**COVER PAGE – STATISTICAL ANALYSIS PLAN (SAP)**

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| Protocol Number: | 812P201 |
| Title: | A Phase I/IIa, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Safety, and Efficacy of SPN-812V in Adults with Attention Deficit Hyperactivity Disorder (ADHD) |
| Sponsor: | Supernus Pharmaceuticals, Inc.<br>9715 Key West Avenue<br>Rockville, MD 20850<br>United States<br>Phone: (301) 838-2500<br>Fax: (240) 403-0065 |
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**SUPERNUS® PHARMACEUTICALS, INC.**

**STATISTICAL ANALYSIS PLAN**

**Protocol Number: 812P201**

# A Phase I/IIa, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Safety, and Efficacy of a Single Dose of SPN-812V in Adults with Attention Deficit Hyperactivity Disorder (ADHD)

**Version:** FINAL 2.0

**Date:** 09 FEB 2011

## SIGNATURE PAGE

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| **Drug:** | Viloxazine HCl |
| **Sponsor:** | Supernus Pharmaceuticals, Inc.<br>1550 East Gude Drive<br>Rockville, MD 20850 |
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| **Reviewer:** | [redacted] |
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| ATC | Anatomical-Therapeutic-Chemical |
| AUC | area under the plasma concentration versus time curve |
| BUN | blood urea nitrogen |
| CAARS | Conners' Adult ADHD Rating Scale |
| CAADID | Conners' Adult ADHD Diagnostic Interview for DSM-IV |
| CFR | Code of Federal Regulations |
| CGI | Clinical Global Impression |
| CGI-S | Clinical Global Impression – Severity of Illness |
| CGI-I | Clinical Global Impression – Global Improvement |
| CL/F | apparent oral clearance |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| C-SSRS | Columbia-Suicide Severity Rating Scales |
| CRO | Contract Research Organization |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders – Text Revision |
| ECG | electrocardiogram |
| FOCP | Females of Childbearing Potential |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |
| HR | Heart rate |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| ITT | intent to treat |
| LNH | Low, normal, high |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PK | pharmacokinetic |
| PK-PD | pharmacokinetic-pharmacodynamic |
| PO | orally |
| PR | Interval from the P wave (atrial contraction or depolarization) to the onset of the Q wave in the measurement of electrical activity of the myocardium |
| QRS | QRS complex refers to ventricular depolarization in the measurement of electrical activity of the myocardium |
| QT | Interval from ventricular depolarization and repolarization in the measurement of electrical activity of the myocardium |
| QTc | QT, corrected |
| QTcF | QT corrected using Fridericia's method |
| RBC | red blood cell |
| SAE | serious adverse event |
| SM | study medication |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |

| | |
|---|---|
| TEAE | treatment-emergent adverse event |
| TID | three times per day |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |
| WHO DD | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to reasonably ensure that the tables, data listings and figures which will be produced, and statistical methodologies that will be used, are complete and allow for the arrival at valid conclusions regarding the study objectives. In the development of this SAP, the following documents were used:

- The Final Protocol 812P201, Version 2.0, 30 June 2010
- eCRF Screen Shots – Phase 1 (Received from Emphusion on 22 June 2010)
- eCRF Screen Shots – Phase 2 (Received from Emphusion on 08 July 2010)
- eCRF and Database Specifications, Version 1.2 (24 August 2010).

# 2. STUDY OBJECTIVES

## 2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the safety of SPN-812V in adults with ADHD.

## 2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To determine the efficacy and of SPN-812V in adults with ADHD
- To explore the single dose and steady state pharmacokinetics of SPN-812V in adults with ADHD.

# 3. DESIGN OF THE STUDY

## 3.1 STUDY DESIGN

This will be a multicenter, randomized, double-blind, placebo-controlled, parallel group study of the safety and efficacy of SPN-812V in adults with ADHD. The target subjects are male or female adults aged 18 to 64 years, inclusive, with a diagnosis of ADHD. A total of fifty subjects will be enrolled at approximately 5 sites in the US. Subjects will be randomized (1:1) to one of two treatment groups, SPN-812V or placebo.

The study will consist of a Screening Period (within 14 days prior to randomization) and a Dosing Period of 6 weeks. The total subject duration in the study will be up to 8 weeks as illustrated in Figure 1.

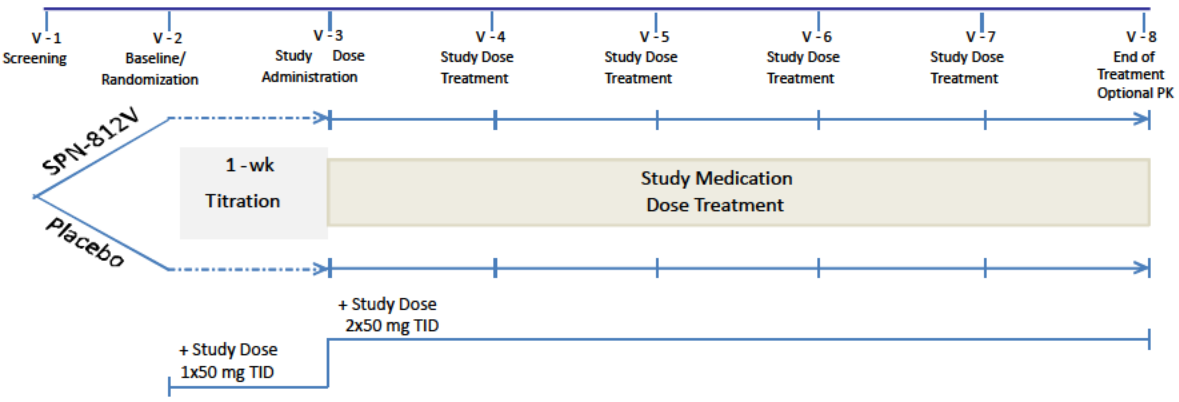


**Figure 1 Study Schematic**

### 3.1.1 Screening

Screening will take place within 14 days prior to randomization to determine subjects' eligibility to participate in the study. Screening procedures will be performed to determine each subject's eligibility to participate in the study and may be carried out over more than one visit during the Screening Period.

