STATISTICAL ANALYSIS PLAN

Protocol Title	Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial
Protocol Number	812P303
Protocol Version	V4.0
Protocol Date:	17Sep2018
Study Drug	Viloxazine Extended-Release Capsules (SPN-812 ER)
Study Phase	III
IND Number	108,864
Sponsor	Supernus Pharmaceuticals, Inc. [redacted]
SAP Version	Final
Date	18Oct2018
[redacted]	[redacted]

SIGNATURE PAGE

Prepared at Supernus Pharmaceuticals, Inc

[redacted]

Reviewed at Supernus Pharmaceuticals, Inc

[redacted]

Reviewed at [redacted]

[redacted]

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS

AE	Adverse event
ADHD-RS-5	Attention Deficit Hyperactivity Disorder Rating Scale
QD	Once daily
CFB	Change from Baseline
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global impression – Severity of illness
Conners 3-PS	Conners 3-Parent Short Form
Conners 3-SRS	Conners 3 – Self-Report Short Form
CRO	Contract Research Organization
CRF	Case report form
EOS	Visit 10 date or date of last visit for dropout subjects
ECG	Electrocardiogram
ITT	Intent-to-treat
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IWRS	Interactive web-based randomization system
LS Mean	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
msec	Millisecond
PK	Pharmacokinetic(s)
PP	Per Protocol
PSI-4-SF	Parenting Stress index, Fourth Edition, Short Form
PT	Preferred term in MedDRA and WHODD
SAE	Serious adverse event
SAP	Statistical analysis plan
SM	Study Medication

SOC	System Organ Class in MedDRA
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
WFIRS-P	Weiss Functional Impairment Rating Scale – Parent Version
WHODD	WHO Drug Dictionary

1 Introduction

This document describes the statistical analyses and data presentations to be performed on Study 812P303. This Phase III, randomized, multicenter, double-blind, 3-arm, parallel-group, and placebo controlled pivotal study of SPN-812 ER is titled "*Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, and Pivotal Trial*."

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of the data prior to database lock. This SAP covers the planned analyses of all data collected on the eCRFs and diary pages, and will identify handling of data issues. It describes the efficacy and safety variables, anticipated data manipulations, and other details of the analyses not provided in the study protocol. The statistical analysis plan presented in this document will supersede the statistical analysis methods described in the clinical protocol. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report. This SAP is based on the protocol 812P303, Version 4.0, dated 17Sept2018.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of SPN-812 extended release (ER) compared to placebo as monotherapy for the treatment of ADHD in children (6 -11 years).

2.2 Secondary Objectives

2.2.1 Key Secondary Objectives:

To assess the effect of SPN-812 ER as assessed by:

1. Clinical Global Impression-Improvement (CGI-I)
2. Conners 3rd edition (Conners 3) – parent
3. Weiss Functional Impairment Rating Scale – Parent report (WFIRS-P)

2.2.2 Additional Secondary Objectives:

1. 50% Responder rate in ADHD-RS-5 Total score
2. Parenting Stress Index, Fourth Edition, Short Form (PSI-4-SF)
3. ADHD-RS-5 Inattention/Hyperactivity/Impulsivity subscale scores

4. Conners 3rd edition (Conners 3) – self, composite T-score (ages 8-11)

2.2.3 Exploratory Objectives

[redacted]

2.2.4 Safety Evaluation

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

2.2.5 Additional Exploratory Objective

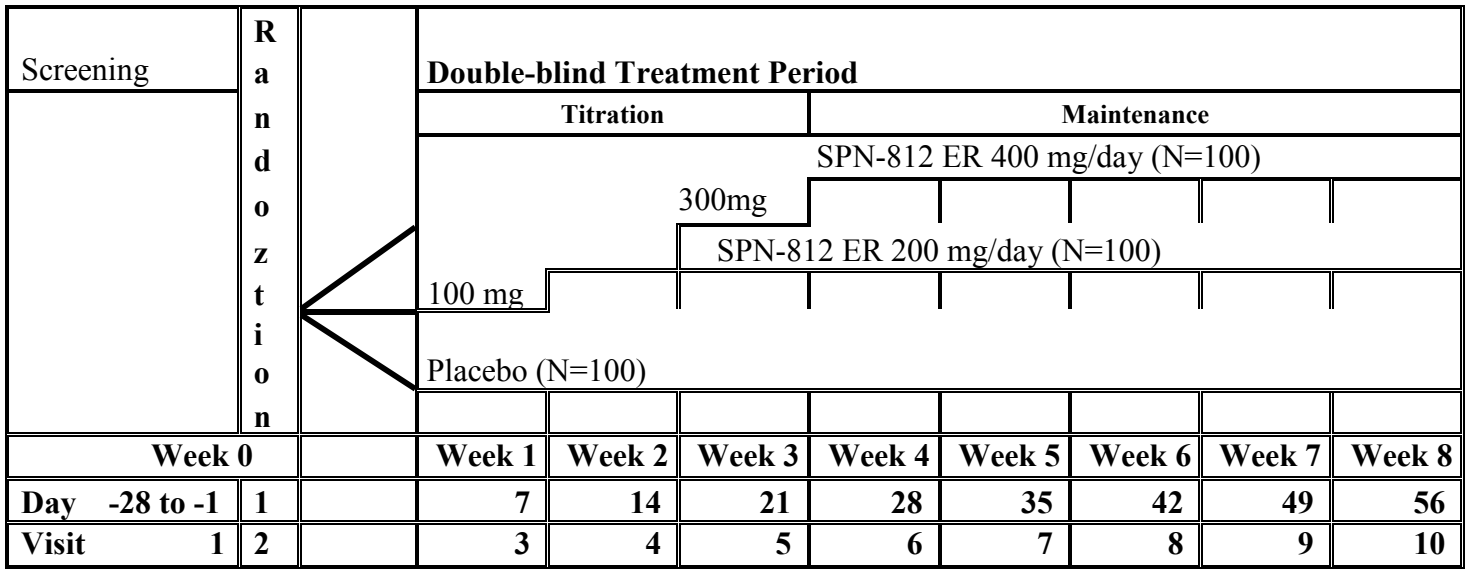
[redacted]

3 Study Description

3.1 Study Design

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 children 6-11 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 200 or 400 mg). Following up to four weeks of screening, subjects will be randomized and undergo three weeks of titration followed by five weeks of maintenance for a total of eight weeks of treatment and total study duration of up to 12 weeks. The study schematic appears in Figure 1.

