SUPERNUS® PHARMACEUTICALS, INC.

STATISTICAL ANALYSIS PLAN

Protocol Number: 810P201

A Randomized, Multicenter, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Tolerability of SPN-810 in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) and Persistent Serious Conduct Problems

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SIGNATURE PAGE

Protocol No.:	810P201
Protocol Title:	A Randomized, Multicenter, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Tolerability of SPN-810 in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) and Persistent Serious Conduct Problems
Drug:	Molindone Hydrochloride

[redacted]

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical
AUC	area under the plasma concentration versus time curve
AUC_{ss}	area under the concentration-time curve at steady state
BAS	Barnes Akathisia Scale
BID	two times per day
BUN	blood urea nitrogen
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
CRO	Contract Research Organization
C_{ss} avg	average steady-state concentration
DBD	Disruptive Behavior Disorder
DSMB	Data Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Text Revision
ECG	electrocardiogram
EEG	electroencephalogram
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
IAF	Informed Assent Form
ICD-10	International Statistical Classification of Diseases and Health Related Problems 10th Revision
ICF	Informed Consent Form
IQ	intelligence quotient
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	intent to treat
IVRS	Interactive Voice Response System
KBIT-2	Kaufman Brief Intelligence Test, Second Edition
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-aged Children—Present and Lifetime Versions
LNH	Low, normal, high
MedDRA	Medical Dictionary for Regulatory Activities
NCBRF-TIQ	Nisonger Child Behavior Rating Form - Typical Intelligence Quotient
ODD	Oppositional Defiant Disorder
PK	pharmacokinetic

PK-PD	pharmacokinetic-pharmacodynamic
PO	orally
QHS	at bedtime
QTcF	QT corrected using Fridericia's method
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SM	study medication
SNAP-IV	Swanson, Nolan and Pelham Rating Scale-Revised
SOC	System Organ Class
SOP	Standard Operating Procedure
TDD	Total Daily Dose
TEAE	treatment-emergent adverse event
TEOSS	Treatment of Early Onset Schizophrenia Spectrum Disorders
TESS	Treatment-emergent signs and symptoms
TID	three times per day
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 and data listings 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 810P201 (Amendment 1), Version 2.0, 09-SEP-2008
- Case Report Forms, Version 1.0, 11-MAR-2008.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the safety and tolerability of four doses of SPN-810 in children with ADHD and persistent serious conduct problems.

2.2 SECONDARY OBJECTIVES

- To explore the relationship between SPN-810 plasma concentration exposure and safety and tolerability endpoints.

- To assess the effect of SPN-810 in reducing persistent serious conduct problems as measured by the conduct problem subscale of the Nisonger Child Behavior Rating Form -Typical Intelligence Quotient (NCBRF-TIQ) after 6 weeks of maintenance treatment.

3. DESIGN OF THE STUDY

3.1 STUDY DESIGN

This will be a randomized, multicenter, parallel group, dose-ranging safety and tolerability study in children with ADHD and persistent serious conduct problems. The target subjects are healthy male or female children aged 6 to 12 years, inclusive, with a diagnosis of ADHD with persistent serious conduct problems. To determine eligibility for the study, subjects will undergo an initial screening visit. Seventy-two subjects will be randomized in the study; assuming a 17% dropout rate, it is anticipated that 60 subjects will complete the study.