### 3.1.2 Dosing Period

Subjects who meet the requirements for study participation will be randomized and proceed to the Dosing Period which will last 6 weeks. Approximately 50 subjects will be randomized at a 1:1 ratio, using a centralized randomization system, to either SPN-812V or placebo. The first dose of SM should be taken the morning after the randomization visit. Subjects who do not tolerate the starting dose will be discontinued from the study.

The first dose of SM should be taken the morning after the randomization visit. Subjects will receive treatment at the 150 mg/day starting dose for one week. Subjects who do not tolerate the starting dose will be discontinued from the study.

Subjects who tolerated the starting dose will then be titrated to receive a study dose of 2x50 mg TID (300mg/day) and continue this treatment regimen for five weeks. Subjects who, after titration to the study dose, do not tolerate treatment at 300 mg/day, will be allowed, at any time, to down-titrate the dose to the 150 mg/day starting dose and continue treatment at the same dose until completion of the study. Subjects will return to the investigational site once a week to undergo safety and efficacy evaluations and to have SM compliance checked.

Subjects who have consented to participate in the optional PK sub study will be given a diary at Visit 7 on which to record time of SM doses taken prior to Visit 8. Subjects who are participating in the optional PK sub study will be given all efficacy assessments prior to blood draws or dosing on the PK day. For subjects not participating in the optional PK sub study, their last dose will be taken the evening before the End of Study Visit (Visit 8).

### 3.1.3 End of Study Visit/Early Termination

At the end of Visit 8, or prior to early discontinuation, subjects will undergo end of study assessments. AEs will be monitored, and safety tests and efficacy scales will be administered unless assessments were performed earlier in the visit. Subjects will return any unused capsules and undergo safety and efficacy evaluations if not already performed as part of that visit.

### 3.1.4 Pharmacokinetic Sampling

On the final visit, there is an optional PK day. All subjects who wish to participate will be dosed with active SM after an overnight fast and after all efficacy assessments are completed, Blood will be drawn for quantitative PK analysis according to the following schedule (all times +/- 30 minutes): Pre-dose and ½, 1, 2, 3, 4, 5, and 6 hours post-dose.

## 3.2 SAMPLE SIZE CONSIDERATION

Approximately 50 subjects (approximately 25 per treatment group) will be randomized in the study. The sample size is not based on any statistical considerations, but it was judged adequate to provide safety, PK, and efficacy information for a proof-of-concept study.

## 3.3 RANDOMIZATION PROCEDURE

The randomization for this study will be managed centrally by an IVRS vendor; specific instructions to conduct subject randomization will be provided in a separate document to all investigational sites, along with site staff access to the system.

Upon admission to the study, subjects will be assigned a 4-digit screening number, in the order that they are entered. Subjects who subsequently meet all eligibility criteria will be assigned a 6-digit randomization number. The first 3 digits will refer to the site, and the last 3 will refer to the subject-specific number, which will be assigned according to the randomization scheme.

## 3.4 SCHEDULE OF VISITS AND PROCEDURE

All subjects who are randomized and take any SM will be followed according to the protocol, unless consent for follow-up is withdrawn. The Sponsor, or the Sponsor's designee, must be notified of all deviations from the protocol visits or procedures and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule.

The exhibit on the next page presents the schedule of visits and procedures for the study (Table 1).

## Table 1. Schedule of Visits and Procedures

| Study Phase | Screening Period | Dose Treatment Period (Visit window +/- 2 days) | | End of Study [b] |
|---|---|---|---|---|
| Activity | Visit 1 Up to 14 Days Prior to Visit 2 | Visit 2 | Visits 3 – 8 | |
| Informed Consent [a] | X | | | |
| Medical and Psychiatric History and Demographics | X | | | |
| Physical Exam | X | | | X |
| ECG (12-lead) | X | | X [c] | X |
| Vital Signs [d] | X | X | X | X |
| Hematology | X | | | X |
| Urinalysis and drug screen | X | | | X |
| CYP2D6 Enzyme Activity Screening | X | | | |
| Serum Chemistry | X | | | X |
| Serum Pregnancy Test (for FOCP only) | X | | | X |
| Urine Pregnancy Test (for FOCP only) | | X | | |
| CAADID | X | | | |
| CGI | X | X | X | X |
| C-SSRS | X | X | X | X |
| CAARS [e] | | X | X | X |
| Concomitant Medication | X | X | X | X |
| Randomization | | X | | |
| SM Dispensed | | X | X | |
| SM Diary Dispensed | | | X [f] | |
| Optional SM Administered On-Site [g] | | | X | |
| Optional PK Blood Sampling | | | X [h] | |
| Adverse Events | | | X | X [i] |

a To be obtained prior to any study procedures being performed.

b To be performed at the end of Visit 8 (unless done previously during Visit 8), or at early discontinuation.

c At Visit 4 only

d Heart rate, seated blood pressure, temperature, and respiratory rate will be measured at every visit. The vital signs readings will be performed within approximately 10 minutes prior to the scheduled blood draws, where applicable. Height will be taken at screening and weight will be assessed at each visit.

e CAARS self-report done only at Visits 2 and 8, CAARS investigator-report done at Visits 2-8

f At Visit 7 to record SM taken prior to Visit 8. Diary to be collected at Visit 8.

g Dose to be administered on-site after the pre-dose draw and an overnight fast at Visit 8; subjects may eat 2 hours after dosing.

h At Visit 8, subjects who wish to participate will be dosed after an overnight fast and have a series of PK samples drawn. Samples will be taken pre-dose, and at Hours ½, 1, 2, 3, 4, 5, and 6.

i Any subject who experiences an adverse event (whether serious or non-serious) or has a clinically significant abnormal laboratory test value(s) will be followed by the Investigator at appropriate intervals based on the severity and nature of the event, until resolved, or when the condition is assessed as stable, causality other than the SM has been found, or the subject is referred to another health care professional.