Figure 1: Design Schematic



Titration to SPN-812 ER 200 mg dose from baseline (Day 1) in the week 1 visit for subjects randomized to SPN-812 ER 200 mg dose by 100 mg. Titration to SPN-812 ER 200 mg, 300 mg, and 400 mg dose from baseline (Day 1) in the week 1, week 2, and week 3 visits, respectively, for subjects randomized to SPN-812 ER 400 mg dose by 100 mg each week.

3.2 Schedule of Visits and Procedures Study

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

Table 1: Schedule of Visits and Procedure

		Treatment Phase			
Period	**Screening**	**Titration**		**Maintenance**	
		Baseline, Randomization			**End of Study[i]**
Visit Number	**1**	**2**	**3, 4**	**5-9**	**10**
Visit Day		**1**	**7, 14**	**21, 28, 35, 42, 49**	**56**
Visit Window (days)	≤28d before V2		±2	±2	±2
Informed Consent/Assent (if applicable)[a]	X				
Medical and Psychiatric History	X				
Mini-KID	X				
Demographics	X				
Urine Drug Screen	X				
Randomization		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
ADHD-RS-5	X	X	X	X	X
WFIRS-P, PSI-4-SF		X			X
Conners 3[e] – parent, self		X			X
Concomitant Medication	X	X	X	X	X
Adverse Events		X[f]	X	X	X[f]
Drug Dispensed		X[g]	X	X	
Drug Return, Compliance			X	X	X
Optional PK Blood Sampling[h]			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 Self report = 8-11 year olds only
f 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.
g Titration will begin after first dose of SM is administered

[h] An optional PK substudy will take place between Visits 3 and 10, inclusive. Samples will be taken pre-dose and post-dose at Hours 1, 2, 4, and 6.

[i] EOS or last visit in the case of early discontinuation.

3.3 Procedures for Discontinuing Treatment and Removal of Subjects from Study

Subjects will be considered to have completed the study if they complete all visits up to and including Week 8 (EOS).

All subjects who discontinue early will complete the procedures listed for Week 8 (EOS).

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

3.4 Study Treatments

3.4.1 Methods 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 200 mg/day, or SPN-812 ER 400 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

3.4.2 Treatment, Dose, and Mode of Administration

SPN-812 (Viloxazine hydrochloride extended-release tablet) or matching placebo tablets will be administered orally (PO) once daily (QD). 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 100 mg/week to the final dose (1:1:1) as follows:

Treatment A: Placebo

Treatment B: SPN-812 ER 200 mg/day (2 ✕ 100 mg SPN-812 ER)

Treatment C: SPN-812 ER 400 mg/day (4 ✕100 mg SPN-812 ER)

3.4.3 Duration of Treatment and Study Duration

Total subject duration on study is approximately 12 weeks.

- Pre-treatment phase: 4 weeks
- Treatment phase: 8 weeks
    - Titration period: 3 weeks
    - Maintenance period: 5 weeks

3.4.4 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.

3.5 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, 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). 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.

4 Definitions and Derivations

1. Baseline: Unless specified otherwise, baseline is defined as the non-missing value collected most recent to and before the time of the very first dose of the SM.
2. The study day (DY) is calculated as Visit date minus Reference date + 1 day if the visit date occurs on or after the reference date or Visit date minus Reference date if the visit date occurs before the Reference date, where the Reference date is defined as the first dose date (DY=1)
3. The change from baseline at a given Visit = observed value at that Visit minus observed value at baseline
4. ADHD-RS-5 total score =sum of scores for the 18 behaviors
5. ADHD-RS-5 Inattention subscale score = sum of scores for the first 9 behaviors
6. ADHD-RS-5 Hyperactivity/Impulsivity Subscale score = sum of scores for the last 9 behaviors
7. Conners 3-Parent Reported score: Composite T-score calculated by averaging over the 6 domains
8. Conners 3-Parent Reported score: T-score for individual domain: inattention, hyperactivity/impulsivity, aggression, executive functioning, learning problems, and relationships
9. Conners 3-Self Reported score domains: Composite T-score over the 5 domains
10. Conners 3-Self Reported score domains: inattention, hyperactivity/impulsivity, aggression, learning problems, and relationships
11. WFIRS-P score=average of all 50 items
12. WFIRS-P subscale scores: average of items of following 6 subdomains: Family, School (learning and behavior), Life Skills, Child's Self-Concept, Social Activities, and Risky Activities
13. PSI-4-SF: score=sum of all 36 items
14. PSI-4-SF: subscale scores: sum of items of following 3 subdomains: parental distress (PD), parent-child dysfunctional interaction (P-CDI), and difficult child (DC)

5 Study Variables

5.1 Primary Efficacy Variable

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-V). The scale consists of 18 items that directly correspond to the 18 DSM-V symptoms and are further subdivided into two subscales: Hyperactivity/Impulsivity and Inattentiveness (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: Child instrument will be administered and scored by Investigator at each weekly visit from Baseline through EOS.

5.2 Secondary Efficacy Variables

5.2.1 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-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.

5.2.2 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 8-18y.o.) 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 scales will be administered at Visit 2 (Baseline) and at Week 8 (EOS) according to subjects' age as follows:

- Age 6-11: Conners 3 – Parent: Short (Conners 3-PS)
- Age 8-11 only: Conners 3 – Self-Report; Short (Conners 3-SRS)

5.2.3 WFIRS-P

The 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 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.

