TITLE PAGE

Protocol Number:	812P304
Title:	Evaluation of SPN-812 ER 400 and 600 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial
Sponsor:	[redacted]
IND number:	108,864
Investigational Medicinal Product:	Viloxazine hydrochloride
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Contract Research Organization (CRO):	[redacted]
CRO Medical Monitor	[redacted]
Phase:	3
Protocol Version:	4.0
Date:	12 October 2018
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with International Conference on Harmonization (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

Name of Product: SPN-812 ER	**Name of Active Ingredient:** Viloxazine Hydrochloride
Protocol Number: 812P304	**Phase of Development:** 3
Full Title of Study: Evaluation of SPN-812 ER 400 and 600 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial	
Investigator(s) / Center(s): Approximately 25 US centers	

Objectives:

Primary

- To evaluate the efficacy of SPN-812 extended-release (ER) compared to placebo as monotherapy for the treatment of ADHD in adolescents (12 -17 years).

Key Secondary

- To evaluate the effect of SPN-812 ER compared to placebo as assessed by:
  - Clinical Global Impression – Improvement (CGI-I) scale
  - Conners 3rd edition (Conners 3) – parent, composite T-score
  - Weiss Functional Impairment Rating Scale – Parent report (WFIRS-P)

Additional Secondary

- To evaluate the effect of SPN-812 ER compared to placebo as assessed by:
  - 50% Responder rate based on the ADHD-RS-5 Total score
  - Stress Index for Parents of Adolescents (SIPA)
  - ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores
  - Conners 3 – Self, composite T-score

Safety

- To evaluate the safety and tolerability of SPN-812 ER in adolescents with ADHD

Exploratory

[redacted]

Study Design: Randomized, double-blind, placebo-controlled, multicenter, 3-arm, parallel-group, efficacy and safety pivotal study

Number of Subjects: Approximately 300 subjects (100 subjects per treatment)

Criteria for Inclusion:

Male and female subjects, 12-17 years of age, diagnosed with ADHD, parents/caregivers and subjects able to give consent/assent and to follow the protocol requirements of the study.

Criteria for Exclusion:

History or presence of significant diseases, evidence of suicidality, allergy to viloxazine, or any other reason that could interfere with the subject's participation in the study as determined by the Investigator.

Treatment, Dose, and Mode of Administration:

Study medication (SM): capsules containing either SPN-812 ER 200 mg or placebo

Mode of administration: Each treatment will be administered once daily (QD) as a single oral dose.

Dose: Subjects will be titrated up at 200 mg/week to the final randomized dose (1:1:1) as follows:

Treatment A: Placebo

Treatment B: SPN 812 ER 400 mg/day (2 x 200 mg SPN-812 ER)

Treatment C: SPN-812 ER 600 mg/day (3 x 200 mg SPN-812 ER)

Duration of Treatment and Study Duration:

Screening window: within 28 days prior to Visit 2 (Baseline Visit)

Titration period: 2 weeks

Maintenance treatment period: 5 weeks

Total subject duration on study: approximately 11 weeks (including up to 28 days of Screening)

Total number of visits: 9

Total duration of study: Approximately 12 months (9 months of enrollment). At the end of the study, eligible subjects will have the option to enroll in a separate open-label extension study.

Treatment Schedule:

Screening (Visit 1): After informed consent and informed assent (if applicable) is obtained, subjects will undergo initial screening evaluation including medical and psychiatric history, ECG, vital signs, physical examination, hematology and chemistry laboratory tests, and urine drug screen. A blood sample will also be drawn for PGx testing. ADHD diagnosis and severity will be confirmed and inclusion/exclusion criteria will be reviewed to confirm eligibility of the subject.

Study Dose Treatment Phase (Visits 2 – 9): This phase will consist of two weeks of Titration followed by five weeks of Maintenance phase until end of study (EOS)/Visit 9.

Baseline, Randomization, and Dispensation of SM (Visit 2): Approximately 300 eligible subjects will be randomized. Within 28 days of the Screening Visit, eligible subjects will return for the Baseline Visit. After confirmation of eligibility (including a urine pregnancy test for Females of Childbearing Potential [FOCP]), subjects will be randomized and receive blinded SM.

Study Dose Treatment: Titration (Visits 2-3): Subjects will return to the clinical site for weekly visits to undergo efficacy and safety evaluations and to pick up the next dosing card.

Study Dose Treatment: Maintenance (Visits 4-9): Subjects will return to the clinical site for weekly visits to undergo efficacy and safety evaluations and to pick up the next dosing card until Visit 9/EOS.

End of Study (Visit 9): Subjects will return for final evaluation (the same evaluation will be done if the subject terminated early).

Optional Substudy: Pharmacokinetic Sampling (Visit 3-9): The following PK samples will be collected: pre-dose and 1, 2, 4, and 6 hours post-dose.

Endpoints:

Primary Endpoint: The primary endpoint in this study is the change from baseline (CFB) to EOS in the ADHD-RS-5 total score.

Key Secondary Efficacy Endpoints: a) CGI-I, b) Conners 3 - Parent composite T-score, and c) WFIRS-P average score

Additional Secondary Efficacy Endpoints: a) Proportion of responders with 50% improvement in ADHD-RS-5 Total score, b) SIPA, c) ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores, and d) Conners 3 - Self composite T-score

[redacted]

Safety Assessments: Safety will be assessed using Adverse Events (AEs), clinical laboratory tests, vital signs, physical examinations, ECGs and the Columbia Suicide Severity Rating Scale (C-SSRS).

Sample Size:

Seventy-two subjects per treatment group in the Intent-To-Treat (ITT) population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of 0.547, which was observed in the comparison of SPN-812 200 mg and placebo in the SPN 812 Phase IIb study (based on the CFB to endpoint in the ADHD-RS-IV total score) and will maintain consistency in the sample size assumption used between this clinical trial and the SPN-812 P302 study (e.g., across the SPN-812 clinical trials in the adolescent population). A total of 300 subjects (100 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.

Analysis Populations:

- The Randomized population will include all enrolled subjects who had a baseline visit and are randomized via the IWRS.
- The ITT population for efficacy will include all randomized subjects who took at least one dose of study medication, and had a Baseline and at least one post-randomization ADHD-RS-5 assessment. Subjects will be analyzed according to the treatment to which they were randomized.
- The Per Protocol (PP) population consists of all subjects in the ITT population who completed all 9 visits with no missing ADHD-RS-5 assessments and no major protocol violations. Subjects will be analyzed according to the treatment they actually received.
- The Safety Population consists of all subjects randomized into the study who receive at least one dose of SM. Subjects will be analyzed according to the treatment they actually received.
- The PK population will include all subjects in the safety population with ≥1 PK sample that is not below the Lower Limit of Quantitation (LLOQ).

Handling of Missing Data:

With respect to the primary analysis, missing ADHD-RS-5 Total scores will be assumed to be missing at random (MAR) and will be handled using a Mixed Model for Repeated Measures (MMRM) method in SAS. The sensitivity analysis for the primary endpoint will be performed by assuming that missing ADHD-RS-5 Total Scores are missing not at random (MNAR). For analysis of secondary endpoints, missing values will be assumed as MAR.

Statistical Methods:

All tabulations of analysis results will include summaries for the following three treatments: SPN-812 ER 600 mg, SPN-812 ER 400 mg, and placebo.

Where appropriate, variables will be summarized descriptively (frequency count and percent for categorical variables, and number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables).

Categorical variables will be analyzed using categorical response methods such as Pearson's Chi-square test. If expected frequencies are less than 5 in a given cell, then exact testing techniques will be used.

Descriptive statistics will be presented for demographics, data from the clinical laboratory tests, vital signs, weight, ECGs, and C-SSRS.

Efficacy Analyses

Primary: The primary efficacy variable, change from baseline in ADHD-RS-5 Total Score to Week 7 (EOS), will be analyzed using a Mixed Model for Repeated Measures (MMRM), which assumes that missing data are missing at random (MAR). The model will include fixed effect terms for baseline ADHD-RS-5 Total Score, age group, treatment, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. In case there is a convergence problem in the MMRM model with the unstructured variance covariance matrix, the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound symmetry.

The adjusted mean (LS Mean) of CFB to EOS for ADHD-RS-5 Total Score for each treatment group (Placebo, SPN-812 ER 400 mg and SPN-812 ER 600 mg) will be presented, along with the corresponding standard error. Each of the active treatment groups (SPN-812 ER 400 and 600 mg) will be compared with placebo. The p-values, Least Squares (LS) of treatment means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.

Sensitivity analysis: The sensitivity analysis assumes that missing ADHD-RS-5 Total Scores are missing not at random (MNAR). Placebo-based multiple imputation will be used to fill in missing values.

Secondary: The secondary analyses will be based on the ITT population with missing values imputed using multiple imputation assuming MAR. All secondary analyses will be analyzed using ANCOVA at Week 7 (EOS) on the change from baseline at Week 7 (EOS) with treatment and baseline as fixed effect.

Analyses of key secondary endpoints will be repeated for the PP population.

Safety Analyses

Safety analyses will be performed by treatment group based on the safety population. The incidence rate, severity, and relationship to SM for all AEs will be summarized by treatment group for each System Organ Class and Preferred Term.

Pharmacokinetic and Pharmacogenomic Methods:
Sampling: For PK analysis, a maximum of five blood samples will be collected at one or more of Visits 3-9. For PGx analysis, a single blood sample will be collected at screening.

Bioanalytical Analysis:

Viloxazine concentrations and 5-hydroxy-viloxazine glucuronide concentrations in plasma will be determined for all treatments using a validated achiral chromatographic method. Viloxazine concentrations will be reported as viloxazine free base.

Pharmacokinetic Analysis:

Plasma concentrations for viloxazine (and 5-hydroxy-viloxazine glucuronide, if applicable) will be provided. Population PK data will be pooled across all subjects who participate in this optional portion of the study and analyzed using nonlinear mixed-effects modeling methods. [redacted] Population PK analyses will be reported separately from the clinical study report.

Pharmacogenomics Analysis:
A blood sample will be collected from each individual at screening for PGx analysis. [redacted]

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-IV/5	ADHD Rating Scale- IV/5
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity of Illness
CGI-I	Clinical Global Impression - Improvement
CI	Confidence Interval
CL/F	Apparent clearance
Conners 3	Conners 3rd edition Rating Scale
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
EOS	End of Study
ER	Extended Release
FDA	Food and Drug Administration
FOCP	Females of Childbearing Potential
GCP	Good Clinical Practice
ICF	Informed Consent Form
IAF	Informed Assent Form
ICH	International Conference on Harmonization
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
LLOQ	Lower Limit of Quantitation
LS	Least Square
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
PGx	Pharmacogenomics
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
QD	Once a day
REML	Restricted Maximum Likelihood

SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIPA	Stress Index for Parents of Adolescents
SOC	System Organ Class
SOP	Standard Operating Procedures
SM	Study Medication
WFIRS-P	Weiss Functional Impairment Rating Scale – Parent Version
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Background

Viloxazine hydrochloride (2-[(2-ethoxyphenoxy) methyl] morpholine hydrochloride) is a structurally distinct bicyclic norepinephrine reuptake inhibitor (NRI) with antagonistic activity observed at 5-HT7 and 5-HT1B receptors and agonistic activity at 5-HT2B and 5-HT2C receptors. Viloxazine was previously marketed in several European countries as an antidepressant. Supernus is currently developing viloxazine (SPN-812) for potential use in the treatment of subjects with attention deficit hyperactivity disorder (ADHD), based on the compelling pharmacological properties and favorable safety profile of viloxazine, as well as on the current unmet medical need for effective long-acting non-stimulant ADHD treatment in children and adolescents.

Compared to other bicyclic antidepressants, viloxazine has generally been found to be well tolerated, with no reports of major toxicity during short or long-term research studies. Anticholinergic-like effects and sedation have been less marked and less frequent than those of the tricyclic antidepressants, but nausea and vomiting have been common complaints with the immediate-release (IR) formulation and may be dose-related.

Viloxazine is similar in structure to reboxetine and atomoxetine and is a racemic mixture of two stereoisomers of similar affinities for many important neurotransmitter receptors. It is an inhibitor of the reuptake of norepinephrine and affects norepinephrine-related functional activities, and although its inhibitory action on serotonin re-uptake appears to be weak, viloxazine may facilitate serotonin activity pre- or post-synaptically. Furthermore, viloxazine is known to upregulate $GABA_B$ binding sites. These neurotransmitters have been implicated in pathophysiology of ADHD, and drugs that are effective in the treatment of ADHD act in noradrenergic and dopaminergic systems.

Viloxazine is rapidly and almost completely absorbed following oral administration to man. Unchanged drug is the major component in blood at all times in man and is probably the pharmacologically active moiety. Viloxazine is metabolized and rapidly excreted in the urine; there are no known active metabolites.

1.2 Clinical Information

Two Phase 2 studies in ADHD patients, one in adults and one in children, and four Phase 1 studies in healthy adults have been conducted with SPN-812 IR or ER. An additional open label extension study in children is ongoing.

Phase 1 Studies

Phase 1 studies included comparison of SPN-812 ER formulation to an immediate-release (IR) formulation at single and multiple doses (812P103), evaluation of maximum tolerable doses and cardiac safety in a single- and multiple-ascending dose study (812P120), and assessment of the effects of food and sprinkling on the relative bioavailability of viloxazine (812P105). In addition, a [^{14}C]-labelled oral IR solution was used to examine absorption, metabolism, and excretion of viloxazine in healthy males (812P111).

[redacted]

[redacted]

Phase 2 Studies

The proof-of-concept Phase 1/2 study (812P201), compared an IR formulation of SPN-812 and placebo in a randomized, blinded study, administered three times a day in a dose range of 150 to 300 mg/d 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 Conner's' Adult ADHD Rating Scale (CAARS) were collected at weekly intervals during the 6-week treatment period. [redacted]

The 812P202 study in children with ADHD assessed the effect of SPN-812 ER in reducing the symptoms of ADHD as measured by the ADHD Rating Scale-IV (ADHD-RS-IV). Subjects aged 6-12 years were randomized in a 1:2:2:2:2 ratio of placebo or active treatment (SPN 812 ER 100, 200, 300, or 400 mg) and received three weeks of titration at 100 mg/week followed by five weeks of maintenance treatment for a total of eight weeks of therapy. Mean ADHD-RS-IV Total Scores improved throughout treatment, in all groups.