## 3.5 EFFICACY MEASURES

### 3.5.1 Primary Efficacy Measure

The primary efficacy measure is the investigator-rated CAARS Total ADHD Symptom Score which is the sum of the Inattention and Hyperactivity/Impulsivity subscales (18 items rated on 4-point scale: 0, 1, 2 and 3).

### 3.5.2 Secondary Efficacy Measures

The secondary efficacy measures are:

- Clinical Global Impression – Improvement (CGI-I)
- Self-rated Conners' Adult ADHD Rating Scale (CAARS). This assessment will be administered at study Visits 2 and 8.

## 3.6 SAFETY MEASURES

Safety measures during the study will consist of AE and SAE monitoring, clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs.

### 3.6.1 Adverse Events

For subjects who receive SM, all AEs will be collected starting from providing informed consent for study participation. All AEs will be collected on the AE Case Report Form (CRF). SAEs will be reported if the Investigator believes the event is at least possibly related to SM. Investigator will assess the severity and the causality of AEs.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g., fever, elevated WBC, cough, abnormal chest X-ray, etc. can all be reported as "pneumonia").

### 3.6.2 Clinical Laboratory Values

The Schedule of Visits and Procedures shows the time points at which blood and urine will be collected for clinical laboratory tests. Laboratory tests should be performed under fasting conditions. Any laboratory abnormality may qualify as an AE in the Investigator's judgment. A complete list of all clinical laboratory assessments is presented in Table 2.

For subjects who participate in the optional PK portion of the study, a total of approximately 32mL (8 PK blood draws $\times$ 4mL) of blood/subject will be taken during the course of the study for the purpose of PK samples, in addition to 30mL (2 blood draws for clinical chemistry $\times$ 15mL) required for laboratory tests for all subjects.

**Table 2. Clinical Laboratory Assessments**

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| Hematocrit<br>Hemoglobin<br>Red blood cell count (RBC)<br>Platelet count<br>White blood cell count (WBC) (with differential) | Albumin<br>Alkaline phosphatase<br>Alanine transaminase (ALT)<br>Aspartate transaminase (AST)<br>Bilirubin- Total and Direct<br>Blood urea nitrogen (BUN)<br>Calcium<br>Chloride<br>Cholesterol- Total, HDL and LDL<br>Creatinine<br>Creatine phosphokinase (CPK)<br>Gamma-glutamyl transpeptidase (GGT)<br>Glucose<br>Inorganic phosphorous<br>Potassium<br>Sodium<br>Total protein<br>Triglycerides<br>Uric acid | Ketones<br>Protein<br>Specific gravity<br>Glucose<br>pH |
| Other tests | | |
| Urine drug panel for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabinoids, methadone, opiates, phencyclidine, propoxyphene, and alcohol)<br><br>Urine pregnancy test (for FOCP)<br><br>CYP2D6 enzyme activity (poor, intermediate and ultra rapid metabolizers) | | |

### 3.6.3 Vital Signs, Height, and Weight Measurements

Vital sign measurements (HR, blood pressure, temperature, and respiratory rate) will be obtained at all visits as designated on the Schedule of Visits and Procedures (Table 1). Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. Height and weight will be obtained at the Screening Visit and weight will be collected at all visits as designated on the Schedule of Visits and Procedures (Table 1).

### 3.6.4 Medical, Psychiatric History and Physical Examinations

Medical and psychiatric history, including smoking history, will be taken at the Screening Visit. Physical examinations will be performed at the Screening Visit and Final Visit as designated on the Schedule of Visits and Procedures (Table 1).

### 3.6.5 Electrocardiograms (ECGs)

ECGs (12-lead) will be obtained at the Screening Visit, Visit 4, and the Final Visit as designated on the Schedule of Visits and Procedures (Table 1). Additional ECGs may be performed at other times if deemed necessary.

The ECG will be recorded while the subject is resting in a supine position. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate. QTc will be reported as QTcF (QT corrected using Fridericia's method).

### 3.6.6 Prior and Concomitant Medications

For subjects who receive SM, prior and concomitant medications and therapies that are ongoing as of the date of informed consent will be recorded on the Concomitant Medication CRF. The Investigator will record all concomitant medications, including over-the-counter medications, on the Concomitant Medication CRF. The Investigator will record the AE for which the concomitant medication was administered on the AE CRF.

## 3.7 COMPLETION/DISCONTINUATION OF SUBJECTS

Subjects will be permitted to leave the study at any time. Subjects can be withdrawn from the study in any of the following circumstances:

- SAE or an AE
- Administrative reasons (e.g., sponsor decision)
- Withdrawal of consent/assent
- If the subject becomes pregnant
- If it is in the best interest of the subject, in the opinion of the Investigator
- Termination of the study.

If a subject is prematurely discontinued from participation in the study for any reason after SM administration, the Investigator must make every effort to perform the Final Visit assessments.

# 4. DATA ANALYSIS

Tabular summaries of the data collected during the study will be presented to provide a general description of the subjects studied and an overview of the efficacy and safety results. Data from all sites will be combined in the computation of these summaries, and summaries will be presented by treatment group. All subjects randomized to SPN-812V 300mg/day group, whether they are maintained on 300mg or reduced to 150mg, will be analyzed under the SPN-812V 300mg/day group. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, and minimum and maximum values). Categorical (nominal) variables will be summarized using frequency tables (number and percentage of subjects in each category). If some values are missing, the percentages will sum to less than 100%.