5.2.4 PSI-4-SF

The Parenting Stress Index, Fourth Edition (PSI-4) questionnaire evaluates the magnitude of stress in the parent-child relationship based on the parent's perception of the child's characteristics, the personal characteristics of the parent, and the interaction between the parent and the child (Abidin, 1995). The short form of the PSI-4 (PSI-4-SF) consists of 36 items divided into three domains: parental distress, parent-child dysfunctional interaction, and difficult child. The PSI-4-SF scale was developed for parents of children ages 1 month to 12 years. This scale will be completed at Baseline and EOS by the parent/caregiver.

5.3 Pharmacokinetic Variables

[redacted]

5.4 Safety Assessments

Safety assessments include adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, ECGs, and the Columbia Suicide Severity Rating Scale (C-SSRS).

6 Statistical Methods

6.1 General Principles

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 creating TLF reports by SAS programming and delivering the reports as well as the programs to Supernus at the completion of the study.

All tabulations of analysis results will include summaries for the following three treatments: SPN-812 ER 400 mg, SPN-812 ER 200 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).

Means, least-squares (LS) means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations and standard errors will be presented to two (2) more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Confidence intervals will be presented using the same number of decimal places as the parameters (e.g., mean). Percentages will be presented to one (1) decimal place. P-values will use four decimal places.

Categorical variables will be analyzed using categorical response methods such as Pearson's Chi-square test. If expected frequencies are too small for asymptotic assumptions, 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. The

"EARLY_TERMINATION VISIT" for early discontinued subjects will be assumed to correspond to Visit 10 for statistical summaries but displayed as is in listings.

Derived analysis datasets will be produced from the SDTM data. Specifications for derived datasets will be developed. Analysis datasets to be created will include ADQS (Questionnaire analysis dataset), ADEFF1 and ADEFF2 (efficacy analysis dataset2), ADSL (subject-level analysis dataset), ADAE (Adverse event analysis dataset) and other as appropriate.

The ADEFF1 analysis dataset will be used for programing the primary analysis table and will contain variables for Subject ID, BASE (Baseline (Visit 2)), AVAL (values at Visit 3 –Visit 10), CHG (for CFB), ITT Flag variable, Treatment, and other necessary variables to be created. For each subject there will be nine records associated with nine visits: Baseline and Visit 3 - Visit 10. The ADEFF2 analysis dataset will be created based on MI assuming MNAR for sensitivity analysis and MI assuming MAR for secondary analyses. The ADEFF2 will contain 100 imputations of each record of each visit for the variables in ADEF1 with IMPUTNR variable.

6.2 Visit Windows

The Visit windows depicted in the table below will be used to evaluate subject compliance with scheduled visits with respect to protocol deviation. However, no visit windows will be used for statistical analysis; data will be analyzed according to the scheduled visit they are associated with in the CRF.

Table 2: Visit Windows and Study Day Ranges

Week	Day	Visit Window
0 (Visit 1-2)	1	<= Day 1
1 (Visit 2-3)	7	Day 2 - Day 9
2 (Visit 3-4)	14	Day 10 - Day 16
3 (Visit 4-5)	21	Day 17 - Day 23
4 (Visit 5-6)	28	Day 24 - Day 30
5 (Visit 6-7)	35	Day 31 - Day 37
6 (Visit 7-8)	42	Day 38 - Day 44
7 (Visit 8-9)	49	Day 45 - Day 51

8 (Visit 9-10)	56	Day 52 - Day 58

For analysis by titration and maintenance period, the periods will be defined as follows: Titration period: First dose date ≤ to ≤ v5 date; Maintenance period: V5 date < to ≤ V10 date.

6.3 Analysis populations

6.3.1 Randomized population

All enrolled subjects that had a Baseline Visit scheduled and are randomized via the IWRS.

6.3.2 Safety population

All subjects randomized into the study, who received at least 1 dose of SM. Subjects will be analyzed according to the treatment they received.

6.3.3 Intent-to-treat (ITT) population

All randomized subjects who received at least 1 dose of study drug and have 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.

6.3.4 Per-Protocol (PP) population

The Per Protocol (PP) population consists of all subjects in the ITT population who have completed all 10 visits with no missing ADHD-RS-5 assessments and no major protocol violations. Subjects will be analyzed according to the treatment they received.

The analysis population will be indicated as a subtitle in each table, listing and figure.

6.4 Subject Disposition

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

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

Within each of the previous categories, the number and percentage of subjects who completed, early discontinued and the reason for early discontinuation from the study will be summarized in Table 14.1.1.1. The reason for early discontinuation may include any of the following:

- Subject withdrew consent
- Lost to follow-up
- Administrative reason
- Adverse event
- Investigator decision
- Failure to follow required study procedures
- Other

Subject randomization schedule will be listed. Subjects whose randomization codes are unblinded during the conduct of the study will be listed along with the reason for un-blinding (Listing 16.1.7).

Subject disposition for screened subjects will be presented in Table 14.1.1.2. Subject enrollment distribution by site will be presented for the ITT population in Tables 14.1.1.3.

Data listing will be presented for subject disposition among all randomized subjects (Listing 16.2.1.1), screen failure among screened subjects (Listing 16.2.1.2), subject visit status at each visit (Listing 16.2.1.3), and visit dates (Listing 16.2.1.4) among all randomized subjects. Subject's inclusion and exclusion criteria response will be listed (Listings 16.2.2.1 - 16.2.2.2).

6.5 Protocol Deviations

The date of and reason for protocol deviations will be documented in all cases. Major protocol deviations will include the following but not limited to:

1) Subjects enrolled in the study but did not meet the inclusion/exclusion criteria.

2) Subjects who missed doses as per the treatment he was randomized to.

3) Subjects who received non-randomized medication.