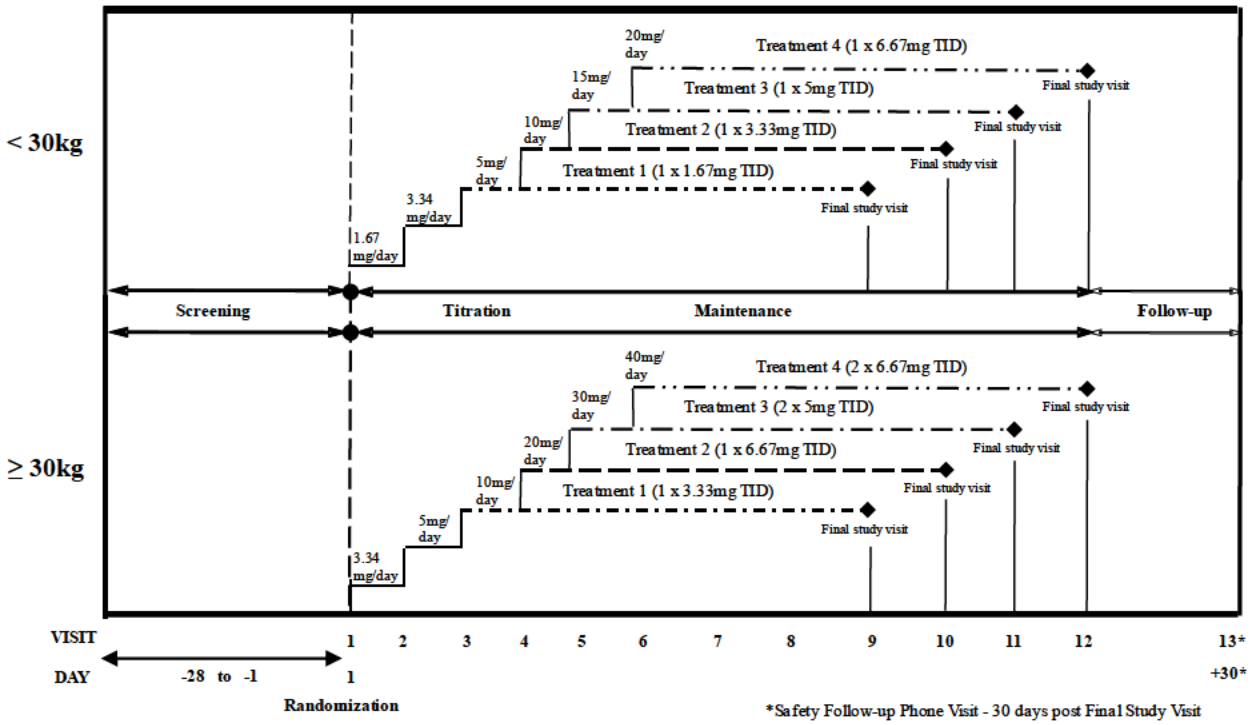
The study will consist of a Screening Period (within 28 days prior to the first dose administration), a Titration Period of 2 to 5 weeks, a Maintenance Period of 6 weeks, and a Safety Follow-up, which will be performed 30 days after the final study visit. The total subject duration in the study will be 16 to 19 weeks depending on the treatment group assignment. The total study duration is anticipated to be 15.5 months.

A total of 72 subjects will be randomized based on weight at baseline, to 1 of 4 treatment groups. A dose titration schedule will be followed (Table 1), where dosing for subjects < 30kg will be initiated at 1.67mg/day and dosing for subjects ≥ 30kg or more will be initiated at 3.34mg/day. The titration schedule will be followed until the target dose (Treatment 1, 2, 3, or 4) is reached. Subjects will remain at the target dose for 6 weeks.

Table 1. Dose Titration Schedules (mg/day)

Week	1	2	3	4	5	6
Treatment / Weight	Titration	Titration	Titration or Treatment 1	Titration or Treatment 2	Titration or Treatment 3	Treatment 4
< 30kg	1.67 (1.67mg qhs)	3.34 (1.67mg bid)	5 (1.67mg tid)	10 (3.33mg tid)	15 (5mg tid)	20 (6.67mg tid)
≥ 30kg	3.34 (1.67mg bid)	5 (1.67mg tid)	10 (3.33mg tid)	20 (6.67mg tid)	30 (10mg tid)	40 (13.33mg tid)

A study schematic is presented below.