In addition to tabular summaries, subject data listings will be provided. All data collected on eCRF and from central laboratory will be presented in data listings. Where appropriate, data will be summarized for each protocol-specified visit. Unscheduled data will be listed and included in the Last Observation Carried Forward (LOCF) analysis.

## 4.1 SUBJECT DISPOSITION

Subject disposition will be summarized by treatment group and by all randomized subjects. The summary will include

- number of subjects randomized

- number of subjects completed the study
- number of subjects discontinued from the study.

Reasons for discontinuation will be summarized by randomized treatment group for all randomized subjects. Table 14.1.1 provides the subject disposition for all screened subjects.

Listing 16.2.1.1 provides screen failures for all screened subjects. Listing 16.2.1.2 provides subject disposition for all randomized subjects.

## 4.2 ANALYSIS POPULATIONS

The population of "All Screened Subjects" will contain all those subjects who entered the screening period to determine their eligibility to participate in the study.

The population of "All Randomized Subjects" will contain all those screened subjects who meet the requirements for study participation and are randomized, using a centralized randomization system, to either SPN-812V or placebo.

The "Intent-to-Treat (ITT) Population" consists of all randomized subjects who took at least one dose of SM, had baseline efficacy assessment and had at least one post-baseline efficacy assessment. The ITT population is the primary population for the efficacy analysis.

The "Restricted ITT Population" consists of all ITT population subjects with at least 1 efficacy assessment after three weeks of treatment.

The ITT and Restricted ITT populations will be analyzed according to treatment assigned. All subjects randomized to SPN-812V 300mg/day group, whether they are maintained on 300mg or reduced to 150mg, will be analyzed under the SPN-812V 300mg/day group.

The "Safety Population" consists of all randomized subjects who receive at least 1 dose of SM.

The PK population consists of all safety subjects who consented to participate in the optional PK sub study and had at least one evaluable (non-BLQ) PK sample drawn.

The safety and PK populations are based on actual treatment received.

Table 14.1.2 provides these analysis populations for all randomized subjects.

Listing 16.2.2 provides inclusion and exclusion criteria violations for all randomized subjects. Listing 16.2.3 gives analysis populations.

## 4.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics data will be summarized by treatment group for the safety, ITT, and restricted ITT populations.

Demographic information (Sex, Race, Ethnicity and Age) will be listed (Listing 16.2.4). Height, weight and BMI will be listed with vital signs (Listing 16.2.9) where height is measured at screening only. Descriptive statistics will be obtained for the continuous variables: age, height, weight and BMI (Table 14.1.3.1.1 through 14.1.3.1.3). Frequencies and percentage of subjects will be tabulated for the categorical variables: sex, race and

ethnicity (Table 14.1.3.2.1 through 14.1.3.2.3).

To calculate age, the following formula will be used:

Age (years) = INT { (date of screening – date of birth) / 365.25 }.

## 4.4 MEDICAL AND PSYCHIATRIC HISTORY

Medical and psychiatric history data recorded prior to dosing will be listed by subject for the safety population. Only those body systems where a condition or abnormality has been reported will be listed (Listing 16.2.5.1 and 16.2.5.2).

The diagnoses present in subjects' medical history and the duration of those medical conditions will be presented by treatment group in Table 14.1.3.3. If start date is incomplete or missing, date of informed consent will be used for imputing the duration.

## 4.5 TREATMENT COMPLIANCE AND EXPOSURE

Tabular summaries of the compliance rate and duration of treatment exposure to SM will be presented for the safety population by treatment group. Summary of treatment compliance and exposure will be provided separately for the first week of start-up dose (Baseline and Randomization Period), study maintenance dose period (Study Dose Treatment Phase), and combined Baseline and Randomization and Study Dose Treatment Phase (Table 14.1.4.1). Listing 16.2.5.3 provides the compliance data.

The number and percentage of subjects maintained on the target dose (300mg) versus those reduced in dose (150mg) during the Study Dose Treatment Phase will be provided (Table 14.1.4.2).

## 4.6 POTENTIAL EXCLUSIONS FROM ITT POPULATION

Study data will be examined during the Blind Data Review (described below in section 4.7) for potential exclusions from ITT population. ICH E9 guideline outlines circumstances where it will usually be acceptable to omit subjects from the ITT population without causing bias. Some of the potential exclusions in this study are:

- Subjects who violate the inclusion/exclusion criteria;
- Subjects who fail to take at least one dose of study medication;
- Subjects who do not provide any post-baseline data;
- Enrollment of a subject who did not meet all inclusion/exclusion criteria which would affect subject safety or would negatively impact data integrity;
- Use of any prohibited concomitant medication that may confound study results;
- Subject dosing error that results in a serious adverse event;
- Having any non-compliance issues raised by the investigator or sponsor prior to breaking the blind;
- Study visit or procedure conducted outside of required time frame that may negatively affect subject safety;
- Subject visit/procedure falls outside of the window of time indicated by the protocol

resulting in increased potential for risk to the subject or any damage to the integrity or completeness of the data.

### 4.7 BLIND DATA REVIEW

The checking and assessment of data to revisit the proposed methods of statistical analysis for the purpose of finalizing the planned analysis prior to the database lock will be conducted. The following lists some of the aspects of analysis that would be considered:

- Checking of data for potential exclusions from ITT population;
- Precise definitions of analysis populations, especially which subjects will be included and which will be excluded;
- Handling of missing data;
- Outlier identification and specific decisions taken on how these will be handled.

The data review will be documented in agreed and signed meeting minutes, which will include a version of Listing 16.2.3 as appendix. The blind data review meeting minutes will be included in Appendix 13.1.

## 5. EFFICACY ANALYSES

Efficacy analyses will be conducted for the ITT population. Where appropriate, a restricted ITT population may also be used.

Descriptive statistics will be presented for all efficacy variables by visit and treatment group.

All significance tests will be performed at the 0.05 level.