4) Subject's treatment compliance < 80% or > 120%.

Major protocol violations will be finalized before the database lock and will be added to the above list.

Protocol violations will be summarized in Table 14.1.1.4.

Subjects with major protocol deviations will be listed based on all randomized subjects. The listing will include a brief description of the deviation, deviation category, and if applicable, study day when deviation occurred along with other pertinent information (Listing 16.2.2.3).

6.6 Handling Missing Data

6.6.1 Missing Efficacy Variables

Missing items in ADHD-RS-5 scale

1. If more than 3 items of ADHD-RS-5 have missing or invalid data, the total score will be set to missing. If the total score is missing then both subscales (inattention or Hyperactivity/ Impulsivity) will be set to missing.

2. If 3 items of ADHD-RS-5 or less have missing or invalid data, the values for the missing items will be imputed using the mean of the non-missing items rounded to the nearest integer.

With respect to the primary analysis, missing ADHD-RS-5 Total Scores will be assumed to be missing at random (MAR) (*See* Panel on Handling Missing Data in Clinical Trials, (2010) National Research Council: The Prevention and Treatment of Missing Data in Clinical Trials) 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. The motivation behind MMRM is to solve the issue of addressing an on-treatment question, i.e. what happens if a typical subject completes their assigned treatment. MMRM does this by conditioning on the previous observations and other covariates that may inform on both missingness and outcome.

A sensitivity analysis will be performed by assuming missing ADHD-RS-5 Total Scores are not missing at random (MNAR) (Yang, 2014), that is, the probability that an observation is missing may depend on its underlying unobserved value. This will be implemented using SAS® PROC MI and SAS® PROC MIANALYZE (SAS/STAT Software).

For secondary endpoints, missing values will be assumed as missing at random (MAR). Missing data will be imputed using SAS® PROC MI (SAS/STAT Software).

6.6.2 Missing Safety Variables

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

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

If a start or end date are completely missing, then the date will be imputed with the dates of the first or last date of treatment, respectively. If an AE is ongoing (AEENRTPT= ONGOING) or a non-study medication is ongoing (CMENRTPT= ONGOING), the end date will be imputed by the end of study date (ADSL.EOSDT).

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

6.7 Demographic and Baseline Characteristics

Demographic/baseline variables include age, age group, sex, ethnicity, race, height and weight at screening, and BMI. Baseline disease characteristics include ADHD-RS-5 total score, inattention subscale score and hyperactivity/impulsivity subscale score. Both will be summarized for the ITT population in Table 14.1.2.1 using descriptive statistics for continuous variables and using counts and percentages for categorical variables.

All demographic and baseline characteristics will be included in the subject data listing among all randomized subjects (Listing 16.2.4.1). The analysis populations will be listed in Listing 16.2.4.2.

Baseline comparability among the treatment groups will be presented in Table 14.1.2.2 using a chi-square test for the categorical variables, and using an F-test for the continuous variables. These p-values will be used for descriptive purposes, and will not be considered as the formal basis for determining factors to be included in statistical analysis model.

Mini-KID data will only be listed (Listings 16.2.4.3.1 and 16.2.4.3.2).

6.8 Medical and Psychiatric History

Medical history will be coded using MedDRA version 20.1. All medical and psychiatric history will be listed. Medical and psychiatric history will be summarized by body system for each treatment group in Table 14.1.2.3 for the safety population. The table will be sorted in alphabetic order by system organ class and the statistics n and % will be presented by treatment where: n is the number of subjects who present at least one occurrence of the medical history, and % is the percentage of subjects. The denominator used for calculating the percentages will be the total number of subjects included in the safety population in each treatment group. The tables will include two (2) parts: is the condition still active at screening (part a) or not (part b).

The pregnancy test results and urine drug screen will be listed in Listings 16.2.4.4.1 and 16.2.4.4.2. The medical history will be listed in Listings 16.2.4.5 - 16.2.4.7.

6.9 Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHODD version 20170901 (Classic) Format B3) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Concomitant medications will be presented for each treatment period during which the medication was taken (Titration period, Maintenance period, and combined Titration and Maintenance period). A tabular summary of concomitant medications by drug class will be presented for the safety population in Table 14.1.2.4.

A subject data listing will be provided to include the reported medication name, the WHODD drug codes, ATC codes, study day and pertinent subject information (Listing 16.2.4.8).

6.10 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).

Treatment duration will be categorized in days as: Day 1 to ≤ Day 9, Day 10 to ≤ Day 16, Day 17 to ≤ Day 23, Day 24 to ≤ Day 30, Day 31 to ≤ Day 37, Day 38 to ≤ Day 44, Day 45 to ≤ Day 51, Day 52 to ≤ Day 58 and ≥ Day 59. The number and percentage of subjects in each duration group will be summarized by treatment group for the Safety population.

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) / [4*(date of last dose minus date of first dose + 1)]}* 100%. If for a certain period no capsules are returned, the data is considered missing and not accounted for, and therefore this period will also not accounted for in the denominator (=number of planned doses).

For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) using number and percent of subjects in each compliance category for the safety population. 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.

The summary of duration of exposure to study medication and compliance will be presented for each treatment period (Titration period, Maintenance period, and combined Titration and Maintenance period) in Table 14.1.2.5 and Listings 16.2.5.1.1 - 16.2.5.1.3.

6.11 Site Pooling

This is a multicenter study. The primary analysis will be performed without site as a factor. However, for certain exploratory analyses small sites (defined as those with sample size <12 ITT subjects/site with uneven distribution of treatment groups) will be pooled to a group based on the geographic proximity. The purpose of pooling is to ensure that each site contains a sufficient number of subjects for statistical analyses that consider site as a factor.

6.12 Multiple Comparisons/Multiplicity

This is a 3-arm parallel group design. To account for the potential Type I error rate inflation due to multiple dose group comparisons to placebo, a sequential testing procedure with a fixed testing method will be used. The details of this multiplicity adjustment are defined in Sections 6.13.1 and 6.14.1.