Following 2 weeks of titration, subjects randomized to Treatment 1 in each weight group will receive Maintenance Treatment 1 (5mg/day for children < 30kg and 10mg/day for children ≥ 30kg), while the remaining subjects will receive the same level of drug as a titration step to the next level (Maintenance Treatment 2: 10mg/day and 20mg/day) and so on until the final subjects in each weight group reach the highest doses (20mg/day and 40mg/day).

Subjects will return to the clinic on a weekly basis for a total of 8 to 11 visits following randomization (2 to 5 weeks of titration and 6 weeks of maintenance treatment). Safety,

tolerability, and efficacy assessments will be performed at each visit. Blood and urine for clinical laboratory tests will be collected at Screening and at Weeks 2 and 6 of the Maintenance Period.

Blood will be drawn at trough for quantitative PK analysis at Weeks 2 and 3 of the Titration Period. At Week 2 of the Maintenance Period and the Final Visit, the subject's next maintenance dose of Study Medication (SM) will be administered in the clinic. The first PK draw will be a trough sample just prior to dosing. The dose will be administered, and a second draw will be performed between 1 and 3 hours post-dose.

Dose decreases will be permitted during the study for subjects randomized to Treatment 4 only, at the discretion of the Investigator in consultation with the Medical Monitor. Only 1 decrease to the next lowest dose (Treatment 3) will be permitted per subject. Benztropine will be permitted for the treatment of emerging extrapyramidal symptoms (EPS), at a starting dose of 0.5mg BID up to a range of 1 to 4mg/day.

3.1.1 Screening Period

A Screening Period will take place within 28 days prior to the first dose administration to determine subjects' eligibility to participate in the study. Prior to conducting any screening procedures, written informed consent/assent must be obtained from the parent or LAR, and subject (when required).

The NCBRF-TIQ will be administered to determine eligibility. The diagnosis of ADHD will be confirmed with the Schedule for Affective Disorders and Schizophrenia for School-aged Children—Present and Lifetime Versions (K-SADS-PL). The Introductory and Screen Interviews will be completed. The Screen Interview will determine which Supplements should be completed. Supplement 4 (Behavioral Disorders) must be completed to assess ADHD, ODD and CD. If an exclusionary diagnosis is confirmed, the remainder of the diagnostic will not be completed.

Other procedures to be performed will include the collection of medical history and demographic data, physical examination, collection of vital signs, height, and weight, electrocardiogram (ECG), blood collection for hematology and chemistry, urine collection for urinalysis, drug screen, and pregnancy test (for female subjects of menstruating age or $\geq$ 11 years old). The Kaufman Brief Intelligence Test, Second Edition (KBIT-2) should be administered if an IQ test has not been performed within the past 12 months prior to screening. Concomitant medication and AE information will be collected once informed consent/assent is obtained.

Unscheduled visits may be conducted at the discretion of the investigator throughout all study periods. The medical monitor should be notified promptly of any need for an unscheduled visit.

3.1.2 Titration Period

Subjects who meet the requirements for study participation will proceed to the Titration Period. Randomization will occur at the first Titration Period visit (Baseline). Subjects < 30kg will be assigned a 1.67mg/day dose (1 week) followed by a 3.34mg/day dose (1 week)

followed by maintenance dosing at 5mg/day or continued titration up to 10, 15 or 20mg/day. Subjects ≥ 30kg or more will be assigned a 3.34mg/day dose (1 week) followed by a 5mg/day dose (1 week) followed by maintenance dosing at 10mg/day or continued titration up to 20, 30, or 40mg/day.

Baseline safety (including Simpson-Angus Scale [SAS], Barnes Akathisia Scale [BAS], Abnormal Involuntary Movement Scale [AIMS]) and efficacy assessments (including NCBRF-TIQ, Clinical Global Impression [CGI] and Swanson, Nolan and Pelham Rating Scale - Revised [SNAP-IV]) will be performed. Inclusion/Exclusion criteria should be re-assessed at this visit. Concomitant medication and AE information will be collected.