### 5.1 GENERAL CONSIDERATIONS AND STATISTICAL/ANALYTICAL ISSUES

#### 5.1.1 Definition of Baseline

Unless stated otherwise, subject's Visit 2 will be considered as Baseline for statistical analyses. If subject's Visit 2 assessment is missing, the last available value on or prior to the first study dose date will be used as baseline.

#### 5.1.2 Treatment Comparisons

Statistical testing to compare treatment groups will be performed for the ITT population only using appropriate statistical methods, as described in the efficacy subsections below. Given the small per-treatment group sample size for the study, the resulting p-values from the statistical testing will be used for descriptive purposes only (i.e., not for inferential purposes), primarily as an aid in the clinical interpretation of the efficacy results.

#### 5.1.3 Pooling of Centers

As sample size per center will be small, all the centers will be pooled together for the analysis.

### 5.1.4 Multiple Comparisons/Multiplicity

Treatment comparisons will be performed at Visit 3 through Visit 8 but without adjustment for multiple comparisons as sample size is small and is not based on any power calculations. P-values will be used only for interpretation.

### 5.1.5 Examination of Subgroups

Subgroup analyses for efficacy will be performed on categories of the following measures:

- Sex
- Race

for the ITT population for the investigator-rated CAARS Total ADHD Symptom Score.

Subgroup analyses will also be carried out for

- investigator-rated CAARS inattention subscale score
- investigator-rated CAARS hyperactivity/impulsivity subscale score.

Investigator-rated CAARS inattention subscale score has 9 items (1, 9, 13, 14, 19, 21, 26, 29 and 30) and investigator-rated CAARS hyperactivity/impulsivity subscale score has 9 items (2, 4, 6, 8, 16, 18, 22, 25 and 27). These two subscales together make up the CAARS Total ADHD Symptom Score.

### 5.1.6 Methods for Handling Dropouts or Missing Data

Subjects who discontinue the study without post-randomization scores will not be included in the analysis of efficacy variables. Last observation carried forward (LOCF) technique will be used in the efficacy analysis for subjects who discontinue the study with post-randomization scores where last observation carried forward will be the last non-missing observation on scheduled or unscheduled visits.

If more than one item of a subscale is missing, the score for the subscale (and the total score) will also be considered missing. If only a single item is missing, the mean score for all other items in the subscale will be imputed as the score for the missing item.

## 5.2 PRIMARY EFFICACY ANALYSIS

The primary efficacy measure is the investigator-rated CAARS Total ADHD Symptom Score which is the sum of the Inattention and Hyperactivity/Impulsivity subscales (18 item measured on 4-point scale).

The changes from baseline to endpoint (Visit 8) in the investigator-rated CAARS Total ADHD Symptom Scores will be compared between the SPN-812V 300mg/day group and placebo using the two-sample t-test if normality assumption is satisfied.

In case of non-normality of scores, Wilcoxon rank-sum test will be used. The Hodges-Lehmann estimate and associated 95% confidence interval will be calculated for the median difference between treatments.

Tables 14.2.1.1 and 14.2.1.2 provide the primary efficacy results for ITT and restricted ITT populations respectively. Figures 14.2.1.3 and 14.2.1.4 provide visit-wise mean change from baseline in investigator-rated CAARS Total ADHD Symptom Score for the two treatments for ITT and restricted ITT populations respectively. Figures 14.2.1.5 and 14.2.1.6 provide cumulative proportion of subjects against change from baseline to the end of study (Visit 8) in investigator-rated CAARS Total ADHD Symptom Score for the two treatments for ITT and restricted ITT populations respectively. Listing 16.2.6.1 provides the investigator-rated CAARS Total ADHD Symptom Score data for the ITT population.

## 5.3 SECONDARY EFFICACY ANALYSES

For the analysis of secondary efficacy variables, no statistical adjustment to the level of significance will be made for multiple endpoints and/or multiple comparisons.

The secondary efficacy analyses for various secondary efficacy measures are as follows.

### 5.3.1 Investigator-Rated CAARS Total ADHD Symptom Score (150mg)

Initial efficacy of SPN-812V starting dose (150 mg/day) when compared to placebo as measured by changes in the investigator-rated CAARS Total ADHD Symptom Score from baseline at week 1 of treatment with starting dose will be analyzed with two-sample t-test if normality assumption is satisfied.

In case of non-normality of scores, Wilcoxon rank-sum test will be used. The Hodges-Lehmann estimate and associated 95% confidence interval will be calculated for the median difference between treatments.

Table 14.2.2.1 provides the secondary efficacy results for ITT population for the investigator-rated CAARS Total ADHD Symptom Score at week 1.

### 5.3.2 Global Improvement (CGI-I)

Actual CGI-I scores at each post-baseline visit and endpoint will be compared among treatment groups using two-sample t-test if normality assumption is satisfied.

In case of non-normality of scores, Wilcoxon rank-sum test will be used. The Hodges-Lehmann estimate and associated 95% confidence interval will be calculated for the median difference between treatments.

Tables 14.2.2.2.1 and 14.2.2.2.2 provide secondary efficacy results for CGI-I for the ITT and restricted ITT populations. Tables 14.2.2.2.3 and 14.2.2.2.4 provide the number and percentage of subjects with CGI-I < 3 at the end of study (EOS) for the two treatment groups for the ITT and restricted ITT populations respectively. Listing 16.2.6.2.1 provides CGI-S and CGI-I data for the ITT population.

### 5.3.3 Investigator-Rated CAARS Total ADHD Symptom Score (300mg)

The changes from baseline in the investigator-rated CAARS Total ADHD Symptom Scores will be compared between the two treatment groups for the Visit 4, 5, 6, 7 and 8 using the two-sample t-test if normality assumption is satisfied.

In case of non-normality of scores, Wilcoxon rank-sum test will be used. The Hodges-Lehmann estimate and associated 95% confidence interval will be calculated for the median difference between treatments at Visits 4, 5, 6, 7 and 8.