6.13 Efficacy Analyses

The efficacy analyses will be based on the ITT population and will be performed on ADHD-RS-5 total score, Conners 3-PS composite T score, Conners 3-SRS composite T score, WFIRS-P total score and PSI-4-SF total scores.

All confidence intervals, statistical tests, and resulting p-values will be reported as two-sided and will be assessed at the 5% significance level and interactions at 10%.

With respect to Analysis of Covariance, the Gamma regression will be used on the original scale, if the normality assumption for the standard ANCOVA model is not met based on diagnostic residual plots based on the data before imputation.

Multiplicity will be adjusted for the primary endpoint and key secondary endpoints.

The mean profiles of ADHD-RS-5 total score, Conners 3-PS composite T score, Conners 3-SRS composite T score, WFIRS-P total score, PSI-4-SF score and CGI-I score will be presented graphically by treatment group and scheduled study visit. In addition, plots of the Cumulative Distribution Functions of Change from Baseline in ADHD-RS-5 will be presented (Figures 14.2.1.1 - 14.2.6.2)

For supportive analysis, the absolute value and change from baseline to Week 8 (EOS) of all efficacy variables will be summarized using descriptive statistics by treatment group and visit (Tables 14.2.5.1- 14.2.5.6).

6.13.1 Analysis of Primary Endpoint

The primary efficacy variable, change from baseline in ADHD-RS-5 Total Score to Week 8 (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 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 200 mg and SPN-812 ER 400 mg) will be presented, along with the corresponding standard error. Each of the treatment groups (SPN-812 ER 200 mg and 400 mg) will be compared with the 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 400 mg group and placebo group and H_{02}: No treatment mean difference between SPN-812 ER 200 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 400 mg and SPN-812 ER 200 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 400 mg is superior to placebo.

The summary of primary analysis will be presented in Table 14.2.1.1.

The corresponding MMRM SAS output will be presented in Listing 16.1.9.1. The ADHD-RS-5 questionnaire, total, subscale scores, and derived ADHD rating scale - 5 (behaviors and scores) and binary variables will be listed in Listings 16.2.6.1 and 16. 2.6.2 and 16.2.6.3.1 and 16.2.6.3.2.

6.13.2 Sensitivity Analysis

The sensitivity analysis assumes that missing ADHD-RS-5 Total Scores are missing not at random (MNAR), that is, the probability that an observation is missing may depend on its underlying unobserved value. (For example, the probability of missing ADHD-RS-5 Total Score at Week 8 is not related to the observed ADHD-RS-5 Total Score at visit 9). 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 by adopting the following three steps.

1) SAS PROC MI (SEED=220877) is applied to the input dataset containing all by-visit ADHD-RS-5 Total Score during the baseline, titration, and maintenance period. Multivariate imputation will be carried out by the fully conditional specification (FCS) method. One hundred (100) multiply-imputed datasets will be created. SAS® PROC MI with the MNAR statement will be implemented by using the following SAS code.

   ```
   PROC MI DATA= EFF NIMPUTE=100 SEED=220877 OUT=MNAROUT
   CLASS TREATMENT;
   VAR BASE WK1– WK8(EOS);
   FCS REG;
   MNAR MODEL (BASE WK1– WK8 (EOS))/MODELOBS= (TREATMENT='A'));
   RUN;
   ```

In the above SAS code, EFF denotes the efficacy data set, Base, WK1– WK8 are analysis values of ADHD-RS-5 total at baseline and each of treatment weeks from Week 1 (at Visit 3) to Week 8 (at Visit 10), and treatment = 'A 'denotes Placebo.

2. For each of the multiply-imputed data sets, CFB to EOS will be computed. For each imputation, the CFB will be analyzed using ANCOVA model, which will include fixed effect terms for treatment and baseline ADHD-RS-5 Total Score as a covariate. Each of the treatment groups (SPN-812 ER 200 mg and 400 mg) will be compared with the Placebo. The LS means of treatment groups, differences between the LS means of treatment groups and placebo, 95% confidence intervals around the differences and p-value will be computed.
3. Finally, to combine estimates (LS means, treatment LS mean differences, 95% CI around the difference and p-value) from the 100 datasets, SAS® PROC MIANALYZE will be used.

The summary of sensitivity analysis will be presented in Table 14.2.1.2. The corresponding full SAS output will be presented in Listing 16.1.9.2.

6.14 Analysis of Secondary Endpoints

All secondary analyses are based on the ITT population with missing values imputed at week 8 (WK8) using multiple imputation (MI) assuming MAR using SEED=2460650. In case imputed values are below or above the range of the applicable scale, values will be imputed to respectively the minimum or maximum value of the scale. The following SAS code will be used MI.

```
PROC MI DATA=EFF NIMPUTE=100 SEED=2460650 OUT=MIOUT;
    CLASS TREATMENT;
    VAR TREATMENT BASELINE WK8(EOS);
    FCS REG;
RUN ;
```

6.14.1 Analyses of Key Secondary Endpoints

The analyses of key secondary objectives will be conducted on the following sequentially ordered endpoints for testing: 1) CGI-I, 2) Conners-3, 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 H01 (i.e. the 400 mg is not superior to placebo) or the primary endpoint analysis rejects only

H01, 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 400 mg group and placebo group and H_{02}: No treatment mean difference between SPN-812 ER 200 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 400 mg and SPN-812 ER 200 mg are superior to Placebo. If H_{02} is not rejected, then it will be concluded that **only** SPN-812 ER 400 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 endpoint.