After the first Titration Period visit, subjects will return to the study site weekly for dose increases, monitoring of AEs, and the administration of safety and efficacy scales. Procedures to be performed are collection of vital signs and weight, and PK blood sampling (at Weeks 2 and 3). Assessments of concomitant medications and drug compliance will be performed.

3.1.3 Maintenance Period

Following dose titration, subjects will be maintained at their designated dose level for 6 weeks. Subjects will return to the study site weekly for monitoring of AEs and the administration of efficacy and safety scales. Procedures to be performed are collection of vital signs and weight at each visit, and blood collection for hematology and chemistry and urine collection for urinalysis (Week 2 only). PK blood sampling will be performed at Week 2 with a first draw at trough drug levels prior to dosing, followed by observed dosing and a second draw 1 to 3 hours post-dose. Assessments of concomitant medications and drug compliance will be performed.

Subjects in the highest dose group (Treatment 4) will be permitted to down titrate once at the Investigator's discretion in consultation with the Medical Monitor. If this down-titration occurs outside a scheduled visit, the subject should be brought into the clinic for evaluation.

For all unscheduled visits, including those unrelated to down-titration, AEs should be documented and vital signs collected. Relevant safety scales should be completed at the discretion of the investigator.

3.1.4 Final Visit/Early Termination

Subjects will return to the study site for a final visit, after completing the 6-week Maintenance Period, or prior to early discontinuation. AEs will be monitored and safety and efficacy scales will be administered. The procedures to be performed will include physical examination, collection of vital signs, height, and weight, ECG, blood collection for hematology and chemistry, urine collection for urinalysis, drug screen, and pregnancy test (for female subjects of menstruating age or ≥ 11 years old). PK blood sampling will be performed, with a first draw at trough drug levels prior to dosing, followed by observed dosing and a second draw 1 to 3 hours post-dose. Assessments of concomitant medications and drug compliance will be performed.

3.1.5 Post-Study Follow-up Visit

The post-study Follow-up visit will consist of a phone call to each subject 30 days after the final visit. New non-serious AEs that started within 7 days after the subject's last dose will be collected. All new SAEs will be collected, and reported if the event is at least possibly related to SM. AEs or SAEs that are ongoing at the subject's last study visit must be followed until resolution or if, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

3.2 SAMPLE SIZE CONSIDERATION

Seventy-two subjects will be randomized in the study. Assuming a 17% dropout rate, it is anticipated that 60 subjects will complete 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.

A randomization scheme will be generated using a pseudo-random number generator in a computer program. The method avoids bias by use of a chance mechanism. Within each weight group, the randomization scheme assigns Treatment 1, Treatment 2, Treatment 3, or Treatment 4 to each randomization number in a 1:1:1:1 ratio.

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.

Once a randomization number has been assigned, no attempt should be made to use that number again, if, for example, a subject is withdrawn. All subjects are randomized only once.

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.

Exhibit: Schedule of Visits and Procedures

PERIOD	Screening	Titration					Maintenance						Final Visit[k]	Follow-up
VISIT	0	1	2	3[b]	4[c]	5[d]	6	7	8	9	10	11	12	13
WEEK	0	1	2	3[b]	4[c]	5[d]	1	2	3	4	5	6	7	
WINDOW (DAYS)	Within 28 days prior to dosing	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 3
Informed Consent/Assent[a]	X													
IVRS Call	X	X											X	
K-SADS-PL	X													
IQ Test (KBIT-2)[e]	X													
Inclusion/Exclusion Criteria	X	X												
Randomization		X												
Medical History	X													
Demographics	X													
Physical Examination	X												X	
ECG (12-lead)	X												X	
Vital Signs, height, and weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/chemistry	X							X					X	
Urinalysis	X							X					X	
PK Blood Sampling			X	X				X[i]					X[i]	
Urine Drug Screen	X												X	
Urine Pregnancy Test[g]	X												X	
Efficacy Scales (NCBRF-TIQ, CGI, SNAP-IV)	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Scales (Simpson-Angus, Barnes, AIMS)		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X[l]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Return and Compliance			X	X	X	X	X	X	X	X	X	X	X	
Drug Dispensation		X	X	X	X	X	X	X	X	X	X	X		