[redacted]

Information and data from clinical studies are available in detail in the SPN-812 ER Investigator's Brochure, version 6.0.

1.3 **Study Rationale**

An initial Phase 2 study demonstrated a 300 mg dose of an immediate-release formulation of SPN-812 was able to significantly lower the CAARS total score in adults with ADHD. [redacted]

When used for over 20 years as an anti-depressant, the IR form of viloxazine was approved at dosages of 200-600 mg/day. Although higher doses were occasionally used and reported, no clear advantage in efficacy was demonstrated and a modest decrease in tolerability could occur (often related to nausea). [redacted]

In addition to assessing the effect of SPN-812 ER treatment on ADHD symptom reduction, the study aims to explore treatment response within other domains of the disorder, including functional impairment and parental stress (Becker, 2011; Wiener, 2016). ADHD is a chronic, debilitating disorder that affects many aspects of daily life and has a substantial burden on family functioning. Children with ADHD exhibit a number of functional impairments, and the motivation in seeking medical treatment typically stems from the need to address dysfunction in social, emotional, academic, and familial domains (Epstein and Weiss, 2012). Therefore, optimal medical and behavioral management should ideally incorporate treatments that do not just improve symptoms of ADHD, but improve broader functioning of a patient, especially in the areas of self-esteem, educational achievement, and relationships with peers, teachers, and family.

2 STUDY OBJECTIVES

2.1 **Primary Objective**

- To evaluate the efficacy of SPN-812 ER compared to placebo as monotherapy for the treatment of ADHD in adolescents (12-17 years).

2.2 Secondary Objectives

Key Secondary

- To evaluate the effect of SPN-812 ER compared to placebo as assessed by:
  - Clinical Global Impression – Improvement (CGI-I) scale
  - Conners 3rd edition (Conners 3) – parent, composite T-score
  - Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P)

Additional Secondary

- To evaluate the effect of SPN-812 ER compared to placebo as assessed by:
  - 50% Responder rate based on the ADHD-RS-5 Total score
  - Stress Index for Parents of Adolescents (SIPA)
  - ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores Conners 3 – Self, composite T-score

Safety

- To evaluate the safety and tolerability of SPN-812 ER in adolescents with ADHD.

2.3 Exploratory Objectives

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]
  - [redacted]
  - [redacted])

3 INVESTIGATIONAL STUDY PLAN

3.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel-group study, to evaluate the efficacy and safety of SPN-812 ER as monotherapy for the treatment of adolescents (12-17 years old) with ADHD. Approximately 300 subjects will be randomized in a 1:1:1 ratio of placebo or one of the two active treatment arms (SPN-812 ER 400 or 600 mg). Following up to four weeks of screening, subjects will be randomized and undergo two weeks of titration followed by five weeks of maintenance for a total of seven weeks of treatment and total study duration of up to 9-11 weeks. The study schematic appears in Figure 1.

Screening (Visit 1): After administering the informed consent form (ICF; and informed assent form [IAF], if applicable), subjects will undergo initial screening evaluation including medical and psychiatric history, ECG, vital signs, physical examination, routine laboratory assessment, PGx sample collection, and urine drug screen. Data from testing may also be used for future research but will not be used for individual genetic characterization. ADHD diagnosis will be confirmed, as will all study inclusion/exclusion criteria. Eligible subjects will be scheduled for a Baseline Visit within 28 days. Subjects receiving ADHD

medication at Screening will undergo a washout of at least one week before the Baseline Visit.

Study Dose Treatment Phase (Visits 2 – 9): This phase will consist of two weeks of Titration followed by five weeks of Maintenance phase until end of study/Visit 9.

Baseline, Randomization, and Dispensation of Study Medication (SM) (Visit 2): At the Baseline Visit, inclusion/exclusion criteria will be reviewed to confirm continued eligibility, including urine pregnancy test for Females of Childbearing Potential (FOCP). Eligible subjects will be randomized and assigned the corresponding blinded dosing kit. The titration card of the blinded SM will be dispensed and the first study dose taken.

Study Dose Treatment: Titration (Visits 2-3): Subjects will return to the clinical site for weekly visits to undergo efficacy and safety evaluations, pick up the next dosing card and return the previous card.

Study Dose Treatment: Maintenance (Visits 4-9): Subjects will return to the clinical site for weekly visits to undergo efficacy and safety evaluations, pick up the next dosing card (except at Visit 9, the last visit) and return the previous card.

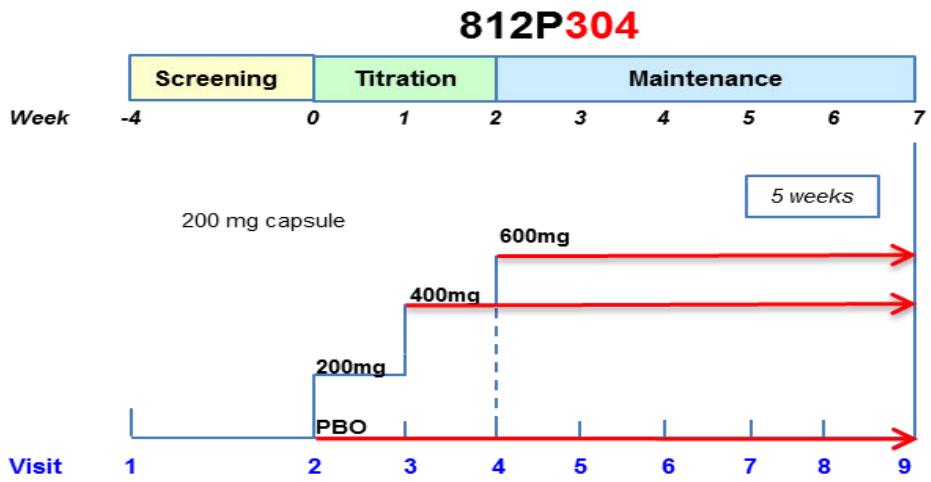
End of Study (Visit 9): Subjects will return for final evaluation (subjects terminated prior to Visit 9 will also undergo EOS evaluations).

Unscheduled visits may be conducted at the discretion of the investigator throughout the study. AEs will be assessed at all unscheduled visits.

An optional PK substudy during Visits 3-9, inclusive, will be conducted to assess the PK characteristics of viloxazine (and its metabolite 5-hydroxy-viloxazine glucuronide, if applicable) in this pediatric population. A total of five blood samples will be taken: pre-dose and 1, 2, 4, and 6 hours post dose. On the day the pre-dose sample is taken, SM must be administered at the site visit. Post-dose samples may be drawn on the same day or alternative visit days. If drawn on alternate visit days, the time the SM was taken that day must be consistent with the dose time for the previous two days and the time of dose administration must be recorded for all three days.

Subjects that have successfully completed this study will have the option of enrolling in a separate, open-label extension study.

Figure 1: Study Schematic



3.2 RATIONALE FOR STUDY DESIGN

812P304 is a randomized, double-blind, placebo-controlled, multicenter, 3-arm, parallel-group, pivotal study of SPN-812 ER as monotherapy for the treatment of adolescents ages 12-17 years with ADHD. This study is designed to demonstrate efficacy of either 400 or 600 mg/day SPN-812 ER compared to placebo using change from baseline to the end of the study of the ADHD-RS-5 Total Score, the measure most commonly used to assess efficacy of drug treatment of ADHD. Study structure and analysis are typical for a Phase 3 pivotal trial.

3.3 STUDY POPULATION

3.3.1 Number of Subjects

Approximately 300 subjects will be randomized (100 subjects per treatment) in this clinical study.

3.3.2 Inclusion Criteria

1. Healthy male or female subjects, 12-17 years of age, inclusive.
2. Diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).
3. Attention Deficit/Hyperactivity Disorder Rating Scale-5, Home Version: Adolescent, Investigator Administered and Scored (ADHD-RS-5) score of at least 28.
4. CGI-S score of at least 4 at screening.
5. Weight of at least 35 kg.
6. Free of medication for the treatment of ADHD for at least one week prior to randomization and agreement to remain so throughout the study.
7. Considered medically healthy by the Investigator via assessment of physical examination, medical history, clinical laboratory tests, vital signs, and electrocardiogram.
8. Written informed consent obtained from the subject's parent or legal representative and informed assent from the subject, if applicable.

9. 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 30 days prior to the first dose, throughout the study:
    a. simultaneous use of male condom and intra-uterine contraceptive device placed at least four weeks prior to the first study drug administration
    b. surgically sterile male partner
    c. simultaneous use of male condom and diaphragm with spermicide
    d. established hormonal contraceptive

3.3.3 **Exclusion Criteria**

1. Current diagnosis of major psychiatric disorders. Subjects with Major Depressive Disorder are allowed in the study if the subject is free of episodes both currently and for the last six months.
2. Current diagnosis of major neurological disorders. Subjects with seizures or a history of seizure disorder within the immediate family (siblings, parents), or a history of seizure-like events are excluded from the study.
3. Current diagnosis of significant systemic disease.
4. Evidence of suicidality (defined as either active suicidal plan/intent or active suicidal thoughts, or more than one lifetime suicide attempt) within the six months before Screening or at Screening.
5. BMI greater than 95th percentile for the appropriate age and gender.
6. History of an allergic reaction to viloxazine or related drugs.
7. Any food allergy, intolerance, restriction or special diet that, in the opinion of the Investigator, could contraindicate the subject's participation in this study.
8. Subjects who received any investigational drug within the longer of 30 days or 5 half-lives prior to Day 1 dosing of SM.
9. Any reason, which, in the opinion of the Investigator, would prevent the subject from participating in the study.
10. Positive drug screen at the Screening Visit. A positive test for amphetamines is allowed for subjects receiving a stimulant ADHD medication at Screening; the subject will be required to discontinue the stimulant for the study, beginning at least one week prior to the Baseline Visit.
11. Pregnancy, breastfeeding, or refusal to practice abstinence or acceptable birth control during the study (for female subjects of childbearing potential).

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 9 (EOS).

All subjects who discontinue early will complete the procedures listed for Visit 9 (EOS).

All reasons for screening failure or for failure to continue study eligibility at Baseline after successful screening 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 the subject at any time in the interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the

Medical Monitor and/or Clinical Research Associate (CRA) before the subject stops SM. Subjects removed from the study for any reason will not be replaced.

Reasons for subject discontinuation may include:

- Withdrawal of consent
- Noncompliance
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

The primary reason for subject discontinuation must be recorded in the subject's medical record and on the 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.

If a subject misses doses of SM during this study, the Investigator shall counsel the subject/caregiver on the importance of compliance. If the subject has consistently missed doses, he or she may be discontinued from the study at the discretion of the Investigator and in consultation with the Medical Monitor; all procedures for discontinuation will be followed.

4 STUDY TREATMENT

4.1 Study Medication Identity, Packaging and Labeling

Test and reference (matching placebo) products are capsules packaged in a double-blind configuration and supplied in labeled blister cards by the Sponsor.

Each SM blister card will include identical capsules containing placebo and/or 200 mg of SPN-812 ER, and will supply a subject with seven days of dosing plus two extra days if needed. Each card will be labeled with identification specific to the study and subject (subject study number and initials).

4.2 Study Medication Administration

Each treatment will be administered as a single oral dose, once-a-day (QD), with or without food as either intact capsule, or as capsule content sprinkled on soft food.

4.3 Method of Assigning Subjects to Treatment Group

Eligible subjects will be randomized in a 1:1:1 ratio at Visit 2 (Baseline) and will receive either placebo, SPN-812 ER 400 mg/day, or SPN-812 ER 600 mg/day.

Allocation of study treatment will occur centrally via an interactive web response system (IWRS) using a randomization schedule to determine the kit assignment for each subject being randomized. Each SM kit contains eight dosing cards. One dosing card will be given to the subject at each weekly visit.

The initial dose may be taken at the clinic during the Baseline Visit, with the next dose taken the next morning. Subjects will be titrated up at 200 mg/week to the final dose (1:1:1) as follows:

Treatment A: Placebo
Treatment B: SPN-812 ER 400 mg/day (2 × 200 mg SPN-812 ER)
Treatment C: SPN-812 ER 600 mg/day (3 × 200 mg SPN-812 ER)

Table 1 below presents the details of the dosing schedule for each treatment group.

Table 1: Dosing Schedule

812P304		TITRATION		MAINTENANCE				
Visit #	1	2 (BL)	3	4	5	6	7	8	9 (EOS)
Study Week		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
	Screening							
PBO		PBO	PBO	PBO	PBO	PBO	PBO	PBO
400mg		200	400	400	400	400	400	400
600mg		200	400	600	600	600	600	600

4.4 Blinding

The subject and all personnel involved with the conduct and the interpretation of the study, including the Investigators, study site personnel, the Sponsor and Contract Research Organization (CRO) clinical staff, including the Medical Monitor, will be blinded to the medication codes. A limited number of Supernus personnel will perform and interpret the plasma assays for the population PK analysis and will be aware of these plasma data during the study. These personnel will not have access to the randomization schedule, are not associated with the clinical conduct of the study, and will not reveal to any clinical personnel involved in the study the treatment to which a subject will be assigned. Randomization schedule data will be kept strictly confidential, filed securely by the IWRS vendor, and accessible only to authorized persons until the time of unblinding.

4.5 Study Medication Handling and Accountability

All SM are supplied to the Investigator by the Sponsor. SM supplies must be kept 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 Harmonization (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 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 Sponsor 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 FDA. The assigned Clinical Research Associate (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 Sponsor 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 Sponsor with a copy of the completed SM disposition form.

4.6 **Concomitant Medications**

Subjects may not be on any prohibited medication as indicated in the Inclusion/Exclusion Criteria. Specific concomitant medication prohibitions include known CYP1A2 substrates (e.g., theophylline, melatonin, olanzapine, duloxetine). No additional concomitant medications are allowed during the study, with the following exceptions:

- Nutritional supplements (e.g. multivitamins, fish oil)
- EMLA® or other numbing cream for venipuncture
- Common over-the-counter (OTC) therapies for minor transient ailments (e.g. acetaminophen for headache, ibuprofen for fever.

All concomitant medications will be recorded in the eCRF.