Tables14.2.2.3.1 and 14.2.2.3.2 provide the secondary efficacy results for ITT and restricted ITT populations for the investigator-rated CAARS Total ADHD Symptom Scores at Visits 4, 5, 6, 7 and 8. Listing 16.2.6.1 provides the investigator-rated CAARS Total ADHD Symptom Score data for the ITT population.

### 5.3.4 Self-Rated CAARS Total ADHD Symptom Score

The changes from baseline at endpoint (Visit 8) in the self-rated CAARS Total ADHD Symptom Scores will be compared between the SPN-812V 300mg/day group and placebo using the two-sample t-test if normality assumption is satisfied.

In case of non-normality of scores, Wilcoxon rank-sum test will be used. The Hodges-Lehmann estimate and associated 95% confidence interval will be calculated for the median difference between treatments.

Table 14.2.2.4 provides the secondary efficacy results for ITT population for the self-rated CAARS Total ADHD Symptom Scores. Listing 16.2.6.2.2 provides the self-rated CAARS Total ADHD Symptom Score data for the ITT population.

## 5.4 SENSITIVITY ANALYSIS

To confirm the results (sensitivity analysis), a mixed model repeated measures (MMRM) analysis will be conducted. MMRM analysis will contain fixed effect terms for treatment, investigative site, visit, and interaction between treatment and visit. Visit will be used as repeated measure. The model will include change from baseline of the investigator-rated CAARS Total ADHD Symptom Score as the dependent variable with a random patient effect and baseline investigator-rated CAARS Total ADHD Symptom Score as a covariate and will use an auto regressive (1) covariance.

Table 14.2.3 provides the sensitivity analysis results for the investigator-rated CAARS Total ADHD Symptom Score for the ITT population.

## 5.5 SUBGROUP ANALYSES

Subgroup analyses for efficacy will be performed on categories of the following measures:

- Sex
- Race

for the ITT population for the investigator-rated CAARS Total ADHD Symptom Score.

Subgroup analyses will also be carried out for

- investigator-rated CAARS inattention subscale score
- investigator-rated CAARS hyperactivity/impulsivity subscale score.

Investigator-rated CAARS inattention subscale score has 9 items (1, 9, 13, 14, 19, 21, 26, 29 and 30) and investigator-rated CAARS hyperactivity/impulsivity subscale score has 9 items (2, 4, 6, 8, 16, 18, 22, 25 and 27).

Table 14.2.4.1 will have results for sex. Table 14.2.4.2 will have results for race. Table 14.2.4.3 will have results for the components of the primary efficacy measure, namely, investigator-rated CAARS inattention and hyperactivity/impulsivity subscale scores.

# 6. SAFETY ANALYSES

The safety and tolerability endpoints will be summarized for the safety population according to the treatment actually received. Statistical testing will be performed for some of the safety endpoints, but the resulting p-values will be used for descriptive purposes only.

Safety will be assessed by the monitoring of AEs, vital signs, clinical laboratory tests, physical examinations, and electrocardiograms (ECG).

## 6.1 ADVERSE EVENTS

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Although a MedDRA term for a subject may be reported more than once, that subject will be counted only once in the incidence count for that MedDRA term. AEs will be presented in the summary tables by preferred term nested within System Organ Class.

Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the subject data listings (Listing 16.2.7.1).

### 6.1.1 Overall Study

Adverse events that occur or worsen after the first administration of study medication are considered treatment-emergent and will be summarized in tables. For missing information, the most conservative interpretation will be assumed. For example, if AE onset time is not collected, the AE starts on the first study dose date.

AEs will be summarized for each treatment group by presenting the incidence of AEs based on the number and percentage of subjects with AEs.

Table 14.3.1.1.1 will provide overall incidence of AEs for the Safety population. Table 14.3.1.1.2 will provide an incidence summary of AEs by System Organ Class, and Preferred Term for the Safety population.

Table 14.3.1.1.3 will provide an incidence summary of AEs by System Organ Class, Preferred Term, and Relationship to Study Drug for the Safety population. If a subject had two or more adverse events in the same system organ class (or with the same preferred term) with different relationships to study drug, then the event with the closest relationship to study drug will be used for that subject.

Table 14.3.1.1.4 will provide an incidence summary of AEs by System Organ Class, Preferred Term, and Severity for the Safety population. If a subject had two or more adverse events in the same system organ class (or with the same preferred term) with different levels of severity, then the event with the worst severity will be used for that subject.

### 6.1.2 By Demographic/Baseline Variables

Tables similar to those for the Overall Study (14.3.1.1.1 – 14.3.1.1.4) will be presented for the demographic/baseline variables: Sex – Tables 14.3.1.2.1 – 14.3.1.2.4, Race – Tables

14.3.1.2.5 – 14.3.1.2.8, Ethnicity – Tables 14.3.1.2.9 – 14.3.1.2.12.

### 6.1.3 Deaths, Serious AEs, and Other Significant AEs

Listings (and tabular summaries, if warranted) of deaths, SAEs, and other significant AEs, including AEs resulting in treatment discontinuation, study drug dose reduction, and study drug interruption will be provided (Listings 16.2.7.2.1 through 16.2.7.2.5).

## 6.2 CLINICAL LABORATORY VALUES

Table summaries and by-patient listings of the laboratory test results will be presented. Laboratory testing will be broken down by Hematology, Serum Chemistry, and Urinalysis tests. Tables 14.3.2.1 through 14.3.2.4 will provide summaries for Hematology and Serum Chemistry respectively and associated shift tables. Listings 16.2.8.1 through 16.2.8.6 will provide by-patient listing for hematology, serum chemistry, urinalysis, CYP2D6 enzymes, urine drug test, and urine pregnancy tests respectively.