a Written consent must be obtained prior to performing any study-related procedure.
b For subjects receiving Treatments 2, 3 and 4 only.
c For subjects receiving Treatment 3 and 4 only.
d For subjects receiving Treatment 4 only.
e IQ test to be administered if not performed 12 months prior to screening.
f Heart rate (HR), blood pressure, temperature, respiratory rate, and weight will be measured weekly. Height will only be measured at Screening and Final Visit.
g To be performed for female subjects of menstruating age or ≥ 11 years old.
h Only NCBRF-TIQ will be performed at screening for purposes of assessing eligibility.
i First draw at trough, then the subject's next maintenance dose is observed in clinic between 1 and 3 hours prior to blood draw for second PK sample. PK sample not drawn at early termination if subject is discontinuing drug for safety or tolerability reasons.
j AEs and SAEs will be followed from the time that the subject signs the ICF.
k To be performed at the end of Maintenance Period or prior to early discontinuation.
l There will be a phone call to each subject 30 days after the final visit. New non-serious AEs that started within 7 days after the last dose will be collected. New SAEs will be collected, and reported if at least possibly related to SM. AEs or SAEs that are ongoing at the last study visit must be followed until resolution, stabilization, or assessed as chronic.

3.5 EFFICACY MEASURES

3.5.1 Primary Efficacy Variable

The NCBRF-TIQ Conduct Problem subscale score is the primary efficacy variable.

The ratings from the NCBRF-TIQ scale are grouped into a single 10-item Positive Social subscale and the following 6 Problem Behavior Subscales: *Overly Sensitive* (4 items), *Oppositional Behavior* (9 items), *Conduct Problem* (14 items), *Hyperactivity* (4 items), *Inattention* (7 items), and *Withdrawal/Dysphoria* (16 items).

Each subscale score is the sum of the scores for the individual items included in the subscale. The Oppositional Behavior and Conduct Problem subscale totals can be combined into a DBD-Total score, and the Hyperactivity and Inattention subscales can be combined into an ADHD-Total score.

3.5.2 Secondary Efficacy Variables

CGI-S, CGI-I, ADHD-Inattention, ADHD-Hyperactivity/Impulsivity, and ADHD-Combined Subscale scores are the 5 secondary efficacy variables as described below.

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. Severity of illness (CGI-S) and global improvement (CGI-I) are both rated on a scale of 0 to 7 with 7 being "extremely ill" or "very much worse", respectively. Successful therapy is indicated by a lower overall score in subsequent testing.

- CGI-S will be evaluated by the Investigator at each visit on a 7-point scale with 1=Normal, 2=Borderline ill, 3=Mildly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, and 7=Extremely ill. CGI-S is a secondary efficacy variable.
- 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. CGI-I is a secondary efficacy variable.

The SNAP-IV rating scale includes 18 ADHD and 8 oppositional defiant disorder (ODD) symptoms as specified in the DSM-IV-TR and International Statistical Classification of Diseases and Health Related Problems 10th Revision (ICD-10) Classification of Mental and Behavioral Disorders. The symptoms are scored by assigning a severity estimate for each symptom on a 4-point scale.

The ratings from the SNAP-IV scale are grouped into the following 3 subscales: ADHD-Inattention (items #1-9), ADHD-Hyperactivity/Impulsivity (items #10-18), and ODD (items #19-26). In addition, the first two subscales are combined to form the ADHD-Combined subscale. Each subscale score is the average of the scores for the individual items included in the subscale.