5 Study Methods

5.1 **Study Visits and Procedures**

All subjects who are randomized and take the initial dose of SM will be followed according to the protocol regardless of the number of doses of SM taken, unless consent for follow-up is withdrawn. The Sponsor or the 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.

Table 2 represents the Schedule of Events and Assessments for the study.

Table 2: Schedule of Events and Assessments

		Treatment Phase[g]			
Period	**Screening**	**Titration**		**Maintenance**	
		Baseline Randomization			**End of Study[h]**
Visit #	**1**	**2**	**3**	**4-8**	**9**
Visit Day		**1**	**7**	**14, 21, 28, 35, 42**	**49**
Visit Window (days)	≤28d before V2		±2	±2	±2
Informed Consent/Assent[a]	X				
Medical and Psychiatric History	X				
Mini-KID	X				
Demographics	X				
Urine Drug Screen	X				
Physical Exam[b]	X				X [c]
Inclusion/Exclusion Criteria	X	X			
ECG (12-lead)	X				X
Vital Signs[d]	X	X	X	X	X
Hematology	X				X
Serum Chemistry	X				X
Pharmacogenomic sample	X				
Urine Pregnancy Test, FOCP only		X			X
CGI-S	X	X			
CGI-I			X	X	X
C-SSRS	X	X	X	X	X
Randomization		X			
ADHD-RS-5	X	X	X	X	X
WFIRS-P, SIPA		X			X
Conners 3-SF parent, self		X			X
Concomitant Medication	X	X	X	X	X
Adverse Events		X [e]	X	X	X[e]
Drug Dispensed		X[f]	X	X	
Drug Return, Compliance			X	X	X
Optional PK Blood Sampling Visit[g]			X	X	X

a To be obtained prior to performing any study procedures.
b Includes height and weight, excludes genitourinary system
c Changes from Screening only
d Seated (5 min) heart rate and blood pressure, temperature, respiratory rate
e At Baseline, AEs are recorded only after SM is administered. Subjects with serious adverse events at EOS will be followed until the event has resolved or considered stable.
f Titration will begin after the first dose administered
g An optional PK visit will take place between Visits 3 and 9 inclusive. Samples will be taken pre-dose, and post-dose at hours 1, 2, 4, and 6.
h EOS or last visit in the case of early discontinuation.

5.1.1 **Visit 1 - Screening (Day -28 to -1)**

Prior to conducting screening procedures, written Informed Consent must be obtained from the parent or legal representative; written Informed Assent must also be obtained from the subject, if applicable according to local requirements. Subject screening procedures will be performed within 28 days prior to Baseline Visit and may be done on more than one day. Abnormal results on screening laboratory tests may be repeated at the discretion of the Investigator. Subjects receiving ADHD drug therapy at Screening must discontinue that therapy for at least one week prior to Visit 2 (Baseline) and must remain off the ADHD drug for the duration of the study.

The following procedures will be performed at Visit 1:

1. Obtain written informed consent/assent.
2. Obtain demographic information, medical and psychiatric history
3. Administer MINI-KID for confirmation of ADHD diagnosis
4. Perform limited (excluding genitourinary system) physical examination, record height and weight
5. Assess Inclusion/Exclusion criteria
6. Perform 12-lead ECG
7. Record vital signs (HR, BP, temperature, and RR)
8. Collect blood samples for hematology, chemistry, and PGx
9. Collect urine sample for drug screen
10. Administer ADHD-RS-5, CGI-S and C-SSRS
11. Assess and record concomitant medications
12. For subjects eligible for study participation based on the above parameters, schedule the Baseline Visit, allowing for at least a one-week washout of any ADHD drug therapy the subject was receiving at Screening.

A positive test for amphetamine is allowed for subjects receiving a stimulant ADHD medication. However, the subject must discontinue the stimulant for the duration of the study starting at least one week prior to the Baseline Visit.

5.1.2 **Visit 2 - Baseline Visit (Day 1)**

1. Confirm eligibility for the study (Inclusion/Exclusion criteria)
2. Collect urine sample for pregnancy test for FOCP
3. Randomize (via IWRS)
4. Administer efficacy and safety scales: ADHD-RS-5, Conners 3 (parent, self), WFIRS-P, SIPA, CGI-S and C-SSRS
5. Record vital signs (HR, BP, temperature, and RR)
6. Record concomitant medications
7. Record AEs after SM dosing only
8. Dispense SM dosing card, observe administration of initial dose (titration starts when the first dose of SM is taken).

Study Visits after Visit 2 will have a visit window of ±2 days. Deviations from this window will be recorded in the eCRF, but will not require separate notification of the Sponsor.

5.1.3 **Visit 3 – 8 - Titration (Days 7, 14 [±2 days]) and Maintenance (Days 21, 28, 35, 42 [±2 days])**

1. Record vital signs (HR, BP, temperature, and RR)

2. Administer efficacy and safety scales: ADHD-RS-5, CGI-I and C-SSRS
3. Record concomitant medications
4. Record AEs
5. Collect returned SM and assess treatment compliance
6. Dispense SM dosing card
7. Optional - blood collection for PK substudy, if applicable

5.1.4 **Visit 9 - End-of Study (Day 49 [±2 days])**

1. Perform limited (excluding genitourinary system) PE (record only changes from baseline), record height and weight
2. Perform 12-lead ECG
3. Record vital signs (HR, BP, temperature, and RR)
4. Collect blood samples for hematology and chemistry
5. Administer efficacy and safety scales: ADHD-RS-5, Conners 3 (parent, self), WFIRS-P, SIPA, CGI-I and C-SSRS
6. Collect urine and perform pregnancy test (FOCP only)
7. Record concomitant medications
8. Record AEs
9. Collect returned SM and assess treatment compliance
10. Optional - blood collection for PK substudy, if applicable
11. Determine if subject wants to participate in the open-label extension study

5.1.5 **Pharmacogenomic Sample Collection**

All subjects will have a blood sample taken at Screening for CYP2D6 pharmacogenomic testing. Results from individual tests will be used for research purposes only and will not be distributed.

Samples will be identified only by the study subject number to maintain confidentiality. If a given subject's PK data warrant evaluation of PGx, DNA will be extracted from that subject's PGx blood sample and tested for any genetic variations associated with CYP2D6 enzyme. This enzyme is involved in the metabolism of viloxazine and genetic variation may affect the pharmacokinetics of the drug. Samples will be stored for up to 10 years for potential future research purposes such as possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile). The DNA analysis will not be used for individual genetic characterization and the subject's identity will be kept confidential.

Data from samples will not have diagnostic value and will not be used for individual genetic characterization or development of a commercial product. At the end of testing or 10 years, any remaining samples will be destroyed. The subject may withdraw consent for pharmacogenomic testing at any time; if consent is withdrawn, the subject's sample will be destroyed.

5.1.6 **Pharmacokinetic Sub-study-Sample Collection**

Participation in the PK Sub-study is optional. All blood samples for PK analysis will be drawn at the clinical site. A maximum of five blood samples (4 mL each) will be taken for PK analysis over the course of the study. Blood may be drawn for quantitative PK analysis during Visits 3-9.

At one of these visits, subjects will arrive at the clinic in the morning prior to taking their morning dose. A PK sample will be drawn pre-dose; after which the dose will be

administered in the clinic. Post-dose PK samples will be taken at approximately 1, 2, 4, and 6 hours after the administered dose. Collection of the post-dose samples may be on the same visit or an alternate visit (dosing at home) if the previous two doses were taken at approximately the same time and the times for that day and the previous two days were recorded.

Blood samples will be collected and processed as per instructions in the Laboratory Manual. The following excursion windows are permitted:

- Pre-dose: up to 30 minutes before dose
- 1-2 hours: ± 15 minutes
- 4 and 6 hours: ± 30 minutes

6 STUDY VARIABLES

6.1 Primary Efficacy Variable

6.1.1 ADHD-RS-5

The primary endpoint in this study is the CFB to EOS in the ADHD-RS-5 Total Score.

The ADHD-RS-5 is an ADHD-specific rating scale designed and validated to assess current ADHD symptomatology as described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The scale consists of 18 items that directly correspond to the 18 DSM-5 symptoms and are further subdivided into two subscales: Hyperactivity/Impulsivity and Inattention (DuPaul, 2016). The ADHD-RS-5 scale rates the frequency and severity of each symptom on a 4-point Likert-type scale from 0 (none) to 3 (severe) and allows assessment of functional impairments linked to each symptom dimension. The ADHD-RS-5 rating scale is one of the most commonly used measures of drug efficacy in the treatment of ADHD and is the primary outcome measure for this study. The ADHD-RS-5 Home Version: Adolescent instrument will be administered and scored by Investigator at each weekly visit from Baseline through EOS.

6.2 Secondary Efficacy Variables

The key secondary efficacy variables include:

a) CGI-I
b) Conners 3 – Parent, composite T-score
c) WFIRS-P average score

Additional secondary variables include:

a) Proportion of responders with 50% improvement in the ADHD-RS-5 Total score (50% Responder rate)
b) SIPA
c) ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores
d) Conners 3 – Self, composite T-score

6.2.1 **Clinical Global Impression – Improvement**

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 a SM (Guy 1976). The Clinical Global Impression – Severity of Illness (CGI-S) is a single item clinician rating of clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The Clinical Global Impression – Improvement Scale (CGI-I) is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. Both CGI-S and CGI-I are rated on a 7-point scale of 1 to 7 with 7 being "extremely ill" or "very much worse", respectively. Successful therapy is indicated by a lower overall score in subsequent testing.

- CGI-S will be evaluated by the Investigator at Screening and Baseline on a 7-point scale with 1=Normal, 2=Borderline ill, 3=Mildly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, and 7=Extremely ill.
- CGI-I, relative to the condition at baseline, will be evaluated by the Investigator at each post-baseline visit 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.

6.2.2 **Conners 3**

The Conners 3rd Edition™ (Conners 3) is a focused diagnostic tool for assessment of ADHD and associated learning, behavior, and emotional problems in children ages 6 to 18 years (Sparrow, 2010). The scale is based on the solid findings and key elements of its predecessor, the Conners' Rating Scales–Revised (CRS–R™), but offers a more refined assessment of ADHD and comorbid disorders (e.g., oppositional defiant disorder and conduct disorder). The Conners 3 instrument includes items related to inattention, hyperactivity, and impulsivity, as well as assessments of executive functioning, learning problems, and relationships. Like previous versions, the Conners 3 combines teacher, parent, and student reports to provide a particularly detailed and comprehensive evaluation of student behavior as observed in different settings. Teacher, parent, and self-report (for 8-18 year-olds) rating scales are all available in long and short versions. The short forms of Parent, Teacher, and Self Reports of Conners 3 are comprised (respectively) of 45, 41, and 41 items. All Conners 3 scale versions are scored on a 4-point scale (0-3), where a higher score indicates more severe symptom presentation.

The Conners 3 – Parent: Short, and Conners 3 – Self-Report: Short assessments will be performed at Visit 2 (Baseline) and at Visit 9 (EOS).

6.2.3 **WFIRS-P**

The Weiss Functional Impairment Rating Scale (WFIRS) instrument evaluates ADHD-related functional impairment (Gajria, 2015; Thompson, 2017). This scale allows the clinician to assess to what degree a patient's behavior and emotional problems affect his/her ability to accomplish daily tasks and interactions and helps to identify specific areas of difficulty. The scale has been validated in the ADHD population. The parent-based version (WFIRS-P) completed by the parent/guardian of a child is used in this study and comprises 50 items grouped into six domains: Family, School (learning and behavior), Life Skills, Child's Self-Concept, Social Activities, and Risky Activities. The items relate to the past month and are scored using a 4-point Likert scale. Higher WFIRS-P scores indicate more severe functional impairment.

This instrument will be completed at Baseline and EOS by the parent/caregiver.

6.2.4 **SIPA**

The Stress Index for Parents of Adolescents (SIPA) is a screening and diagnostic instrument that identifies areas of stress in parent-adolescent interactions and is appropriate for parents of adolescents aged 11-19 years (Sheras, 1998). The SIPA scale is a 112-item questionnaire that yields scores across three domains (Adolescent Domain, Parent Domain, and Adolescent-Parent Domain) and the Life Stressors Scale. The Adolescent and Parent Domains are further subdivided into four subscales that focus on the parent's perception of their child's personality and on the parent's characteristics and behaviors. The Life Stressor Scale assesses external life factors contributing to stress experienced by a parent. The Index of Total Parenting Stress (TS) is the composite score of all items across all domains and reflects the total stress experienced as a function of parenting a particular adolescent.

The SIPA questionnaire will be completed at Baseline and at EOS by the parent/caregiver.

6.3 **Safety Variables**

The safety variables for the study are AEs, clinical laboratory test results, vital signs, ECG results, and treatment-emergent suicidal ideation.

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.

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.

6.4 **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.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease, intercurrent 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.

6.4.1 **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.

6.4.2 Recording and Evaluation of Adverse Events

All subjects who are screened (Visit 1) will be questioned regarding the occurrence of AEs. At each contact with the subject, the 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 screening 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 drug is taken, or that worsened following first administration of study drug. All AEs in this study will be recorded after administration of SM, therefore all will be treatment-emergent. The clinical course of each AE should be followed 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?

6.4.3 Criteria for Assessing Severity

The 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.

6.4.4 Criteria for Assessing Causality

The 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)**.

6.4.5 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.

6.4.6 Investigator Responsibilities for Reporting SAEs

The 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 Investigator or study 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.

[redacted]

6.4.7 Other Events Requiring Immediate Reporting

The 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. Pregnancy should be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor; the 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.

6.4.8 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.

6.5 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 Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, 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.

6.5.1 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). 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 instrument has been validated and used successfully in both children and adolescent 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.

6.5.2 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.

6.5.2.1 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.

6.5.2.2 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 one week and/or refer him/her to a qualified mental health professional.

6.5.2.3 Non-acute Suicidal Risk

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

6.6 Clinical Measurements

6.6.1 Laboratory Tests

All clinical laboratory tests will be performed by a central laboratory as specified in the reference binder.

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 2) shows the time points at which blood and urine samples will be collected for clinical laboratory tests (and plasma concentration levels for those subjects that choose to participate in the PK substudy).

Table 3 presents the clinical laboratory tests to be performed.

