATION

8.1. Adherence to the Protocol

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

8.2. Changes to the Protocol

Changes to the protocol will not be made without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB, and in some cases, filings to the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor, and IRB must be notified promptly.

Changes to the protocol which are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor or CRO will send a letter to the IRB detailing such changes.

8.3. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by the Sponsor's Quality Assurance team or qualified designee, which is an independent function from the study conduct team.

8.3.1. Data Collection

The primary source document will be the subject's medical record. If separate research records are maintained by the Investigator(s), both the medical record and the research

record will be considered the source documents for the purposes of monitoring and auditing the study.

Electronic data collection techniques will be used to collect data directly from the study sites using eCRFs. The electronic data will be stored centrally in a fully validated clinical database.

Data recorded on source documents will be transcribed into the eCRFs in accordance with the eCRF Completion Instructions that are provided to the study sites. The Investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source documents. The eCRFs will be monitored for completeness and accuracy against the source documents by the CRA(s) on a regular basis. Inconsistencies between the eCRFs and source documents will be resolved in accordance with the principles of GCP.

8.3.2. Clinical Data Management

Data from eCRFs and other external data (e.g., laboratory data) will be entered into or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

8.3.3. Database Quality Assurance

In accordance with the vendor's procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

8.4. Retention of Records

The Investigator has the responsibility to retain all study "essential documents", as described in ICH E6 for at least two years after approval of a marketing application or after formal discontinuation of the clinical program. Essential documents include but not limited to the protocol, eCRFs, source documents, laboratory test results, SM inventory records, Investigator's Brochure, regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB correspondence). The Investigator must obtain written permission from Supernus prior to the destruction of any study document.

8.5. Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor and the CRO immediately that this request has been made.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 Code of Federal Regulation (CFR) 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

8.6. Publication of Results

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor's site. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until all Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

8.7. Financing and Insurance

Financing and Insurance information will be set forth in a separate document between the Investigator and Sponsor (provided by the Sponsor or designee).

8.8. Disclosure and Confidentiality

The contents of this protocol, any amendments, and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work, including publications, without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

8.9. Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

9. ETHICS

9.1. Institutional Review Boards

The IRB that approved this study and the approval letters will be included in the clinical study report for this protocol.

The protocol, any protocol amendments, and the ICF will be reviewed and approved by the appropriate IRB before subjects are enrolled. The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

9.2. Ethical Conduct of the Study

This study will be conducted in accordance with SOPs from both the Sponsor and the CRO. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.
- United States (US) CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent/Assent and IRB regulations).
- Local, national legal guidelines.

9.3. Investigators and Study Personnel

This study will be conducted by qualified Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor).

Contact persons at the Sponsor and the CROs are listed in the reference binder provided to each investigational site. The study will be monitored by qualified personnel from the Sponsor or their designees, such as the CROs, for their respective sites. Medical writing, data management, and statistical analyses will be performed by the CROs. Laboratory tests will be conducted by a central laboratory as designated in the reference binder.

9.4. Subject Information and Consent

The Investigator (or designee) will inform the subject of all aspects pertaining to the subject’s participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and subject must sign and date the ICF before the subject can participate in the study. The subject will be given a copy

of the signed and dated ICF and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is entirely voluntary. The Investigator (or designee) must emphasize to the subject that consent, regarding study participation, may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use the amended ICF (including ongoing subjects).

10. REFERENCES

Adler LA, Clemow DB, Williams DW, Durell TM. Atomoxetine effects on executive function as measured by the BRIEF-A in young adults with ADHD: a randomized, double-blind, placebo-controlled study. PLoS One. 2014 Aug 22; 9(8):e104175.

Briars L and Todd T. A review of pharmacological management of attention-deficit/hyperactivity disorder. J Pediatr Pharmacol Ther. 2016;21(3):192-206.

Brod M, Johnston J, Able S, Swindle R. Validation of the adult attention-deficit/hyperactivity disorder quality-of-life Scale (AAQoL): a disease-specific quality-of-life measure. Qual Life Res. 2006;15(1):117-129.

Brod M, Adler LA, Lipsius S, Tanaka Y, Heinloth AN, Upadhyaya H. Validation of the adult attention-deficit/hyperactivity disorder quality-of-life scale in European patients: comparison with patients from the USA. Atten Defic Hyperact Disord. 2015;7(2):141-150.

Fava M, Johe K, Ereshefsky L, Gertsik LG, English BA, Bilello JA, Thurmond LM, Johnstone J, Dickerson BC, Makris N, Hoeppner BB, Flynn M, Mischoulon D, Kinrys G, Freeman MP. A Phase 1B, randomized, double-blind, placebo-controlled, multiple-dose escalation study of NSI-189 phosphate, a neurogenic compound, in depressed patients. Mol Psychiatry. 2016 Oct;21(10):1372-1380.

First MB, Williams JBW, Karg RS, Spitzer RL: *Structured Clinical Interview for DSM-5 Disorders, Clinical Trials Version (SCID-5-CT)*. Arlington, VA, American Psychiatric Association, 2015.

FDA Guidance for Industry: *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2012.

Guy W. *Clinical global impressions*. *ECDEU Assessment manual for Psychopharmacology*, Rockville, MD: US National Institutes of Health, Psychopharmacology Research Branch, 1976.

McCann BS and Roy-Byrne P. Screening and diagnostic utility of self-report attention deficit hyperactivity disorder scales in adults. Compr Psychiat 2004;45(3):175-183.

Papakostas GI, Johe K, Hand H, Drouillard A, Russo P, Kay G, Kashambwa R, Hoeppner B, Flynn M, Yeung A, Martinson MA, Fava M. A phase 2, double-blind, placebo-controlled study of NSI-189 phosphate, a neurogenic compound, among outpatients with major depressive disorder. Mol Psychiatry. 2019 Jan 9.

Pedrelli P, Blais MA, Alpert JE, Shelton RC, Walker RS, Fava M. Reliability and validity of the Symptoms of Depression Questionnaire (SDQ). CNS Spectr. 2014 Dec;19(6):535-546.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-1277.

Roth R, Isquith P, Gioia G. Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A). Psychological Assessment Resources, Inc.: Lutz, FL; 2005.

Roth RM, Lance CE, Isquith PK, Fischer AS, Giancola PR. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function-Adult version in healthy adults and application to attention-deficit/hyperactivity disorder. Arch Clin Neuropsychol. 2013 Aug; 28(5):425-434.

Spencer TJ, Adler LA, Meihua Q, Saylor KE, Brown TE, Holdnack JA, et al. Validation of the adult ADHD investigator symptom rating scale (AISRS). J Atten Disord. 2010;14(1):57-68.

Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry.1992;49(8):624-629.

Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-1097.