6.14.1.1 Clinical Global Impression – Improvement (CGI-I)

The absolute value of CGI-I at week 8(EOS) will be analyzed using ANCOVA with treatment as a fixed classification variable and baseline CGI-S as a covariate. This ANCOVA analysis supersedes the ANOVA analysis described in the protocol. Each of the treatment groups (SPN-812 ER 200 mg and 400 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 200 mg minus Placebo and SPN-812 ER 400 mg minus Placebo), 95% confidence intervals for the treatment differences will be computed. The summary of this analysis will be presented in Table 14.2.2.1.1 and listed in Listings 16.2.6.3.2- 16.2.6.5.

6.14.1.2 Conners 3-Parental Short Form

The Conners 3-PS will include 6 domains (subscales): inattention, hyperactivity/impulsivity, aggression, executive functioning, learning problems, and relationships.

The data for Conners 3-PS comprise derived T-scores for each domain rounded to the nearest integer. If a T-score ≤ 40 then the T-score will be set to 40 and if a T-score ≥ 90 then the T-score will be set to 90. If 1 of the subdomains is missing then the total score will be missing and the missing value will be handled using multiple imputation under MAR. A composite T-score will be calculated by averaging over the six domains (rounded to the nearest integer) and the change from baseline to Week 8 (EOS) in the composite T-score will be analyzed using ANCOVA model with fixed classification variable for treatment and baseline as a covariate. Each of the treatment groups

(SPN-812 ER 200 mg and 400 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. The summary of this analysis will be presented in Table 14.2.2.1.2 and Listings 16.2.6.6, 16.2.6.7 and16.2.6.8.

6.14.1.3 Weiss Functional Impairment Rating Scale – Parent Version (WFIRS-P)

WFIRS-P 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 (0, 1, 2 and 3) Likert scale. Higher WFIRS-P scores indicate more severe functional impairment. Missing items do not include omitted responses in the scoring (i.e., treat as "not applicable"). Each of the six domains is scored omitting items with a missing or 'not applicable' response. The WFIRS-P average score will be calculated over the 50 items as sum of all items with a response divided by total number of items that have been endorsed (e.g., do not include 'not applicable' items in the total). The same approach will be used for the subscores. The change from baseline in WFIRS-P to Week 8 (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 200 mg and 400 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. The summary of this analysis will be presented in Table 14.2.2.1.3 and Listings 16.2.6.9, 16.2.6.10 and16.2.6.11.

6.14.2 Analysis of Additional Secondary endpoints

6.14.2.1 Responder Analysis (50% responder rate)

For each subject, the response indicator variable will be set equal to 'YES' if a subject's % reduction ≥ 50% or 'NO' otherwise. Percent reduction will be calculated as: % reduction =100*(ADHD-RS-5 Total Score at Week 8 (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-812 200 mg ER minus Placebo, SPN-812 400 mg ER minus Placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented. The summary of this analysis will be presented in Table 14.2.2.2.1.

6.14.2.2 Short form of the PSI-4 (PSI-4-SF)

PSI-4-SF consists of 36 items divided into three domains: parental distress, parent-child dysfunctional interaction, and difficult child, which is scored using a 5-point as 1 (Strongly disagree), 2 (Disagree), 3 (Not sure), 4 (Agree), 5 (Strongly agree). For Item-32, the subject's original response

categories from the Answer Sheet are rated as 1 = "much harder than I expected" to 5 = "much easier than I expected". This will be reversed prior to calculating the subscale and total domain scores. The reversed Item-32 will be scored as from 5 = "much harder than I expected" to 1 = "much easier than I expected".

Scores will be calculated if:

1. No more than 1 item is missing from any subscale

If the above criteria are met, then the missing data convention is:

1. Identify the domain from which the item response is missing
2. Compute the average raw score for the completed items within that subscale, and round the average to the nearest whole number.
3. Assign the rounded whole number score to the missing item and then the subscale score

Domains and Subscales:

1. Sum responses items 1-12 = **PD** - Parental Distress
2. Sum responses items 13-24 = **P-CDI** - Parental-Child Dysfunctional Interaction
3. Sum responses items 25-36 = **DC** - Difficult Child

Total Stress Score (TS) = PD + P-CDI + DC

The change from baseline in PSI-4 total score to Week 8 (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 200 mg and 400 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. The summary of this analysis will be presented in Table 14.2.2.2.2 and Listings 16.2.6.12 - 16.2.6.14.

6.14.2.3 ADHD-RS-5 Hyperactivity/Impulsivity and Inattention Subscales

The change from baseline to EOS in ADHD-RS-5 Inattention and the change from baseline to Week 8 (EOS) in Hyperactivity/Impulsivity subscales will be analyzed using ANCOVA model with fixed effects for treatment, age group and baseline as a covariate. Each of the treatment groups (SPN-812 ER 200 mg and 400 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. The summary of this analysis will be presented in Table 14.2.2.2.3.

6.14.2.4 Conners 3rd edition (Conners 3) – self (ages 8-11)

The Conners 3-PS analysis from Section 6.14.1.2 will be repeated here. The summary of this analysis will be presented in 14.2.2.2.4.

6.14.2.5 Categorical Analysis of CGI-I

Categorical analysis will be performed using Pearson's Chi-square test by dichotomizing the CGI-I score as 'Improved' if the score is 'very much improved' or 'much improved' and 'Not Improved', otherwise, and will be presented for each visit in Table 14.2.2.2.5.

6.14.3 Exploratory Analyses

6.14.3.1 [redacted]

[redacted]

6.14.3.2 [redacted]

[redacted]

6.14.3.3 [redacted]

[redacted]

6.14.3.4 [redacted]

[redacted]

6.1.4 Supplementary Analyses

Supplementary analyses, based on the per protocol population, will be performed as in the following.

1. The primary endpoint (change from baseline in ADHD-RS-5 Total Score to Week 7 (EOS)) will be analyzed using ANCOVA model using treatment and baseline as fixed effect independent variables. This analysis will be summarized in Table 14.2.4.1.
2. The above analysis will be repeated for the Key secondary endpoints (Tables 14.2.4.2 – 14.2.4.4).