Table 3: Clinical Laboratory Tests

Category	Parameters
Hematology	Red Blood Cell count, hemoglobin, hematocrit, platelet count, and White Blood Cell count with differential
Chemistry	**Electrolytes**: Na^+, K^+, chloride
	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
Drug Screen, urine	cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine propoxyphene
Pregnancy test, urine	FOCP only

6.6.2 Vital Signs

Vital sign measurements (e.g., blood pressure, heart rate, temperature, and respiratory rate) and weight will be obtained at each visit. Blood pressure and heart rate will be measured after the subject has been sitting for 5 minutes. Vital signs may be taken at any other time, as deemed necessary by the Investigator.

6.6.3 Physical Examinations

The physical examination conducted at Screening will include assessments of all body systems other than genitourinary. Measurement of height and weight will be performed at Screening and EOS. Any findings during screening will be recorded as medical history and any clinically significant abnormal findings during treatment will be recorded as an AE. At the EOS physical examination, only changes from baseline (Screening visit) will be noted.

6.6.4 Electrocardiograms (ECGs)

A 12-lead ECG will be obtained as per the Schedule of Events and Assessments (Table 2). 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).

6.7 Exploratory Variables

[redacted]

[redacted]

7 STATISTICAL METHODS

7.1 General Considerations

All statistical analysis will be performed using SAS version 9.2 or higher by [redacted], which is the designated CRO. [redacted] will be responsible for developing a unique program for each TLF to create a TLF report and deliver to Supernus at the completion of the study.

All tabulations of analysis results will include summaries for the following three treatments: SPN-812 ER 600 mg, SPN-812 ER 400 mg, and placebo.

Where appropriate, variables will be summarized descriptively (frequency count and percent for categorical variables, and number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables).

Categorical variables will be analyzed using categorical response methods such as Pearson's Chi-square test. If expected frequencies are less than 5 in a given cell, then exact testing techniques will be used.

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 electronic case report forms (eCRFs) will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings.

Complete 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

With respect to the primary analysis, missing ADHD-RS-5 Total Scores will be assumed to be missing at random (MAR), that is, given the observed data, the reason for the missing data does not depend on the unseen data. The Mixed Model for Repeated Measures (MMRM) method, implemented via SAS® PROC MIXED (SAS/STAT Software), will be used for handling missing ADHD-RS-5 Total Scores under MAR assumption. Under MAR, the propensity for a data point to be missing is not related to the missing data, but is related to some of the observed data.

The sensitivity analysis for the primary endpoint will be performed by assuming that missing ADHD-RS-5 Total Scores are missing not at random (MNAR) meaning that the probability that an observation is missing may depend on its underlying unobserved value.

For analysis of secondary endpoints, missing values will be assumed as MAR.

For safety analyses, missing dates for AEs and non-study medication use will be imputed as described in the SAP. Missing data for all other safety endpoints will not be imputed.

7.3 Analysis Populations

- The Randomized population will include all enrolled subjects who had a baseline visit and are randomized via the IWRS.

- The Intent-to-Treat (ITT) population for efficacy will include all randomized subjects who took at least one dose of study medication and had a Baseline and ≥1 post-randomization ADHD-RS-5 assessment. Subjects will be analyzed according to the treatment to which they were randomized.
- The Per Protocol (PP) population consists of all subjects in the ITT population who complete all 9 visits with no missing ADHD-RS-5 assessments and no major protocol violations. Subjects will be analyzed according to the treatment they actually received.
- The Safety Population consists of all subjects randomized into the study who receive at least one dose of SM. Subjects will be analyzed according to the treatment they actually received.
- The PK population will include all subjects in the safety population who had at ≥1 PK sample that is not below the LLOQ.

7.4 **Demographics and Baseline Analysis**

Demographic/baseline variables including age, age group, sex, ethnicity, race, height and weight at screening, 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 treatment group for the randomized population and ITT population.

Baseline disease characteristics will include ADHD-RS-5 Total score, subscale scores, and hyperactivity/impulsivity score. These will be summarized for the ITT population.

Baseline comparability among the treatment groups will be summarized using a chi-square test for categorical variables and F-test for continuous variables. P-values will be used for descriptive purposes only.

7.5 **Subject Disposition**

A disposition of subjects will include the number and percentage of subjects in each of the following categories:

- Subjects in the ITT population
- Subjects in the PP population
- Subjects in the safety population

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and the 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
- 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 study treatment. 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 study drug compliance is defined as {(number of capsules dispensed minus number of capsules returned) /3 × (date of last dose minus date of first dose + 1)}* 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, standard deviation, median, minimum, and maximum) for each treatment.

Summaries of treatment compliance and exposure will be presented separately for the Titration Period, Maintenance Period, and combined Titration and Maintenance Periods.

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

7.8.1 Primary Efficacy Analysis

7.8.1.1 Primary analysis

The primary efficacy variable, change from baseline in ADHD-RS-5 Total Score to Week 7 (EOS), will be analyzed using MMRM, which assumes that missing data are MAR. The model will include fixed effect terms for baseline ADHD-RS-5 Total Score, age group, treatment, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. In case there is a convergence problem in the MMRM model with the unstructured variance-covariance matrix, the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound symmetry.

The adjusted mean (LS Mean) of CFB to EOS for ADHD-RS-5 Total Score for each treatment group (Placebo, SPN-812 ER 400 mg and SPN-812 ER 600 mg) will be presented, along with the corresponding standard error. Each of the treatment groups (SPN-812 ER 400 and 600 mg) will be compared with placebo. The p-values, Least Squares (LS) of treatment means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.

To maintain the Type I error rate at 5% level, a sequential testing (Westfall et al,1999) of the null hypotheses H_{01}: No treatment mean difference between SPN-812 ER 600 mg group and placebo group and H_{02}: No treatment mean difference between SPN-812 ER 400 mg group and placebo group will be performed. If H_{01} is not rejected, then H_{02} will not be tested and the conclusion will be that neither dose groups are efficacious. If H_{01} is rejected, then H_{02} will be tested. If H_{02} is rejected then it will be concluded that both SPN-812 ER 600 mg and SPN-812 ER 400 mg are superior to placebo. If H_{01} is rejected and H_{02} is not rejected then it will be concluded that only SPN-812 ER 600 mg is superior to placebo.

7.8.1.2 **Sensitivity Analyses**

The sensitivity analysis assumes that missing ADHD-RS-5 Total Scores are MNAR. Placebo-based multiple imputation will be used to fill in missing values. This approach may be considered "worst-case" sensitivity analyses as it assumes that after discontinuation, subjects from the active treatment arms would adopt the outcome model estimated from the placebo arm. The placebo-based imputation will be implemented as described in the SAP.

7.8.2 **Secondary Efficacy Analyses**

The secondary analyses will be based on the ITT population with missing values imputed using multiple imputation assuming MAR.

All secondary analyses will be analyzed using ANCOVA at Week 7 (EOS) on the change from baseline at Week 7 (EOS) with treatment and baseline as fixed effect. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, Least Squares means of the treatment groups, differences between the LS treatment means and placebo (SPN-812 ER 400 mg minus Placebo and SPN-812 ER 600 mg minus Placebo), and 95% confidence intervals for the treatment differences will be computed.

7.8.2.1 **Key secondary efficacy analyses**

The analyses of key secondary objectives will be conducted on the following sequentially ordered endpoints for testing: 1) CGI-I, 2) Conners 3 - Parent composite T-score, and 3) WFIRS-P.

To preserve the overall type I error rate at 0.05 for the key secondary endpoints, a sequential testing procedure will be used. First, only dose or doses that are significantly different from placebo for the primary endpoint will be tested for secondary endpoints. If the primary endpoint analysis does not reject H_{01} (i.e., the 600 mg is not superior to placebo) or the primary endpoint analysis rejects only H_{01}, then no multiplicity adjustment is required. Otherwise, multiplicity adjustment will be performed with the following features.

The first of the secondary endpoints (CGI-I) will be used to test each treatment group to placebo using a sequential testing of the null hypotheses H_{01}: No treatment mean difference between SPN-812 ER 600 mg group and placebo group and H_{02}: No treatment mean difference between SPN-812 ER 400 mg group and placebo group will be performed. If H_{01} is not rejected, then H_{02} will not be tested and the conclusion will be that neither dose groups are efficacious. If H_{01} is rejected, then H_{02} will be tested. If H_{02} is rejected, then it will be concluded that both SPN-812 ER 600 mg and SPN-812 ER 400 mg are superior to Placebo. If H_{02} is not rejected, then it will be concluded that only SPN-812 ER 600 mg is superior to placebo. Then, the second secondary endpoint (Conners 3) will be tested in the same manner but only using those doses that were retained from the primary and the first secondary endpoint. Finally, the third key secondary endpoint (WFIRS-P) will be tested in the same manner but only using those doses that were retained from the primary, the first key secondary endpoint, and the second key secondary endpoints.

a) CGI-I – The absolute value of CGI-I at Week 7 (EOS) will be analyzed using ANCOVA with treatment as a fixed classification variable and baseline CGI-S as a covariate. To compare the treatment groups, the difference in LS means (SPN-812 ER 400 mg minus Placebo and SPN-812 ER 600 mg minus Placebo) will be

presented along with the 95% confidence interval (CI) around the difference and p-value.

b) Conners 3 Parent - A composite T-score will be calculated by averaging over the six domains, and the change from baseline to Week 7 (EOS) in the composite T-score will be analyzed using ANCOVA model with fixed effects for treatment and baseline as a covariate. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, Least Squares means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.
c) WFIRS-P - The change from baseline in WFIRS-P to Week 7 (EOS) will be analyzed using ANCOVA model with fixed effects for treatment and baseline as a covariate. Missing Subscale scores and Total Score will be handled using multiple imputation under MAR assumption for inferential analyses. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, LS means of treatment groups, differences between the LS means and placebo, and 95% confidence intervals for the treatment differences will be computed.

7.8.2.2 **Additional secondary analyses**

Additional secondary analyses of the secondary efficacy variables will include:

a) 50% Responder rate for ADHD-RS-5 - Percent reduction will be calculated as: % reduction = 100*(ADHD-RS-5 Total Score at Week 7 (EOS) - Baseline ADHD-RS-5 Total Score)/Baseline ADHD-RS-5 Total Score. The proportion of responders will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 ER 400 mg minus Placebo, SPN-812 ER 600 mg minus Placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented.
b) SIPA - The change from baseline in SIPA total score to Week 7 (EOS) will be analyzed using ANCOVA model with fixed effects for treatment and baseline as a covariate. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, LS means of treatment groups, differences between the LS means and placebo will be presented.
c) ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscales - The primary analysis for ADHD-RS-5 Total score will be repeated for the change from baseline to EOS in ADHD-RS-5 Inattention and the change from baseline to Week 7 (EOS) in Hyperactivity/Impulsivity subscales.
d) Conners 3 - Self – The analysis for Conners 3 - Parent will be repeated for Self scores.

The key secondary analyses will be repeated for the per protocol population for supplementary analyses.

7.8.3 **Subgroup Analyses**

The primary and key secondary efficacy variable analyses may be repeated by the following subgroups to explore the heterogeneity of treatment effect:

a) Gender (male, female)
b) Age (12-14 years, 15-17 years)
c) Race (white, non-white)

7.8.4 **Exploratory Analyses**

Exploratory analyses of the key exploratory efficacy variables will include:

[redacted]

7.9 **Sample Size and Power Considerations**

Seventy-two subjects per treatment group in the ITT population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of 0.547, which was observed in the comparison of SPN-812 200 mg and placebo in the SPN 812 Phase IIb study (based on the CFB to endpoint in the ADHD-RS-IV total score) and will maintain consistency in the sample size assumption used between this clinical trial and the SPN-812 P302 study (e.g., across the SPN-812 clinical trials in the adolescent population). A total of 300 subjects (100 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.

7.10 **Interim Analysis**

No interim analysis will be performed.

7.11 **Pharmacokinetic Analyses**

Plasma concentrations for viloxazine (and 5-hydroxy-viloxazine glucuronide, If applicable) will be provided.

[redacted] Population PK data analysis will be performed using nonlinear mixed-effects modeling program (NONMEM). The structural model for viloxazine (and 5-hydroxy-viloxazine glucuronide, if applicable) may include data from studies in which sampling was more intensive than in the present study. Inclusion of covariates in the pharmacokinetic model will be accomplished through a systematic process. For each NONMEM run, covariate graphics will be examined for relationships between covariates and the post hoc etas. Covariates of interest will include (but not be limited to) age, gender, body size, etc. Population PK analyses will be reported separately from the clinical study report.

7.12 **Pharmacogenomic Analysis**

If PGx testing is performed, individual data will be presented as a listing and summaries will be tabulated using descriptive statistics.

7.13 **Safety Analysis**

Safety analysis as described below will be conducted on the Safety Population. Safety data that will be evaluated include concomitant medications, AEs, clinical laboratory results, vital signs, ECGs, and findings from the physical examinations. Suicidal ideation and suicidal behavior will be measured by C-SSRS.

The incidence rate of AEs will be calculated by treatment group for each System Organ Class (SOC) and Preferred Term (PT). The severity of the AEs and the relationship to SM will be summarized by treatment group for each SOC and PT.

AEs will be summarized using discrete summaries at the subject and event level by System Organ Class and Preferred Term, and by severity and relationship separately for each treatment group. 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 treatment group using descriptive statistics for hematology and biochemistry. For quantitative laboratory parameters, both actual values and change from Screening values will be summarized.

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

ECG results will be summarized by visit by treatment group 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 treatment groups.

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/IAF, 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. The procedure for handling missing data will be addressed in the SAP. 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.

8.3.4 **Bioanalytical Sample Handling**

Viloxazine and 5-hydroxy-viloxazine glucuronide concentrations in plasma samples will be determined using a validated chromatographic method. Viloxazine concentrations will be reported as viloxazine free base. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the clinical study report for this protocol.

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, copies of paper CRFs or 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 any 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/IAF 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 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) at approximately 25 study sites in the US.

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.

The study will be monitored by qualified personnel from Supernus. Data management and statistical analyses will be the responsibility of the CRO data management and biostatistics groups.