## 6.3 VITAL SIGNS, HEIGHT, WEIGHT AND BMI

Summary table of vital signs (HR, blood pressure, temperature, respiratory rate) and height and weight will be presented by treatment and by visit. This summary table will also include change from baseline by treatment and visit. Descriptive summary statistics (mean, SD, median, and range) for vital sign data and height and weight will be evaluated by treatment group. Table 14.3.4 provides the summary table for vital signs, heights, weights and BMI.

Individual listings will also be provided for these parameters (Listing 16.2.9).

## 6.4 ECG RESULTS

Table 14.3.5.1 provides overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant). Table 14.3.5.2 summarizes ECG results (both actual values and change from baseline values) by visit by treatment group using descriptive statistics for quantitative ECG parameters: PR Interval (msec), QRS Duration (msec), QT Interval (msec), and QTcF Interval (msec). Table 14.3.5.3 presents the ECG Shift Table from Baseline to Post-Baseline Visits for qualitative ECG parameters.

Table 14.3.5.4 provides the number and percentage of subjects with any QTcF value including >= 500 msec for all assessments made during the study as well as by scheduled collection and treatment group. This table also provides the number and percentage of subjects with any change from baseline in the QTcF value including >= 60 msec over all assessments made during the study as well as by visit and treatment group. This table is constructed to identify outliers.

Listing 16.2.10 provides ECG Findings.

## 6.5 PHYSICAL EXAMINATION

Findings from the physical examinations will be summarized through shift tables that, for each system or area examined, compare the normal/abnormal finding at Baseline to the normal/abnormal finding at the Final Visit. Table 14.3.6 gives the results of physical examination. Listing 16.2.11 provides physical examination findings.

### 6.6 PRIOR AND CONCOMITANT MEDICATIONS

A table (Table 14.3.7) summarizing frequencies of prior and current use of concomitant medications will be presented for the safety population and its treatment group subsets.

Prior and Concomitant medications and therapies that are ongoing as of the date of informed consent and all medications taken since the time of dosing of SM until the end of the study (the last visit) will be listed (Listing 16.2.12). If non-SM's taken time is not collected, the medication taken on and after the first dose date of SM until the end of study will be listed. Concomitant medications will be assigned an 11-digit code using the WHO Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification.

### 6.7 COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

A table (Table 14.3.8) summarizing frequencies of Suicidal Ideation and Behavior at Baseline and During the Trial will be presented for the safety population and its treatment group subsets. P-values will be calculated using Fisher's Exact Test for interpretation purposes. Listings 16.2.13.1 and 16.2.13.2 will provide C-SSRS Baseline values and During the Trial (Since Last Visit Version) values respectively for the Safety Population. Histograms displaying highest level of Suicidal Ideation (Figure 16.2.13.3) and Suicidal Behavior (Figure 16.2.13.4) respectively against their categories for the two treatment groups will be constructed.

## 7. PHARMACOKINETIC ANALYSIS

Population PK data will be pooled across the PK populations and analyzed using nonlinear mixed-effects modeling methods. The objective of the population PK analyses is to derive individual-specific estimates of apparent oral clearance (CL/F) but not to fully characterize the PK of this formulation of SPN-812V.

The methodology and results of this exploratory population PK analysis will be presented in a separate report and included as an addendum to the CSR.

Listings 16.2.14.1 and 16.2.14.2 will provide PK fasting status and PK blood collection data for the PK population.

## 8. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Any changes to the statistical analysis plan after database lock should be addressed in a separate document. That document will be approved separately and included as an addendum to the final SAP.

## 9. PROGRAMMING SPECIFICATIONS

All summary tables, data listings, figures and other statistical output will be produced with the SAS system (version 9.1 or above) and will be incorporated into a MS Word document for easy integration into the CSR production process. Summary tables, data listings, and figures will be produced in the order that they appear in the textual sections of the plan.

The SAS generated output will adhere to the following specifications.

## 9.1 FORMAT OF TABLES AND LISTINGS

Tables and listings will be produced in landscape orientation. To ensure the print window is usable for both A4 paper size (21 x 29.7 cm; 8.27 x 11.69 inches) and US letter paper size (21.59 x 27.94 cm; 8.5 x 11 inches), the following page size and margins will be used:

- Print window: 15.88 x 22.61 cm (6.25 x 8.9 inches)
- Top and bottom margins approximately:
  A4: 2.54 cm (1 inch);
  US: 2.85 cm (1.25 inches).
- Left and right margins approximately:
  A4: 3.56 cm (1.4 inches);
  US: 2.54 cm (1 inch).

A fixed space font (Courier New or SAS Monospace) with point size 9 will be used for all tables and listings. Under very limited circumstances, reducing the point size to 8 or 7.5 for a listing may be considered if the reduction is absolutely necessary to fit all columns on one page, and splitting the listing into two or more pages is not a viable option.

### 9.1.1 Title of a Table/Listing

The first line of the title will immediately follow the header line (i.e., no blank line in between). The title of a table/listing will be centered. The first letter of each imperative word will be capitalized. Up to 6 lines of the page are available to enter the title. (Note: There will be no blank title lines.)

The title will state the table/listing number, describe the table/listing briefly, and describe the population that is included in the table/listing, i.e.:

Line 1 of title: Table xx.x.
Line 2 of title: *Main title*
Line 3 of title (optional): *Subtitle*
Line 4 of title: *XXX* Population

If Line 3 is not utilized, then Line 4 will be moved up.

The table/listing numbering will be consecutive, with no skipping of numbers. Up to 5 levels of numbering (i.e., xx.x.x.x.x or xx.x.x.x.x) are allowed. If the same table/listing is produced for multiple analysis populations (e.g., ITT Population and restricted ITT Population) or data imputations (e.g., Observed Data and LOCF Data), the resulting multiple tables/listings should share the same table/listing number, except for the last level, which will be consecutively numbered 1, 2, 3,…, t where t is the total number of tables/listings generated (e.g., 4.2.1 for ITT Population and 4.2.2 for restricted ITT Population).