6.15 Examination of Subgroups

The primary and key secondary efficacy variables may be repeated by subgroup to explore the heterogeneity of the treatment effect across subgroups. Subgroups are defined as follows:

1. Gender (Male, Female)
2. Ages (6-9 years, 10-11 years)
3. Race (White, non-white).

This analyses will be summarized in Tables 14.2.3.1.1 to 14.2.3.1.3 for ADHD-RS-5 total score, Tables 14.2.3.2.1 to 14.2.4.2.3 for CGI-I, Tables 14.2.3.3.1 to 14.2.3.3.3 for Conners 3-PS composite T-score, and Tables 14.2.3.4.1 to 14.2.4.4.3 for WFIRS-P total score.

6.16 Pharmacokinetic (PK) Data Analysis

Plasma concentrations will be provided at the end of the study in SAS format to an external PK Scientist. This SAS data set will include subject number, visit, nominal timepoint, actual draw date, actual draw time, deviation from nominal timepoint, and concentration. Blood collection time and SM administration will be presented in Listing 16.2.13.

The Population PK model will be created separately and the analyses are not included in this SAP.

6.17 Safety Analyses

The assessment of overall safety will be based on adverse events, laboratory values, vital signs, ECGs and C-SSRS. Unless specified otherwise, comparison will be made to baseline as defined in Section 4 of the SAP.

All summary tables related to safety analyses will use the safety population. All subjects in the safety analysis set will be analyzed according to the treatment received.

6.17.1 Adverse Events

Adverse events (AEs) are described in Section 6.4 of Protocol 812P303. AEs will be classified into standardized medical terminology from the Verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1).

AEs will be summarized for each treatment period separately (Titration period, Maintenance period, and combined Titration and Maintenance period).

The overall incidence of AEs will be presented in Table 14.3.1.1. Subject data listing will be provided for all adverse events (Listing 16.2.7.1). Included in the listing are the reported term, PT, SOC, TEAE flag, study day when AE starts, duration, relationship, severity, action taken, outcome, and seriousness category. Data listings will be provided for subjects who experienced SAEs, have TEAEs leading to study drug discontinuation, or death (Listing 16.2.7.2, Listing 16.2.7.3, and Listing 16.2.7.4).

6.17.1.1 Treatment Emergent Adverse Events

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. TEAEs will be analyzed separately from those AEs that were not treatment-related. Only TEAE tables will be summarized. If a subject experiences more than 1 episode of a particular AE, the subject will be counted only once for that event. If a subject has more than 1 AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than 1 AE within a system organ class, the subject will be counted only once in that system organ class.

TEAEs will be summarized at the subject level by system organ class and preferred term for each treatment group in Table 14.3.1.2.

6.17.1.2 Severity of TEAEs

Based on the investigators determination, the severity of TEAEs will be classified as mild, moderate or severe.

If a subject experiences more than one episode of a coded TEAE, the subject will be counted only once by the maximum severity of the episode (preferred term). Similarly, if a subject has more than one TEAE within a system organ class, the subject will be counted only once by the maximum severity among TEAEs in that system organ class. TEAEs with missing severity will be considered as severe. The severity of TEAEs will be presented in Table 14.3.1.3.

6.17.1.3 Relatedness of TEAEs to SM

Based on the investigators determination, the relationship between the SM and a TEAE will be classified as not suspected (not related or unlikely related) or suspected (possibly related or definitely related). TEAE relatedness to SM will be summarized based on derived binary values as: "Drug Related" if the relationship to SM is probably or definitely related or "Not Related" if the relationship to SM is not related or unlikely related.

If a subject experiences more than one episode of a coded AE, the subject will be counted only once by the maximum relatedness of these episodes (preferred term). Similarly, if a subject has more than one AE within a system organ class, the subject will be counted only once by the maximum relatedness among AEs in that system organ class. AEs with missing relatedness will be counted as definitely related.

The summary of TEAE relatedness to SM will be presented in Table 14.3.1.4

In addition, number and percent of patients reporting common AEs (≥5% in any group) will be presented by PT in Table 14.3.1.5 and AEs leading to study drug discontinuation will be presented by SOC and PT in Table 14.3.1.6.

6.17.1.4 Serious Adverse Events

Serious adverse events (SAEs) are described in Section 6.4.5 of Protocol 812P303. A listing of SAEs and AEs leading to discontinuation will be presented. All subject deaths during this study will be collected and presented in a listing. The information presented will include date of death, days on study, cause of death, and relationship of death to study drug

Adverse event data will be presented in Listings 16.2.7.1, 16.2.7.2, and 16.2.7.3.

6.17.2 Laboratory Data

The change from baseline will be calculated as post-baseline value minus baseline value.

For each laboratory parameter, the following will be displayed for baseline and Week 8 (EOS).

- Summary statistics (n, mean, SD, median, minimum, and maximum) by treatment group for the actual and change from baseline values will be presented in Tables 14.3.2.1.1 and 14.3.2.2.1.
- Laboratory values will be flagged as abnormally low (L) if the value < lower limit of the normal range, normal (N) if the value is within normal range or abnormally high (H) if the value > upper limit of the normal range. Shift tables for the change from baseline to endpoint Week 8 (EOS) will be presented in Tables 14.3.2.1.2 and 14.3.2.2.2. Laboratory data will be presented in Listings 16.2.8.1 and 16.2.8.2.

6.17.3 Vital Signs

Vital signs parameters include: heart rate, diastolic and systolic blood pressure, respiratory rate, and temperature.

The change from baseline will be calculated as post-baseline value– baseline value.

Table 3: Vital Signs Normal ranges

Parameter, unit	Normal range	
	Lower limit	Upper limit
Pulse, bpm	70	120
DBP, mmHg	50	80
SBP, mmHg	90	120
Temperature, °C	35.5	37.5
Respiratory rate, bpm	18	25

Source: http://www.pedscases.com/pediatric-vital-signs-reference-chart

Values equal to the boundaries are still considered normal (N).