9.4 Subject Information and Consent/Assent

The Investigator (or designee) will inform the caregiver and 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/assent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and caregiver/subject must sign and date the ICF/IAF before the subject can participate in the study. The caregiver/subject will be given a copy of the signed and dated ICF/IAF 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/IAF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF/IAF by the IRB and use the amended ICF/IAF (including ongoing subjects).

10 REFERENCES

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SUMMARY OF CHANGES

INCLUDED IN THE PROTOCOL AMENDMENT OF:

812P304

Evaluation of SPN-812 ER 400 and 600 mg Efficacy and Safety in Adolescents with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial

Current Protocol	**Version 3.0**	**07 September 2017**
Amended Protocol	**Version 4.0**	**12 October 2018**

IND # 108,864

SUMMARY OF REVISIONS

This amendment incorporates the following protocol revisions:

- Updates and clarifications to the secondary and exploratory objectives and endpoints
- Increase in sample size
- Revisions and clarifications to the Statistical Methods sections (based on the revised Statistical Analysis Plan)
- [redacted]
- Expanded concomitant medications prohibitions to include CYP1A2 substrates
- Other minor editorial and administrative changes to improve clarity and correct errors

RATIONALE

1. The 812P304 Statistical Analysis Plan (SAP) was revised and updated based on FDA review comments (FDA Advice Letter dated 19 July 2018, Ref ID 4294123). The protocol was amended to reflect the changes in the revised SAP, including the following updates:
   - The secondary objectives and endpoints were updated and clarified to identify those considered "key" for data analysis and interpretation purposes. The exploratory objectives and endpoints were updated accordingly.
   - To maintain consistency across similar study protocols and to increase the probability of success, the same effect size from the SPN-812 ER 200 mg and placebo in the SPN-812 ER Phase IIb study was used for the power calculation for 812P304, and the sample size was increased accordingly.
   - Methods for handling missing data and for conducting the sensitivity analyses were revised (e.g., the LOCF method will no longer be used).

- Clarifications were made to the definitions of the analysis populations and to the subject disposition categories.
- The section on the primary endpoint analysis was updated to include a fixed effect of age group and to provide new details with respect to the analysis of covariance (per FDA suggestion).
- The Secondary Efficacy Analyses Sections were expanded to include descriptions of the key secondary analyses, additional secondary analyses, and subgroup analyses. The Exploratory Analyses section was also added for the newly identified exploratory efficacy variables.

2. [redacted]

3. [redacted]

4. Some information was reorganized or slightly revised to provide clarifications, describe study procedures in a greater detail, and for consistency with the SAP. Section numbers have been reformatted throughout the protocol as needed to clarify the content and to incorporate new information.

Detailed Listing of Revisions

Detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions).

#	Global Changes
1	Throughout the amended protocol, the protocol version and version date are updated to Version 4.0 and 12 October 2018, respectively.
2	The Table of Contents is updated to reflect current document pagination.
3	Section numbers have been reformatted to reflect information that was added, deleted, or relocated.
4	ADHD-RS-V and DSM-V have been replaced with ADHD-RS-5 and DSM-5, respectively, to reflect the DSM-5 nomenclature

#	812P304 Protocol Version 3.0 dated 07 September 2017	812P304 Protocol Version 4.0 dated 12 October 2018	Rationale
5	Protocol Approval Page, p.3 [redacted] Approver: [redacted]	Protocol Approval Page, p.3 Author**s**: [redacted] Reviewer**s**: [redacted] Approver**s**: [redacted]	Administrative change
6	Clinical Protocol Synopsis, Objective, p.4 Secondary • To assess the effect of SPN-812 ER as assessed by: ○ Conners 3rd edition (Conners 3) – parent, self ○ 30% Responder rate (Attention Deficit/Hyperactivity Disorder Rating Scale V [ADHD-RS-V] Total Score) ○ Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V ○ Weiss Functional Impairment Rating Scale – Parent report (WFIRS-P) ○ Stress Index for Parents of Adolescents (SIPA) ○ Clinical Global Impression – Severity of Illness and Improvement (CGI-S/I) Scale	Clinical Protocol Synopsis, Objective**s**, p.4 **Key** Secondary • To ~~assess~~ **evaluate** the effect of SPN-812 ER **compared to placebo** as assessed by: **o Clinical Global Impression – Improvement (CGI-I) scale** o Conners 3rd edition (Conners 3) – parent, ~~self~~ **composite T-score** ~~o 30% Responder rate (Attention Deficit/Hyperactivity Disorder Rating Scale V [ADHD-RS-V] Total Score)~~ ~~o Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V~~ o Weiss Functional Impairment Rating Scale – Parent report (WFIRS-P) ~~o Stress Index for Parents of Adolescents (SIPA)~~	Update to secondary objectives and endpoints

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		~~o Clinical Global Impression - Severity of Illness and Improvement (CGI-S/I) Scale~~ **Additional Secondary** • **To evaluate the effect of SPN-812 ER compared to placebo as assessed by:** **o 50% Responder rate based on the ADHD-RS-5 Total score** **o Stress Index for Parents of Adolescents (SIPA)** **o ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores** **o Conners 3 – Self, composite T-score** **Safety** • To evaluate the safety and tolerability of SPN-812 ER in adolescents with ADHD	
	• To evaluate the safety and tolerability of SPN-812 ER in adolescents with ADHD		
7	Clinical Protocol Synopsis, Objective, Exploratory, p.4 n/a	Clinical Protocol Synopsis, Objective**s**, Exploratory, p.4 **(Added)** • **To evaluate the effect of SPN-812 ER compared to placebo as assessed by:** **o Conners 3 – Parent, individual domain scores** **o Conners 3 – Self, individual domain scores** **o WFIRS-P individual domain scores** **o SIPA individual domain scores**	Update to exploratory objectives and endpoints
8	Clinical Protocol Synopsis, Objective, Exploratory, p.4 • [redacted]	Clinical Protocol Synopsis, Objective**s**, Exploratory, p.4 • [redacted]	Assessment of viloxazine metabolite

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9	Clinical Protocol Synopsis, Number of Subjects, p.4 Approximately 234 subjects (78 subjects per treatment)	Clinical Protocol Synopsis, Number of Subjects, p. 5 Approximately ~~234~~ **300** subjects (~~78~~ **100** subjects per treatment)	Increased sample size
10	Clinical Protocol Synopsis, Treatment Schedule, Study Dose Treatment Phase (Visits 2-9), p.5 Baseline, Randomization, and Dispensation of SM (Visit 2): Approximately 234 eligible subjects will be randomized.	Clinical Protocol Synopsis, Treatment Schedule, Study Dose Treatment Phase (Visits 2-9), p.5 Baseline, Randomization, and Dispensation of SM (Visit 2): Approximately ~~234~~ **300** eligible subjects will be randomized.	Increased sample size
11	Clinical Protocol Synopsis, Endpoints, p.5 Key Secondary Endpoints: a) Conners 3, b) 30% Responder Rate, and c) Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V Additional Secondary Endpoints will include: a) WFIRS-P, b) SIPA, and c) CGI-S/I	Clinical Protocol Synopsis, Endpoints, p.6 Key Secondary **Efficacy** Endpoints: ~~CFB to EOS in scores for~~ a) **CGI-I, b)** Conners 3 – Parent, **composite T-score** ~~self, teacher (optional), b) 30% Responder Rate (ADHD-RS-V total score)~~, and c) **WFIRS-P average score** ~~Inattentive and Hyperactive subscales of ADHD-RS-V~~ Additional Secondary **Efficacy** Endpoints ~~will include~~: a) ~~WFIRS-P,~~ **Proportion of responders with 50% improvement in ADHD-RS-5 Total score,** b) SIPA, ~~and~~ c) ~~CGI-S/I~~ **ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores, and d) Conners 3 – Self composite T-score**	Update to secondary objectives and endpoints
12	Clinical Protocol Synopsis, Endpoints, p.5 Exploratory Endpoints: [redacted]	Clinical Protocol Synopsis, Endpoints, p.6 Exploratory Endpoints: [redacted]	Update to exploratory objectives and endpoints
13	Clinical Protocol Synopsis, Sample Size, p.5 Fifty-six per treatment group in the Intent-To-Treat (ITT) population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of 0.623, observed in the comparison of SPN-812 ER 400 mg and placebo in the SPN-812 ER	Clinical Protocol Synopsis, Sample Size, p. 6 ~~Fifty-six~~ **Seventy-two subjects** per treatment group in the Intent-To-Treat (ITT) population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of ~~0.623~~ **0.547**, observed in the comparison of SPN-812 ER ~~400~~ **200** mg and	Increased sample size

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	Phase IIb study (based on the CFB to endpoint in the ADHD-RS-IV total score). A total of 234 subjects (78 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.	placebo in the SPN-812 ~~ER~~ Phase IIb study (based on the CFB to endpoint in the ADHD-RS-IV total score). **To keep consistency with the sample size assumption used in the SPN-812 P302 study (adolescent population),** a total of ~~234~~ **300** subjects (~~78~~ **100** subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.	
14	Clinical Protocol Synopsis, Analysis Populations, p.6 • The ITT population for efficacy will include all randomized subjects who took at least one dose of study medication, and had a Baseline and at least one post-Baseline assessment of ADHD-RS-V. • The Per Protocol (PP) population consists of all subjects in the ITT population with no missing visits or ADHD-RS-V assessments and no major protocol violations. • The Safety Population consists of all subjects who receive at least one dose of SM. • The PK population will include all subjects in the safety population with ≥1 non-below-the limit-of-quantitation PK sample drawn.	Clinical Protocol Synopsis, Analysis Populations, p.6 • **The Randomized population will include all enrolled subjects who had a baseline visit and are randomized via the IWRS.** • The ITT population for efficacy will include all randomized subjects who took at least one dose of study medication, and had a Baseline and at least one post-~~Baseline~~ **randomization ADHD-RS-5** assessment ~~of ADHD-RS-V~~. **Subjects will be analyzed according to the treatment to which they were randomized.** • The Per Protocol (PP) population consists of all subjects in the ITT population **who completed all 9 visits** with no missing ~~visits or~~ ADHD-RS-~~V~~**5** assessments and no major protocol violations. **Subjects will be analyzed according to the treatment they actually received.** • The Safety Population consists of all subjects **randomized into the study** who receive at least one dose of SM. **Subjects will be analyzed according to the treatment they actually received.** • The PK population will include all subjects in the safety population with ≥1 ~~non-below the limit of quantitation~~ PK sample ~~drawn~~ **that is not below the Lower Limit of Quantitation (LLOQ)**.	Updated for consistency with revised SAP
15	Clinical Protocol Synopsis, Handling of Missing Data, p.6 For primary efficacy analysis, missing data will be assumed as missing at random	Clinical Protocol Synopsis, Handling of Missing Data, p.6 ~~For~~ **With respect to the** primary ~~efficacy~~ analysis, missing ~~data~~ **ADHD-RS-5 Total**	LOCF method no longer used

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	(MAR) and will be handled using a Mixed Models Repeated Measures (MMRM) technique according to the MMRM paradigm. For secondary and first sensitivity analyses, missing data will be imputed using the last observation carried forward (LOCF) method.	**scores** will be assumed ~~as~~ **to be** ~~M~~**m**issing at ~~R~~**r**andom (MAR) and will be handled using **a** Mixed Model~~s~~ **for** Repeated Measures (MMRM) ~~technique according to the MMRM paradigm~~ **method in SAS**. ~~For secondary and first sensitivity analyses, missing data will be imputed using the last observation carried forward (LOCF) method.~~ **The sensitivity analysis for the primary endpoint will be performed by assuming that missing ADHD-RS-5 Total Scores are missing not at random (MNAR). For analysis of secondary endpoints, missing values will be assumed as MAR.**	
16	Clinical Protocol Synopsis, Statistical Methods, p.6 In general, continuous variables will be summarized with standard descriptive statistics including number of subjects (n), means, standard deviations, medians, minimum, and maximum. Categorical variables will be summarized with frequencies and percentages.	Clinical Protocol Synopsis, Statistical Methods, p.6 ~~In general, continuous variables will be summarized with standard descriptive statistics including number of subjects (n), means, standard deviations, medians, minimum, and maximum. Categorical variables will be summarized with frequencies and percentages.~~ **All tabulations of analysis results will include summaries for the following three treatments: SPN-812 ER 600 mg, SPN-812 ER 400 mg, and placebo.** **Where appropriate, variables will be summarized descriptively (frequency count and percent for categorical variables, and number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables).** **Categorical variables will be analyzed using categorical response methods such as Pearson's Chi-square test. If expected frequencies are less than 5 in a given cell, then exact testing techniques will be used.** **Descriptive statistics will be presented for demographics, data from the clinical laboratory tests, vital signs, weight, ECGs, and C-SSRS.**	Updated for consistency with revised SAP

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17	Clinical Protocol Synopsis, Statistical Methods, Efficacy Analyses, p.6 The primary analysis, based on the ITT population, will be performed using a longitudinal MMRM and a restricted maximum likelihood (REML) approach. An unstructured (co)variance structure will be used to model the within-subject errors. Primary: Each of the active treatment groups (SPN-812 ER 400 and 600 mg) will be compared with placebo. The p-values, Least Squares (LS) of treatment means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.	Clinical Protocol Synopsis, Statistical Methods, Efficacy Analyses, p.7 ~~The primary analysis, based on the ITT population, will be performed using a longitudinal MMRM and a restricted maximum likelihood (REML) approach. An unstructured (co)variance structure will be used to model the within-subject errors.~~ Primary: **The primary efficacy variable, change from baseline in ADHD-RS-5 Total Score to Week 7 (EOS), will be analyzed using a Mixed Model for Repeated Measures (MMRM), which assumes that missing data are missing at random (MAR). The model will include fixed effect terms for baseline ADHD-RS-5 Total Score, age group, treatment, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. In case there is a convergence problem in the MMRM model with the unstructured variance covariance matrix, the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound symmetry.** **The adjusted mean (LS Mean) of CFB to EOS for ADHD-RS-5 Total Score for each treatment group (Placebo, SPN-812 ER 400 mg and SPN-812 ER 600 mg) will be presented, along with the corresponding standard error.** Each of the active treatment groups (SPN-812 ER 400 and 600 mg) will be compared with placebo. The p-values, Least Squares (LS) of treatment means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed. **Sensitivity analysis: The sensitivity analysis assumes that missing ADHD-RS-5 Total**	Updated for consistency with revised SAP, and LOCF no longer used