3.5.3 Exploratory Efficacy Variable

The ODD subscale score (items #19-26 from the SNAP-IV scale) is an exploratory efficacy variable.

NCBRF-TIQ subscale (*Overly Sensitive Oppositional*, *Hyperactivity*,*Inattention*, and *Withdrawal/Dysphoria)* scores are considered exploratory efficacy variables. Additional exploratory variables will be the DBD-Total score, and the ADHD-Total score from the NCBRF-TIQ.

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. Assessment of possible neurological side effects will be performed using the Simpson-Angus scale, Barnes Akathisia scale, and AIMS.

3.6.1 Adverse Events

For subjects who receive SM, all AEs (learned of through spontaneous reports or subject interview) will be collected starting from providing informed consent for study participation. Collection will continue through 7 days after the last dose of SM for non-serious AEs, and through the 30 day Follow-up Visit for SAEs. 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 below.

Hematology	Serum Chemistry (fasting)	Urinalysis
Hematocrit Hemoglobin Red blood cell count (RBC) Platelet count White blood cell count (WBC) (with differential)	Albumin Alkaline phosphatase Alanine transaminase (ALT) Aspartate transaminase (AST) Bilirubin- Total and Direct Blood urea nitrogen (BUN) Calcium Chloride Cholesterol- Total, HDL and LDL Creatinine Creatine phosphokinase (CPK) Glucose Inorganic phosphorous Potassium Sodium Total protein Triglycerides Uric acid	Ketones Protein Specific gravity Glucose pH
Other tests		
Insulin Prolactin Urine drug panel for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabinoids, methadone, opiates, phencyclidine, propoxyphene, and alcohol) Urine pregnancy test (for female subjects of menstruating age or ≥11 years old)		

3.6.3 Vital Signs, Height, and Weight Measurements

Vital sign measurements (HR, blood pressure, temperature, respiratory rate) and height and weight will be obtained at all visits as designated on the Schedule of Visits and Procedures. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. Pulse should not be recorded on Screening and Final Visits when ECGs are performed.

3.6.4 Medical History and Physical Examinations

Medical 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.

3.6.5 Electrocardiograms (ECGs)

ECGs (12-lead) will be obtained at the Screening visit and the Final Visit as designated on the Schedule of Visits and Procedures. 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.

All ECG tracings will be reviewed within 24 hours by the Investigator or sub-Investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid

measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

3.6.6 Concomitant Medications

For subjects who receive SM, concomitant medications and therapies that are ongoing as of the date of informed consent will be recorded on the Concomitant Medication CRFs. 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.

3.6.7 Other Special Tests for Extrapyramidal Symptoms (EPS)

Simpson-Angus Scale

The Simpson-Angus scale is a 10-item rating scale that is widely used for assessment of neuroleptic-induced Parkinsonism. It consists of 1 item measuring gait, 6 items measuring rigidity, and three items measuring glabella tap, tremor and salivation, respectively. This assessment will be administered at all post-screening study visits.

Barnes Akathisia Scale

The Barnes Akathisia scale is a rating scale for drug-induced akathisia and includes components for rating the observable, restless movements characteristic of akathisia, the awareness of restlessness, and any distress associated with the condition. This assessment will be administered at all post-screening study visits.

Abnormal Involuntary Movement Scale (AIMS)

The AIMS test is a rating scale used to measure tardive dyskinesia. There are 12 items that rate involuntary movements of various areas of the subject's body. This assessment will be administered at all post-screening study visits.

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.

When an event such as a family emergency, a transient illness (such as a cold) unrelated to SM, or a remediable act of non-compliance prevents a subject from participating in a scheduled visit, but the subject wishes to continue in the study, the Investigator will attempt

to reschedule the visit and retain the subject in the study on a case by case basis, rather than discontinue the subject's participation.