A value is classified as abnormally low (L) when the value < lower limit of the normal range.

A value is classified as abnormally high (H) when the value > upper limit of the normal range.

Vital signs will be summarized by treatment group using descriptive statistics (for quantitative parameters) in Table 14.3.3.1 and frequency tables (categorical variables) in Table 14.3.3.2.

Subject Listing of Vital Signs will be presented in Listings16.2.9.1 and 16.2.9.2.

16.17.4 Twelve (12)-Lead ECG

ECG parameters include HR, QRS, PR, and QTc.

If there is no original QTc in the database, then the QTc will be calculated using the following formulae:

Fridericia's cube-root corrected QT : QTcF (ms) = QT (ms) $\times \sqrt[3]{\frac{HR(bpm)}{60}}$

Table 4: Normal ECG ranges

Parameter, unit	Normal range	
	Lower limit	Upper limit
HR, bpm	60	140

PR, ms	90	170
QRS, ms	40	90

Source: http://learn.pediatrics.ubc.ca/body-systems/cardiology/approach-to-pediatric-ecg/

Values within boundaries and equal to the boundaries are still considered normal (N).

A value is classified as abnormally low (L) when the value < lower limit of the normal range.

A value is classified as abnormally high (H) when the value > upper limit of the normal range.

For the QT and QTc parameters, the following categorizations will be done:

- of the actual values: ≤ 450 ms, 450 ms < to ≤ 480 ms, 480 < to ≤ 500 ms, >500 ms
- of the changes from baseline: ≤ 30 ms (including all decreases in QT), 30 < to ≤60 ms, >60 ms.

ECG parameters will be summarized by treatment group using descriptive statistics (for quantitative ECG parameters) in Table 14.3.4.1 and frequency tables (for categorical parameters) in Table 14.3.4.2, Table 14.3.4.3, and Table 14.3.4.4.

Subject Listing of ECG: Parameters for actual and derived variables will be presented Listings 16.2.10.1 and 16.2.10.2.

16.17.5 Physical examinations

All physical examination findings will be presented in Listing 16.2.11.1.

Actual values and changes from baseline will be calculated at EOS for weight, height and BMI and presented in Listing 16.2.11.2.

16.17.6 C-SSRS

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 (Table 14.3.5).

Suicidal ideation and Suicidal behavior will be presented in Listings 16.2.12.1 - 16.2.12.2.

7 Validation

Supernus seeks to ensure the quality of the reports provided by [redacted] in the form of TLFs and derived datasets must pass a rigorous validation process involving the following processes.

- Derived datasets for AEs and the primary efficacy parameter must be independently reprogrammed by a second programmer based on analysis data specifications. The separate datasets produced by the 2 programmers must match 100% or in case of any differences, an explanation should be given and documented.

- Furthermore, all derived datasets will be independently programmed by BAIM institute based on analysis data specifications.
- Tables for AEs and the primary efficacy endpoint must be independently reprogrammed by a second programmer and the results from both programs must match 100% or in case of any differences, an explanation should be given and documented. Furthermore, all tables (efficacy, AEs, an all other summary tables) will be validated by BAIM institute.
- Figures must be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings must be checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TLF must be checked for completeness and consistency prior to its delivery to Supernus.

The above validation process must be repeated any time TLFs are redelivered using different data. Execution of this validation process must be documented through the study in a tracking sheet which containing TFL names, name of the primary programmer, name of the QC programmer and comment. The validation tracking sheet must be submitted at each delivery of TFLs.

8 References

Abidin, R. R. (1995). Parenting Stress Index, Third Edition: Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc.

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-5 for Children and Adolescents: Checklists, Norms, and Clinical Interpretation. New York, NY: The Guilford Press. 2016.

Gajria K et al (2015) Psychometric validation of the Weiss Functional Impairment Rating Scale-Parent Report Form in children and adolescents with attention-deficit/hyperactivity disorder. Health and Quality of Life Outcomes 13:184.

Guy, W. (1976). "Clinical Global Impression (CGI). Early Clinical Drug Evaluation Unit (ECDEU) Assessment Manual for Psychopharmacology". Rockville, MD: U.S. Department of Health, Education, and Welfare; Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs. pp. 218–222.

Lawson, A, (1983). Journal of the Royal Statistical Society. Series D (The Statistician), Vol. 32, No. 3 pp. 331-337

Panel on Handling Missing Data in Clinical Trials, (2010) National Research Council: The Prevention and Treatment of Missing Data in Clinical Trials.
https://www.nap.edu/download/12955

Protocol 812P303: Evaluation of SPN-812 ER 200 and 400 mg Efficacy and Safety in Children with ADHD - A Double-Blind, Placebo-Controlled, Pivotal Trial, Supernus Pharmaceuticals Inc., 17 September 2018

SAS/STAT Software, Copyright (c) 2002-2012 by SAS Institute Inc., Cary, NC, USA.

Sparrow EP Essentials of Conners Behavior Assessments. Hoboken, NJ: John Wiley & Sons, Inc. 2010

Thompson et al 2017. The Weiss Functional Impairment Rating Scale-Parent Form for assessing ADHD: evaluating diagnostic accuracy and determining optimal thresholds using ROC analysis. Qual Life Res. 26:1879–1885.

Westfall, Peter H., Tobias, Randall D., and Wolfinger, Russell D., (1999). Multiple Comparisons and Multiples Tests Using SAS®, Cary, NC: SAS Institute Inc.

Wyrwich, KW. et al 2015. Evaluation of Neuropsychiatric Function in Phenylketonuria: Psychometric Properties of the ADHD Rating Scale-IV and Adult ADHD Self-Report Scale Inattention Subscale in Phenylketonuria. Value in Health. Vol. 18, No 4, pp 404-412.

Yang Y. (2014), Sensitivity Analysis in Multiple Imputation for Missing Data