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	Secondary: The CFB to EOS for continuous key secondary and additional endpoints will be analyzed using ANCOVA or ANOVA as appropriate based on the ITT population with LOCF. The mean of each treatment group will be compared with the mean of the placebo group. For responder analyses, the proportion each active treatment group will be compared with the proportion of the placebo group	**Scores are missing not at random (MNAR). Placebo-based multiple imputation will be used to fill in missing values.** Secondary: ~~The CFB to EOS for continuous key secondary and additional endpoints will be analyzed using ANCOVA or ANOVA as appropriate based on the ITT population with LOCF. The mean of each treatment group will be compared with the mean of the placebo group. For responder analyses, the proportion each active treatment group will be compared with the proportion of the placebo group~~ **The secondary analyses will be based on the ITT population with missing values imputed using multiple imputation assuming MAR. All secondary analyses will be analyzed using ANCOVA at Week 7 (EOS) on the change from baseline at Week 7 (EOS) with treatment and baseline as fixed effect.** **Analyses of key secondary endpoints will be repeated for the PP population.**	
18	Clinical Protocol Synopsis, Statistical Methods, Safety Analyses, p.6 Descriptive statistics will be presented for demographics, data from the clinical laboratory tests, vital signs, weight, ECGs, and physical examinations.	Clinical Protocol Synopsis, Statistical Methods, Safety Analyses, p.7 (Deleted) ~~Descriptive statistics will be presented for demographics, data from the clinical laboratory tests, vital signs, weight, ECGs, and physical examinations.~~	Statement moved for clarification purposes
19	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Sampling, p.6 A maximum of five blood samples will be collected at one or more of Visits 3-9.	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Sampling, p.8 **For PK analysis, a**~~A~~ maximum of five blood samples will be collected at one or more of Visits 3-9. **For PGx analysis, a single blood sample will be collected at screening.**	Clarification
20	Clinical Protocol Synopsis Pharmacokinetic and Pharmacogenomic Methods, Bioanalytical Analysis, p.6 Viloxazine concentrations in plasma will be determined for all treatments using a validated achiral chromatographic method. Concentrations will be reported as viloxazine free base.	Clinical Protocol Synopsis Pharmacokinetic and Pharmacogenomic Methods, Bioanalytical Analysis, p.8 Viloxazine concentrations **and 5-hydroxy-viloxazine glucuronide concentrations** in plasma will be determined for all treatments using a validated achiral chromatographic method. **Viloxazine** concentrations will be reported as viloxazine free base.	Assessment of viloxazine metabolite

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21	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacokinetic Analysis, p.6 n/a	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacokinetic Analysis, p.8 [redacted]	Assessment of viloxazine metabolite
22	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacokinetic Analysis, p.6 The analyses' report will be a stand-alone document.	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacokinetic Analysis, p.8 ~~The analyses' report will be a stand-alone document.~~ **Population PK analyses will be reported separately from the clinical study report.**	Clarification
23	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacogenomics Analysis, p.7 The DNA will be extracted and tested for any genetic variations associated with CYP2D6 enzyme.	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacogenomics Analysis, p.8 ~~The~~ **If a given subject's PK data warrant evaluation of PGx,** [redacted]	Clarification
24	Clinical Protocol Synopsis, Parmacokinetic and Pharmacogenomic Methods, Pharmacogenomics Analysis, p.7 The PGx report may be a stand-alone document.	Clinical Protocol Synopsis, Pharmacokinetic and Pharmacogenomic Methods, Pharmacogenomics Analysis, p.8 ~~The PGx report may be a stand-alone document.~~ **If PGx testing is performed, individual data will be presented as a listing and summaries will be tabulated using descriptive statistics.**	Clarification
25	List of Abbreviations, p.12 ADHD-RS-IV/V ADHD Rating Scale- IV/V ANOVA Analysis of Variance DSM-V Diagnostic and Statistical Manual of Mental Disorders-V ET Early Termination LOCF Last Observation Carried Forward MMRM Mixed Models Repeated Measures	List of Abbreviations, p.13 ADHD-RS-IV/~~V~~**5** ADHD Rating Scale- IV/~~V~~5 ~~ANOVA Analysis of Variance~~ DSM-~~V~~**5** Diagnostic and Statistical Manual of Mental Disorders-~~V~~**5** ~~ET Early Termination~~ **LLOQ Lower Limit of Quantitation** ~~LOCF Last Observation Carried Forward~~ MMRM Mixed Models~~s~~ **for** Repeated Measures **MNAR Missing Not At Random**	Editorial change

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26	1.2 Clinical Information, Phase 2 Studies, p.15 Information and data from clinical studies are available in detail in the SPN-812 ER Investigator's Brochure, version 5.0.	1.2 Clinical Information, Phase 2 Studies, p.16 Information and data from clinical studies are available in detail in the SPN-812 ER Investigator's Brochure, version ~~5.0~~ **6.0**.	Correction
27	2.2 Secondary Objectives, p.16 • To assess the effect of SPN-812 ER compared to placebo as assessed by: ○ Conners 3rd edition – parent, self ○ 30% Responder rate (ADHD-RS-V) ○ Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V ○ Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) ○ Stress Index for Parents of Adolescents (SIPA) ○ Clinical Global Impression - Severity of Illness and Improvement (CGI-S/I) Scale • To evaluate the safety and tolerability of SPN-812 ER in 12-17 year-olds.	2.2 Secondary Objectives, p.18 **Key Secondary** • To ~~assess~~ **evaluate** the effect of SPN-812 ER compared to placebo as assessed by: ○ **Clinical Global Impression - Improvement (CGI-I) scale** ○ Conners 3rd edition **(Conners 3)** – parent, ~~self~~ **composite T-score** ~~○ 30% Responder rate (ADHD-RS-V)~~ ~~○ Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V~~ ○ Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) ~~○ Stress Index for Parents of Adolescents (SIPA)~~ ~~○ Clinical Global Impression – Severity of illness and Improvement (CGI-S/I) Scale~~ **(Added) Additional Secondary** • **To evaluate the effect of SPN-812 ER compared to placebo as assessed by:** ○ **50% Responder rate based on the ADHD-RS-5 Total score** ○ **Stress Index for Parents of Adolescents (SIPA)** ○ **ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores** ○ **Conners 3 – Self, composite T-score** **Safety** • To evaluate the safety and tolerability of SPN-812 ER in ~~12-17 year-olds~~ **adolescents with ADHD**.	Update to secondary objectives and endpoints
28	2.3 Exploratory, p.17 n/a	2.3 Exploratory **Objectives**, p.18 **(Added)**	Update to exploratory objectives and endpoints

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		• **To evaluate the effect of SPN-812 ER compared to placebo as assessed by:** ○ [redacted]	
29	2.3 Exploratory, p.16 [redacted]	2.3 Exploratory **Objectives**, p.18 • To gain information about ~~viloxazine~~**:** ○ [redacted]	Assessment of viloxazine metabolite
30	3.1 Overall Study Design and Plan, p.17 This is a multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel-group study, to assess the efficacy and safety of SPN-812 ER as monotherapy for the treatment of adolescents (12-17 years old) with ADHD. Approximately 234 subjects will be randomized in a 1:1:1 ratio of placebo or one of the two active treatment arms (SPN-812 ER 400 or 600 mg). Screening (Visit 1): After administering the informed consent form (ICF; and informed assent form [IAF], if applicable), subjects will undergo initial screening evaluation including medical and psychiatric history, ECG, vital signs, physical examination, routine laboratory assessment, PGx testing, and urine drug screen.	3.1 Overall Study Design and Plan, p.18 This is a multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel-group study, to ~~assess~~ **evaluate** the efficacy and safety of SPN-812 ER as monotherapy for the treatment of adolescents (12-17 years old) with ADHD. Approximately ~~234~~ **300** subjects will be randomized in a 1:1:1 ratio of placebo or one of the two active treatment arms (SPN-812 ER 400 or 600 mg). Screening (Visit 1): After administering the informed consent form (ICF; and informed assent form [IAF], if applicable), subjects will undergo initial screening evaluation including medical and psychiatric history, ECG, vital signs, physical examination, routine laboratory assessment, PGx ~~testing~~ **sample collection**, and urine drug screen.	Editorial change *and* Increased sample size

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31	3.1 Overall Study Design and Plan, p.18 An optional PK substudy during Visits 3-9, inclusive will be conducted to assess viloxazine PK characteristics in this pediatric population.	3.1 Overall Study Design and Plan, p.19 An optional PK substudy during Visits 3-9, inclusive**,** will be conducted to assess ~~viloxazine~~ **the** PK characteristics **of viloxazine (and its metabolite 5-hydroxy-viloxazine glucuronide, if applicable)** in this pediatric population.	Assessment of viloxazine metabolite
32	3.3.1 Number of Subjects, p.18 Approximately 234 subjects will be randomized (78 subjects per treatment) in this clinical study.	3.3.1 Number of Subjects, p.20 Approximately ~~234~~ **300** subjects will be randomized (~~78~~ **100** subjects per treatment) in this clinical study.	Increased sample size
33	3.3.3 Exclusion Criteria, p.19 1. Current diagnosis of major psychological disorders.	3.3.3 Exclusion Criteria, p.21 1. Current diagnosis of major ~~psychological~~ **psychiatric** disorders.	Clarification
34	4.6 Concomitant Medications, p.22 n/a	4.6 Concomitant Medications, p.24 **(Added) Specific concomitant medication prohibitions include known CYP1A2 substrates (e.g., theophylline, melatonin, olanzapine, duloxetine).**	New restriction on concomitant medications metabolized by CYP1A2
35	5.1.1 Visit 1 Screening (Day -28 to -1), p.24 8. Collect blood samples for hematology, chemistry and pharmacogenomic testing	5.1.1 Visit 1 Screening (Day -28 to -1), p.26 8. Collect blood samples for hematology, chemistry and ~~pharmacogenomic testing~~ **PGx**	Clarification
36	5.1.5 Pharmacogenomic Sample Collection, p.25 The DNA will be extracted and tested for any genetic variations associated with CYP2D6 enzyme.	5.1.5 Pharmacogenomic Sample Collection, p.27 ~~The~~ **If a given subject's PK data warrant evaluation of PGx,** [redacted]	Clarification
37	5.1.5 Pharmacogenomic Sample Collection, p.25 n/a	5.1.5 Pharmacogenomic Sample Collection, p.27 **(Added) The DNA analysis will not be used for individual genetic characterization and the subject's identity will be kept confidential**.	Clarification
38	6.1 Primary Efficacy Variable, p.26 The scale consists of 18 items that directly correspond to the 18 DSM-V symptoms and are further subdivided into two	6.1 Primary Efficacy Variable, p.28 **6.1.1 ADHD-RS-5** The scale consists of 18 items that directly correspond to the 18 DSM-~~V~~**5** symptoms and are further subdivided into two	Editorial change

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	subscales: Hyperactivity/Impulsivity and Inattentiveness (DuPaul, 2016).	subscales: Hyperactivity/Impulsivity and ~~Inattentiveness~~ **Inattention** (DuPaul, 2016).	
39	6.2 Key Secondary Efficacy Variables: , p.26 a) Conners 3 b) 30% Responder Rate c) Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V	6.2 ~~Key~~ Secondary Efficacy Variables~~:~~, p.28 **The key secondary efficacy variables include:** a) ~~Conners 3~~ **CGI-I** b) ~~30% Responder Rate (ADHD-RS-V Total Score)~~ **Conners 3 – Parent, composite T-score** c) ~~Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V~~ **WFIRS-P average score**	Update to secondary objectives and endpoints
40	6.3 Additional Secondary Efficacy Variables:, p. 26 d) WFIRS-P e) SIPA f) CGI-S/I	~~6.3~~ Additional **s**econdary ~~Efficacy~~ **v**ariables ~~will~~ **include:**, p.28 **a**) ~~WFIRS-P~~ **Proportion of responders with 50% improvement in the ADHD-RS-5 Total score (50% Responder rate)** **b**) SIPA **c**) ~~CGI-S/I~~ **ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores** **d) Conners 3 – Self, composite T-score**	Update to secondary objectives and endpoints
41	Version 4.0, **(Added) 6.2.1 Clinical Global Impression - Improvement**, p.29 **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 a SM (Guy 1976). The Clinical Global Impression – Severity of Illness (CGI-S) is a single item clinician rating of clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The Clinical Global Impression – Improvement Scale (CGI-I) is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. Both CGI-S and CGI-I are rated on a 7-point scale of 1 to 7 with 7 being "extremely ill" or "very much worse", respectively. Successful therapy is indicated by a lower overall score in subsequent testing.** • **CGI-S will be evaluated by the Investigator at Screening and Baseline on a 7-point scale with 1=Normal, 2=Borderline ill, 3=Mildly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, and 7=Extremely ill.** • **CGI-I, relative to the condition at baseline, will be evaluated by the Investigator at each post-baseline visit 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.**		Editorial change (section moved with no change to content)

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42	6.4.3 WFIRS-P, p.27 The WFIRS instrument evaluates ADHD-related functional impairment (Gajria, 2014 Thompson, 2017). The parent-based version completed by the parent/guardian of a child is used in this study and comprises 50 items grouped into six domains: Family, School (learning and behavior), Life Skills, Child's Self-Concept, Social Activities, and Risky Activities.	**6.2.3** WFIRS-P, p.29 The **Weiss Functional Impairment Rating Scale (**WFIRS**)** instrument evaluates ADHD-related functional impairment (Gajria, ~~2014~~ **2015**; Thompson, 2017). The parent-based version **(WFIRS-P)** completed by the parent/guardian of a child is used in this study and comprises 50 items grouped into six domains: Family, School (learning and behavior), Life Skills, Child's Self-Concept, Social Activities, and Risky Activities.	Editorial change
43	Version 3.0, (Deleted) 6.4.5 CGI-S/I, p.27 ~~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 a SM (Guy 1976). The Clinical Global Impression – Severity of Illness (CGI-S) is a single item clinician rating of clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The Clinical Global Impression – Improvement Scale (CGI-I) is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. Both CGI-S and CGI-I are rated on a 7-point scale of 1 to 7 with 7 being "extremely ill" or "very much worse", respectively. Successful therapy is indicated by a lower overall score in subsequent testing.~~ • ~~CGI-S will be evaluated by the Investigator at Screening and Baseline on a 7-point scale with 1=Normal, 2=Borderline ill, 3=Mildly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, and 7=Extremely ill.~~ • ~~CGI-I, relative to the condition at baseline, will be evaluated by the Investigator at each post-baseline visit 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.~~		Editorial change (section moved with no change to content)
44	6.5 Safety Variables and Assessments, p.28 Safety assessments will consist of monitoring of and recording of all concomitant medications and AEs, clinical laboratory tests, measurement of vital signs and 12-lead ECGs, suicidality monitoring, and the performance of	**6.3** Safety Variables ~~and Assessments~~, p.30 **(Added) The safety variables for the study are AEs, clinical laboratory test results, vital signs, ECG results, and treatment-emergent suicidal ideation.** Safety assessments **include** ~~will consist of~~ monitoring, **evaluation**, ~~of~~ and recording of all concomitant medications**,** and **the evaluation of** AEs, clinical laboratory test **result**s, ~~measurement of~~ vital signs and 12-lead ECGs, ~~suicidality monitoring~~ **C-SSRS**, and the performance of physical	Clarification