For numeric variables, the appropriate unit will be added to the column heading. For frequency tables, only those categories for which there is at least one subject represented in one or more groups should be included. Within data listings, subjects will be ordered by treatment, investigator number, subject number, randomization number, visit, visit date and time of collection (if available).

Verbose titles should be avoided. In the case where a title line is too wide for the page, then the title line will wrap on to the next line, and all subsequent lines will increment by one.

If there is stratification or subgrouping of the population (e.g., Sex) with summaries to be presented for each subgroup on a separate page, the subgrouping label on a page (e.g., Males) will appear, left-aligned with the body of the table/listing, on the line immediately below the last title line.

There will be a solid horizontal line across the page immediately below the last title line (or the subgroup label, if present), as wide as the body of the table/listing.

### 9.1.2 Footnotes to a Table/Listing

There will be a solid horizontal line across the page, as wide as the upper horizontal line, signifying the end of the body of the table/listing for that page. Footnotes are immediately below this horizontal line, with the exception of the documentation line, which appears on the bottom line of the page. Footnotes will be left-aligned with the body of the table/listing. If the footnote is a complete sentence, then the usual sentence construction will be followed. If the footnote is a single word or a phrase, then the first letter of the first word will be capitalized. Up to 9 lines of the page are available to enter footnotes.

For a table, the first footnote will name the listing(s) where the data used in the table came from, in the following format:

Source: Listing xx.x

Footnotes that apply to the table/listing in general will precede footnotes that apply to a specific item (e.g., title line, row label, column header, specific count, descriptive statistic, p-value, or data) on the table/listing. An example of a general footnote is as follows: "A subject who has the same TEAE more than once during the study was counted once in the total number of subjects per system organ class calculation." An example of an item-specific footnote is as follows: "*Significant at the 0.050 level".

The use of superscripting in footnotes is not recommended. If there is only one item-specific footnote on a table/listing, one of the symbols #, *, and @ will be used to tag the item, with a single blank space between the item and the symbol. In general, the asterisk will be reserved for tagging items related to the presentation of p-values. The footnote will begin with the symbol, followed by a single blank space, and then the footnote text, e.g.:

*# footnote text here*

If there are multiple item-specific footnotes on a table/listing, "(x)" will be used to tag each item, with the x's being either all numbers (1, 2, 3, etc.) or all letters (a, b, c, etc.), and with a single blank space between the item and the corresponding "(x)". The footnote will begin with the "(x)", followed by a single blank space, and then the footnote text, e.g.:

(x) *footnote text here*

The use of self-explanatory or commonly used abbreviations to tag an item for footnoting may supersede the conventions described in the two preceding paragraphs. Examples of commonly used abbreviations include the following: H=Above upper normal limit, W=Within

normal limits, and L=Below lower normal limit; ND=Not done; N/A=Not applicable; and NAV=Not available. Note that in these examples, the letters are not in parentheses and have the equal sign connecting the letters with the footnote text.

When a general footnote exceeds one line in length, the text will wrap on to the next line, with no indentation if there is only one general footnote (excluding the source footnote) and with two-space indentation if there are more than one general footnote. When an item-specific footnote exceeds one line in length, the lines after the first one will be left-aligned with the first line, minus the "(x)", e.g.:

(x) *first line of footnote text here*
*second line of footnote text here*

### 9.1.3 Header and Footer

Although not depicted on the shell outputs, every output will have the following Header:

```
Supernus Pharmaceuticals, Inc.                                    Page x of xx
Protocol No.: 812P201
```

and the following Footer:

```
Program:  Programname.sas  DDMMMYYYY HH:MM          Produced: DDMMMYYYY HH:MM
```

## 9.2 DATA FORMAT

Unless otherwise specified, the estimated mean and median for a set of values will be printed out to one more decimal place than the individual units of measurement, and the standard deviation and coefficient of variation will be printed out to one additional place further. P-values will be given with 3 decimals. P-values < .001 will be shown as "<0.001". All fractional numeric values will be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3 etc.). Unless otherwise specified, percentage values will be printed with one digit to the right of the decimal point (e.g., 52.3%, 8.9% etc.). Dates will be presented as YYYY/MM/DD and time values will be presented as HH:MM:SS or HH:MM in all listings.

## 9.3 CODING LISTS

The coding of the data is performed with the following coding lists:

| Data | Coding list |
|---|---|
| Adverse events | MedDRA |
| Medication names | WHO Drug Dictionary |

# 10. SUMMARY TABLES, DATA LISTINGS AND FIGURES (TLFS)

Shells of summary tables, data listings and figures are presented as separate documents in order to provide a framework for the display of data and results of statistical analyses for this study. These shells may change due to unforeseen circumstances.

## 11. REFERENCES

Supernus Pharmaceuticals, Inc. Protocol No. 812P201 (Amended: Version 2.0): A Phase I/IIa, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Safety, and Efficacy of SPN-812V in Adults with Attention Deficit Hyperactivity Disorder (ADHD). 30 June 2010.

Michelson D, Adler L, Spencer T, Reimherr FW, West SA, Allen AJ, Kelsey D, Wernicke J, Dietrich A and Milton D. Atomoxetine in Adults with ADHD : Two Randomized, Placebo-Controlled Studies. Biol Psychiatry. 2003 ; 53 :112-120.

## 12. FINAL VERSION REVISION HISTORY

| Version Number | Date of Revision | Author | Summary of Change(s) From Final Version 1.0 |
|---|---|---|---|
| Version 2.0 | 31Jan2011 | [redacted] | Section 4.2: Clarified that the treatment assigned will be used for the ITT and Restricted ITT populations, and the treatment received will be used for the Safety and PK populations.<br><br>Section 5.4: Re-specified that the auto regressive (1) covariance will be used in the MMRM analysis. |
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## 13. APPENDICES

### 13.1 APPENDIX I: DATA REVIEW MEETING MINUTES