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	physical examinations as detailed in the Schedule of Events and Assessments.	examinations as detailed in the Schedule of Events and Assessments.	
45	Version 4.0 **(Added) 6.7 Exploratory Variables**, p.35 **Exploratory variables include:** [redacted]		Update to secondary objectives and endpoints *and* Assessment of viloxazine metabolite
46	7.1 General Considerations, p.34 All data analyses will be performed by the designated CRO after the study is completed and the database is released. Statistical programming and analyses will be performed All data will be analyzed using SAS (SAS Institute, Inc., Version 9.2 or later). In general, continuous variables will be summarized with standard descriptive statistics including number of subjects (n), means, standard deviations, medians, minimum, and maximum. Categorical variables will be summarized with frequencies and percentages.	7.1 General Considerations, p.36 ~~All data analyses will be performed by the designated CRO after the study is completed and the database is released. Statistical programming and analyses will be performed. All data will be analyzed using SAS (SAS Institute, Inc., Version 9.2 or later).~~ **All statistical analysis will be performed using SAS version 9.2 or higher by [redacted], which is the designated CRO. [redacted] will be responsible for developing a unique program for each TLF to create a TLF report and deliver to Supernus at the completion of the study.** ~~In general, continuous variables will be summarized with standard descriptive statistics including number of subjects (n), means, standard deviations, medians, minimum, and maximum. Categorical variables will be summarized with frequencies and percentages.~~ **All tabulations of analysis results will include summaries for the following three treatments: SPN-812 ER 600 mg, SPN-812 ER 400 mg, and placebo.** **Where appropriate, variables will be summarized descriptively (frequency count and percent for categorical variables, and number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables).**	Updated for consistency with revised SAP

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	If expected frequencies are too small for asymptotic assumptions, exact testing techniques will be used.	If expected frequencies are ~~too small for asymptotic assumptions,~~ **less than 5 in a given cell, then** exact testing techniques will be used.	
47	7.1 General Considerations, p.34 When inferential analyses are conducted for continuous variables, they will primarily be based on parametric general linear models such as analysis of covariance or analysis of variance. For variables that do not meet the normality assumptions, nonparametric methods, such as the Wilcoxon rank-sum method, will be used. Treatment effects for all efficacy variables will be evaluated based on a two- sided significance level of 0.05 and the interaction effects at 0.10. Subject characteristics are assumed to be comparable at the start of the study, as randomization is designed to ensure balance between the groups on the baseline characteristics, so no formal statistical group comparisons will be conducted on the subject characteristics.	7.1 General Considerations, p.36 (Deleted) ~~When inferential analyses are conducted for continuous variables, they will primarily be based on parametric general linear models such as analysis of covariance or analysis of variance.~~ (Deleted) ~~For variables that do not meet the normality assumptions, nonparametric methods, such as the Wilcoxon rank-sum method, will be used.~~ (Deleted) ~~Treatment effects for all efficacy variables will be evaluated based on a two- sided significance level of 0.05 and the interaction effects at 0.10.~~ (Deleted) ~~Subject characteristics are assumed to be comparable at the start of the study, as randomization is designed to ensure balance between the groups on the baseline characteristics, so no formal statistical group comparisons will be conducted on the subject characteristics.~~	Updated for consistency with revised SAP
48	7.2 Handling of Missing Data, p.34 For primary efficacy analysis, missing data will be assumed as Missing at Random (MAR) and will be handled using Mixed Models Repeated Measures (MMRM) technique according to the MMRM paradigm. Under MAR, the propensity for a data point to be missing is not related to the missing data, but is related to some of the observed data. For secondary and first sensitivity analyses, the last observation carried forward (LOCF) method of imputation will be used. The underlying assumption for using the LOCF method is based on the fact that 35% of subjects early terminated (ET) before completion of the Phase II 202 study as lost-to-follow-up. It is assumed that majority of subject dropout in the Phase III trial will follow the same pattern and hence, the assumption of Missing Completely at Random (MCAR)	7.2 Handling of Missing Data, p.36 ~~For~~ **With respect to the** primary ~~efficacy~~ analysis, missing ~~data~~ **ADHD-RS-5 Total Scores** will be assumed ~~as~~ **to be ~~M~~m**issing at ~~R~~**r**andom (MAR)**, that is, given the observed data, the reason for the missing data does not depend on the unseen data.** ~~and will be handled using~~ **The** Mixed Model~~s~~ **for** Repeated Measures (MMRM) ~~technique according to the MMRM paradigm~~ **method, implemented via SAS® PROC MIXED (SAS/STAT Software), will be used for handling missing ADHD-RS-5 Total Scores under MAR assumption**. Under MAR, the propensity for a data point to be missing is not related to the missing data, but is related to some of the observed data. ~~For secondary and first sensitivity analyses, the last observation carried forward (LOCF) method of imputation will be used. The underlying assumption for~~	LOCF method no longer used

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	can be applied and the LOCF imputation for missing data can be used.	~~using the LOCF method is based on the fact that 35% of subjects early terminated (ET) before completion of the Phase II 202 study as lost-to-follow-up. It is assumed that majority of subject dropout in the Phase III trial will follow the same pattern and hence, the assumption of Missing Completely at Random (MCAR) can be applied and the LOCF imputation for missing data can be used.~~ **(Added)** **The sensitivity analysis for the primary endpoint will be performed by assuming that missing ADHD-RS-5 Total Scores are missing not at random (MNAR) meaning that the probability that an observation is missing may depend on its underlying unobserved value.** **For analysis of secondary endpoints, missing values will be assumed as MAR.** **For safety analyses, missing dates for AEs and non-study medication use will be imputed as described in the SAP. Missing data for all other safety endpoints will not be imputed.**	
49	7.3 Analysis Populations, p.35 • The Intent-to-Treat (ITT) population for efficacy will include all randomized subjects who took at least one dose of study medication and had a Baseline and ≥1 post-Baseline ADHD-RS-V assessment. Subjects will be analyzed according to the treatment to which they were randomized • The Per Protocol (PP) population consists of all subjects in the ITT population with missing visits or ADHD-RS-V assessments and no major protocol violations. Subjects will be	7.3 Analysis Populations, p.36 • **The Randomized population will include all enrolled subjects who had a baseline visit and are randomized via the IWRS.** • The Intent-to-Treat (ITT) population for efficacy will include all randomized subjects who took at least one dose of study medication and had a Baseline and ≥1 post-~~Baseline~~ **randomization** ADHD-RS-~~V~~**5** assessment. Subjects will be analyzed according to the treatment to which they were randomized. • The Per Protocol (PP) population consists of all subjects in the ITT population **who complete all 9 visits** with no missing ~~visits or~~ ADHD-RS-~~V~~**5** assessments and no major protocol violations. Subjects will be	Updated for consistency with revised SAP

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	analyzed according to the treatment they actually received. • The Safety Population consists of all subjects who receive at least one dose of SM. • PK population will include all subjects in the safety population who had at ≤1 non-below-the-limit-of-quantitation PK sample drawn.	analyzed according to the treatment they actually received. • The Safety Population consists of all subjects **randomized into the study** who receive at least one dose of SM. **Subjects will be analyzed according to the treatment they actually received.** • **The** PK population will include all subjects in the safety population who had ~~≤~~ **≥** 1 ~~non-below-the-limit-of-quantitation~~ PK sample ~~drawn~~ **that is not below the LLOQ**.	
50	7.4 Demographics and Baseline Analysis, p.35 Demographic/baseline variables include age, sex, ethnicity, race, height and weight at screening, and medical history will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables.	7.4 Demographics and Baseline Analysis, p.37 Demographic/baseline variables includ~~e~~**ing** age, **age group,** sex, ethnicity, race, height and weight at screening, and ~~medical history~~ **BMI** will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables.	Updated for consistency with revised SAP
51	7.4 Demographics and Baseline Analysis, p.35 n/a	7.4 Demographics and Baseline Analysis, p.37 **(Added)** **Baseline disease characteristics will include ADHD-RS-5 Total score, subscale scores, and hyperactivity/impulsivity score. These will be summarized for the ITT population.** **Baseline comparability among the treatment groups will be summarized using a chi-square test for categorical variables and F-test for continuous variables. P-values will be used for descriptive purposes only.**	Updated for consistency with revised SAP
52	7.5 Subject Disposition, p.35 • Subjects in the randomized population • Subjects in the ITT population • Subjects treated (safety population)	7.5 Subject Disposition, p.37 ~~• Subjects in the randomized population~~ • Subjects in the ITT population **• Subjects in the PP population** • Subjects ~~treated (~~**in the** safety population~~)~~ Within each of the previous categories, the number and percentage of subjects who	Updated for consistency with revised SAP

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	Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and the primary reason for discontinuation will be summarized. The reason for discontinuation may include any of the following:	completed and discontinued from the study and the primary reason for **early** discontinuation will be summarized. The reason for **early** discontinuation may include any of the following:	
53	7.6 Study Medication Exposure and Compliance, p.35 Duration of Treatment exposure will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). Percent of study drug compliance is defined as {(number of capsules dispensed minus number of capsules returned) / (date of last dose minus date of first dose + 1)}* 100%.	7.6 Study Medication Exposure and Compliance, p.37 Duration of ~~T~~**t**reatment exposure **will be summarized by duration category and** will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). Percent of study drug compliance is defined as {(number of capsules dispensed minus number of capsules returned) /**3 ×** (date of last dose minus date of first dose + 1)}* 100%.	Updated for consistency with revised SAP
54	7.8.1.1 Primary analyses, p.35 The primary endpoint is change from baseline in ADHD-RS-V Total Score and the primary analysis, based on the ITT population, will be performed using a longitudinal MMRM and a restricted maximum likelihood (REML) approach. The model will include the fixed, categorical effects of treatment, investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-subject errors. If this analysis fails to converge, the Compound Symmetry and Toeplitz structures will be tested. The covariance structure converging to the best fit as determined by Akaike's information criterion will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.	7.8.1.1 Primary analysis, p.38 (Deleted) ~~The primary endpoint is change from baseline in ADHD-RS-V Total Score and the primary analysis, based on the ITT population, will be performed using a longitudinal MMRM and a restricted maximum likelihood (REML) approach. The model will include the fixed, categorical effects of treatment, investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction.~~ (Deleted) ~~An unstructured (co)variance structure will be used to model the within-subject errors. If this analysis fails to converge, the Compound Symmetry and Toeplitz structures will be tested. The covariance structure converging to the best fit as determined by Akaike's information criterion will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.~~ **(Added) The primary efficacy variable, change from baseline in ADHD-RS-5 Total**	Updated for consistency with revised SAP

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		Score to Week 7 (EOS), will be analyzed using MMRM, which assumes that missing data are MAR. The model will include fixed effect terms for baseline ADHD-RS-5 Total Score, age group, treatment, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. In case there is a convergence problem in the MMRM model with the unstructured variance-covariance matrix, the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound symmetry.	
	Each of the treatment groups (SPN-812 ER 200 and 400 mg) will be compared with placebo. The p-values, Least Squares (LS) of treatment means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.	**The adjusted mean (LS Mean) of CFB to EOS for ADHD-RS-5 Total Score for each treatment group (Placebo, SPN-812 ER 400 mg and SPN-812 ER 600 mg) will be presented, along with the corresponding standard error.** Each of the treatment groups (SPN-812 ER ~~200~~ **400** mg and ~~400~~ **600** mg) will be compared with placebo. The p-values, Least Squares (LS) of treatment means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.	
	To maintain the Type I error rate at 5% level, a sequential testing of hypotheses will be performed.	To maintain the Type I error rate at 5% level, a sequential testing ~~of~~ **(Westfall et al, 1999) of the null** hypotheses **H_{01}: No treatment mean difference between SPN-812 ER 600 mg group and placebo group and H_{02}: No treatment mean difference between SPN-812 ER 400 mg group and placebo group** will be performed. **If H_{01} is not rejected, then H_{02} will not be tested and the conclusion will be that neither dose groups are efficacious. If H_{01} is rejected, then H_{02} will be tested. If H_{02} is rejected then it will be concluded that both SPN-812 ER 600 mg and SPN-812 ER**	

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	Let μ_1, μ_2, and μ_3 be the LS Means of SPN-812 ER 600 mg, SPN-812 ER 400 mg and Placebo, respectively, for CFB to EOS in the ADHD-RS-V Total Score. The first step will be to test H_0:$\mu_1 = \mu_3$ vs. H_1: $\mu_1 < \mu_3$, a comparison of the LS mean of SPN-812 ER 600 mg dose group and with the LS mean of Placebo group, at the 5% significance level. If H_0 is not rejected, then formal testing stops and the conclusion will be that there is insufficient evidence to conclude that both the LS mean of SPN-812 ER 600 mg dose and the LS mean of SPN-812 ER 400 mg are less than the LS mean of the Placebo group. In other words, neither dose group is efficacious. If H_0 is rejected, then formal testing will be performed at step two with a test of H_0: $\mu_2 = \mu_3$ vs. H_1: $\mu_2 < \mu_3$, a comparison of the LS mean of SPN-812 ER 400 mg and with the LS mean of Placebo group at the 5% significance level. If the null hypothesis is not rejected, then formal testing stops and the conclusion is that there is only sufficient evidence to conclude that the LS mean of SPN-812 ER 600 mg is less than the LS mean of the Placebo group. If H_0 is rejected, then it will be concluded that both the LS means of SPN-812 ER 600 mg and SPN-812 ER 400 mg doses are less than the LS mean of the placebo group. In other words, the superiority of both arms to placebo will be claimed.	**400 mg are superior to placebo. If H_{01} is rejected and H_{02} is not rejected then it will be concluded that only SPN-812 ER 600 mg is superior to placebo.** ~~Let μ1, μ2, and μ3 be the LS Means of SPN-812 ER 4600 mg SPN-812 ER 400 mg and Placebo, respectively, for CFB to EOS in the ADHD-RS-V Total Score.~~ ~~The first step will be to test H_0:μ1 =μ3 vs. H_1: μ1 < μ3, a comparison of the LS mean of SPN-812 ER 600 mg dose group and with the LS mean of Placebo group, at the 5% significance level. If H_0 is not rejected, then formal testing stops and the conclusion will be that there is insufficient evidence to conclude that both the LS mean of SPN-812 ER 600 mg dose and the LS mean of SPN-812 ER 400 mg are less than the LS mean of the Placebo group. In other words, neither dose group is efficacious.~~ ~~If H_0 is rejected, then formal testing will be performed at step two with a test of H_0: μ2 = μ3 vs. H_1: μ2 < μ3, a comparison of the LS mean of SPN-812 ER 400 mg and with the LS mean of Placebo group at the 5% significance level. If the null hypothesis is not rejected, then formal testing stops and the conclusion is that there is only sufficient evidence to conclude that the LS mean of SPN-812 ER 600 mg is less than the LS mean of the Placebo group. If H_0 is rejected, then it will be concluded that both the LS means of SPN-812 ER 600 mg and SPN-812 ER 400 mg doses are less than the LS mean of the placebo group. In other words, the superiority of both arms to placebo will be claimed.~~	
55	7.8.1.2 Sensitivity Analyses, p.37 To confirm the results of the primary analysis, two sensitivity analyses will be performed. First Sensitivity Analysis - the CFB to EOS will be analyzed using an analysis covariance (ANCOVA) model with treatment as fixed effect and baseline	7.8.1.2 Sensitivity Analyses, p.39 ~~To confirm the results of the primary analysis, two sensitivity analyses will be performed.~~ ~~First Sensitivity Analysis - the CFB to EOS will be analyzed using an analysis covariance (ANCOVA) model with treatment as fixed effect and baseline~~	LOCF method no longer used

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	ADHD-RS-V Total Score as a covariate based on the ITT population. The last observation carried forward (LOCF) method of imputation will be used for handling missing data. The assumption for using LOCF is described in Section 7.2-Handling Missing Data. Second Sensitivity Analysis - The first sensitivity analysis will be repeated for the PP population.	~~ADHD-RS-V Total Score as a covariate based on the ITT population. The last observation carried forward (LOCF) method of imputation will be used for handling missing data. The assumption for using LOCF is described in Section 7.2-Handling Missing Data.~~ ~~Second Sensitivity Analysis - The first sensitivity analysis will be repeated for the PP population.~~ **The sensitivity analysis assumes that missing ADHD-RS-5 Total Scores are MNAR. Placebo-based multiple imputation will be used to fill in missing values. This approach may be considered "worst-case" sensitivity analyses as it assumes that after discontinuation, subjects from the active treatment arms would adopt the outcome model estimated from the placebo arm. The placebo-based imputation will be implemented as described in the SAP.**	
56	7.8.2 Secondary Analyses, p.37 n/a	7.8.2 Secondary **Efficacy** Analyses, p.39 **(Added)** **The secondary analyses will be based on the ITT population with missing values imputed using multiple imputation assuming MAR**. **All secondary analyses will be analyzed using ANCOVA at Week 7 on the change from baseline at Week 7 (EOS) with treatment and baseline as fixed effect. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, Least Squares means of the treatment groups, differences between the LS treatment means and placebo (SPN-812 ER 400 mg minus Placebo and SPN-812 ER 600 mg minus Placebo), and 95% confidence intervals for the treatment differences will be computed.**	Updated for consistency with revised SAP

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57	7.8.2.1 Key secondary analyses, p.37 Key secondary analyses will include: a) Conners 3 - Treatment comparisons will be performed using ANCOVA or ANOVA on CFB to EOS, as appropriate. b) 30% Responder Rate - The proportion of subjects with ≥30% improvement (decrease) from baseline to EOS in ADHD-RS-V Total Score will be calculated for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 ER dose minus Placebo) and the p-value from Pearson's chi-squared test will be presented. c) Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V – analyzed as for Conners 3	7.8.2.1 Key secondary **efficacy** analyses, p.39 ~~Key secondary analyses will include:~~ **The analyses of key secondary objectives will be conducted on the following sequentially ordered endpoints for testing: 1) CGI-I, 2) Conners 3 - Parent composite T-score, and 3) WFIRS-P.** **To preserve the overall type I error rate at 0.05 for the key secondary endpoints, a sequential testing procedure will be used. First, only dose or doses that are significantly different from placebo for the primary endpoint will be tested for secondary endpoints. If the primary endpoint analysis does not reject H_{01} (i.e., the 600 mg is not superior to placebo) or the primary endpoint analysis rejects only H_{01}, then no multiplicity adjustment is required. Otherwise, multiplicity adjustment will be performed with the following features.** **The first of the secondary endpoints (CGI-I) will be used to test each treatment group to placebo using a sequential testing of the null hypotheses H_{01}: No treatment mean difference between SPN-812 ER 600 mg group and placebo group and H_{02}: No treatment mean difference between SPN-812 ER 400 mg group and placebo group will be performed. If H_{01} is not rejected, then H_{02} will not be tested and the conclusion will be that neither dose groups are efficacious. If H_{01} is rejected, then H_{02} will be tested. If H_{02} is rejected, then it will be concluded that both SPN-812 ER 600 mg and SPN-812 ER 400 mg are superior to Placebo. If H_{02} is not rejected, then it will be concluded that only SPN-812 ER 600 mg is superior to placebo. Then, the second secondary endpoint (Conners 3) will be tested in the same manner but only using those doses that were retained from the primary and the first secondary endpoint. Finally, the third key secondary endpoint (WFIRS-P)**	Updated for consistency with revised SAP

		will be tested in the same manner but only using those doses that were retained from the primary, the first key secondary endpoint, and the second key secondary endpoints. a) **CGI-I – The absolute value of CGI-I at Week 7 (EOS) will be analyzed using ANCOVA with treatment as a fixed classification variable and baseline CGI-S as a covariate. To compare the treatment groups, the difference in LS means (SPN-812 ER 400 mg minus Placebo and SPN-812 ER 600 mg minus Placebo) will be presented along with the 95% confidence interval (CI) around the difference and p-value.** **b)** Conners 3 **- Parent** - ~~Treatment comparisons will be performed using ANCOVA or ANOVA on CFB to EOS as appropriate.~~ **A composite T-score will be calculated by averaging over the six domains, and the change from baseline to Week 7 (EOS) in the composite T-score will be analyzed using ANCOVA model with fixed effects for treatment and baseline as a covariate. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, Least Squares means, differences between the LS treatment means and placebo, and 95% confidence intervals for the treatment differences will be computed.** ~~b) 30% Responder Rate - The proportion of subjects with ≥30% improvement (decrease) from baseline to EOS in ADHD-RS-V Total Score will be calculated for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 ER dose minus Placebo) and the p-value from Pearson's chi-squared test will be presented.~~ **c) WFIRS-P - The change from baseline in WFIRS-P to Week 7 (EOS) will be analyzed using ANCOVA model with fixed effects for treatment and baseline as a covariate. Missing Subscale scores and Total Score will be handled using multiple imputation under MAR assumption for inferential analyses. Each of the treatment groups (SPN-812 ER 400**	

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		mg and 600 mg) will be compared with the Placebo. The p-values, LS means of treatment groups, differences between the LS means and placebo, and 95% confidence intervals for the treatment differences will be computed. ~~c) Hyperactivity/Impulsivity and Inattention subscales of ADHD-RS-V – analyzed as for Conners 3~~	
58	7.8.2.2 Additional secondary analyses, p.37 Additional secondary analyses include treatment comparisons using ANCOVA or ANOVA on CFB to EOS, as appropriate.: a) WFIRS-P b) SIPA c) CGI-S/I	7.8.2.2 Additional secondary analyses, p.40 Additional secondary analyses **of the secondary efficacy variables will** include**:** ~~treatment comparisons using ANCOVA or ANOVA on CFB to EOS, as appropriate.~~ a) ~~WFIRS-P~~ **50% Responder rate for ADHD-RS-5 - Percent reduction will be calculated as: % reduction = 100*(ADHD-RS-5 Total Score at Week 7 (EOS) - Baseline ADHD-RS-5 Total Score)/Baseline ADHD-RS-5 Total Score. The proportion of responders will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 ER 400 mg minus Placebo, SPN-812 ER 600 mg minus Placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented.** b) SIPA **- The change from baseline in SIPA total score to Week 7 (EOS) will be analyzed using ANCOVA model with fixed effects for treatment and baseline as a covariate. Each of the treatment groups (SPN-812 ER 400 mg and 600 mg) will be compared with the Placebo. The p-values, LS means of treatment groups, differences between the LS means and placebo will be presented.** c) ~~CGI-S/I~~ **ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscales - The primary analysis for ADHD-RS-5 Total score will be repeated for the change from baseline to EOS in ADHD-RS-5 Inattention and the change from baseline to Week 7**	Updated for consistency with revised SAP

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	The primary and secondary analyses will be repeated for the per protocol population.	**(EOS) in Hyperactivity/Impulsivity subscales.** **d) Conners 3 - Self – The analysis for Conners 3 - Parent will be repeated for Self scores.** The ~~primary and~~ **key** secondary analyses will be repeated for the per protocol population **for supplementary analyses**.	
59	Version 4.0, **(Added) 7.8.3 Subgroup Analyses**, p.40 **The primary and key secondary efficacy variable analyses may be repeated by the following subgroups to explore the heterogeneity of treatment effect:** **a) Gender (male, female)** **b) Age (12-14 years, 15-17 years)** **c) Race (white, non-white)**		Updated for consistency with revised SAP
60	Version 4.0 **(Added) 7.8.4 Exploratory Analyses**, p.41 **Exploratory analyses of the key exploratory efficacy variables will include:** [redacted]		Updated for consistency with revised SAP
61	7.9 Sample Size and Power Considerations, p.37 Fifty-six subjects per treatment group in the ITT population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of 0.623, observed in the comparison of SPN-812 400 mg and placebo in the SPN-812 ER Phase IIb study (based on the CFB to endpoint in the ADHD-RS-IV total score). A total of 234 subjects (78 subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.	7.9 Sample Size and Power Considerations, p.41 ~~Fifty-six~~ **Seventy-two** subjects per treatment group in the ITT population will yield 90% power at a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the treatment groups. This assumes an effect size of ~~0.623~~ **0.547**, observed in the comparison of SPN-812 ~~400~~ **200** mg and placebo in the SPN-812 ~~ER~~ Phase IIb study (based on the CFB to endpoint in the ADHD-RS-IV total score). A total of ~~234~~ **300** subjects (~~78~~ **100** subjects in each of the three treatment groups) will be randomized to account for an anticipated 27.9% of randomized subjects not completing the study.	Increased sample size

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62	7.11 Pharmacokinetic Analyses, p.38 n/a [redacted]	7.11 Pharmacokinetic Analyses, p.41 [redacted] in the present study.	Assessment of viloxazine metabolite
63	7.11 Pharmacokinetic Analyses, p.38 n/a	7.11 Pharmacokinetic Analyses, p.41 **(Added) Population PK analyses will be reported separately from the clinical study report.**	Clarification
64	7.12 Pharmacogenomic Analysis, p.38 Individual data will be presented as a listing and summaries will be tabulated using descriptive statistics.	7.12 Pharmacogenomic Analysis, p.41 **If PGx testing is performed,** ~~i~~individual data will be presented as a listing and summaries will be tabulated using descriptive statistics.	Clarification
65	7.13 Safety Analysis, p.38 Verbatim description and all Medical Dictionary for Regulatory Activities (MedDRA) level terms, including the Lower Level Terms, for all AEs will be contained in the subject data listings. For quantitative laboratory parameters, both actual values an change from Visit 2 will be summarized. Both actual values and change from Visit 2 to Visit 9 will be summarized.	7.13 Safety Analysis, p.42 Verbatim description and ~~all~~ Medical Dictionary for Regulatory Activities (MedDRA) **SOCs and PTs** ~~level terms, including the Lower Level Terms,~~ for all AEs will be contained in the subject data listings. For quantitative laboratory parameters, both actual values an change from ~~Visit 2~~ **Screening** will be summarized. Both actual values and change from ~~Visit 2 to Visit 9~~ **baseline** will be summarized.	Clarification
66	8.3.4 Bioanalytical Sample Handling, p.40 Viloxazine concentrations in plasma samples will be determined using a validated chromatographic method.	8.3.4 Bioanalytical Sample Handling, p.43 Viloxazine **and 5-hydroxy-viloxazine glucuronide** concentrations in plasma samples will be determined using a validated chromatographic method.	Assessment of viloxazine metabolite

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		(Added) Viloxazine concentrations will be reported as viloxazine free base.	
67	10 References, p.43 Gajria K, Kivote V, Sikirica V, Reilly K, Kosinski M, Erder MH. Validation of the Weiss Functional Impairment Rating Scale – Parent Report Form in attention deficit/hyperactivity disorder. European Neuropsychopharmacology, Volume 24, S711 - S712.	10 References, p.46 Gajria K, Kivote V, Sikirica V, Reilly K, Kosinski M, Erder MH. **(2015)** Validation of the Weiss Functional Impairment Rating Scale – Parent Report Form in attention deficit/hyperactivity disorder. European Neuropsychopharmacology, Volume 24, S711 - S712. **(Added) Westfall, Peter H., Tobias, Randall D., and Wolfinger, Russell D., (1999). Multiple Comparisons and Multiples Tests Using SAS®, Cary, NC: SAS Institute Inc.**	Editorial change