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. Within each treatment group, summaries will also be presented by weight category at baseline (< 30kg, ≥ 30kg), where appropriate. All subjects randomized to Treatment 4, whether they are maintained on Treatment 4 or reduced to Treatment 3, will be analyzed under the Treatment 4 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 CRF 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 but not summarized.

4.1 ANALYSIS POPULATIONS

The enrolled population consists of all subjects with ICFs signed by their parent or LAR (and IAFs signed by the subjects, where applicable).

The safety population consists of all randomized subjects who receive at least 1 dose of SM.

The intent-to-treat (ITT) population consists of all safety population subjects with at least 1 post-baseline efficacy assessment.

The restricted ITT population consists of all ITT population subjects with at least 1 efficacy assessment during the Maintenance Period.

The PK population consists of safety population subjects with at least 1 PK measurement.

The safety, ITT, restricted ITT, and PK populations are based on actual treatment received. Table 4.1.1 provides these analysis populations for all randomized subjects.

Listing 4.1.1 provides inclusion and exclusion criteria violations for all randomized subjects. Listing 4.1.2 gives analysis populations.

4.2 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 4.2.1 provides the subject disposition for all randomized subjects.

Listing 4.2.1 provides subject disposition for all randomized subjects.

4.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics data will be summarized by treatment group.

Demographic/baseline variables include sex, race, ethnicity, age, baseline height, baseline weight, and medical history. Tables 4.3.1, 4.3.2, and 4.3.3 will provide tabular summaries of the demographic and baseline variables for the safety, ITT, and restricted ITT populations, except for medical history, which will be summarized for the safety population only (Table 4.3.4).

Listing 4.3.1 provides sex, race, ethnicity, age, baseline height, baseline weight for all randomized subjects. Listing 4.3.2 provides medical history for all randomized subjects.

4.4 TREATMENT COMPLIANCE AND EXPOSURE

Records of SM and doses administered will be kept during the study. The Clinical Research Associates (CRAs) will review drug accountability during investigational site visits and at the completion of the study.

Duration of treatment exposure to SM will be summarized by treatment group for the safety population using descriptive statistics. Summaries of exposure will be provided separately for the Titration Period, Maintenance Period, and combined Titration and Maintenance Periods (Table 4.4.1).

For subjects randomized to Treatment 4, the number and percentage of subjects maintained on the target dose versus those reduced in dose (to Treatment 3 level) during the Maintenance Period will be provided (Table 4.4.2).

4.5 POTENTIAL EXCLUSIONS FROM ITT POPULATION

Study data will be examined during the Data Review (described below in section 4.6) 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.

4.6 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;
- Pooling of centers;
- 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 4.1.2 as appendix. The data review will be included in Appendix 13.1.

5. EFFICACY ANALYSES

5.1 GENERAL CONSIDERATIONS AND STATISTICAL/ANALYTICAL ISSUES

5.1.1 Definition of Baseline

Unless stated otherwise, the first Titration Period visit will be considered as Baseline for statistical analyses. For calculation of changes from baseline, the last available measurement/assessment before the first study drug application will be used as Baseline measure.

5.1.2 Treatment Comparisons

Statistical testing to compare treatment groups (overall and pairwise) will be performed for the ITT population only using appropriate statistical methods, as described in the efficacy subsections below. Dose-response relationship will be assessed based on a review of the results of the complete set of pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4, without adjustment for

multiple testing. 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 Adjustments for Covariates

Appropriate analysis of covariance (ANCOVA) will be conducted with treatment and weight group as the main factors and the baseline value as the covariate.

5.1.5 Multiple Comparisons/Multiplicity

Pairwise comparisons (Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) will be performed but without adjustment for multiple comparisons.

5.1.6 Examination of Subgroups

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

- Gender
- Race
- Weight

for the ITT population. Subgroup analysis will comprise of summary statistics only, i.e. there will be no statistical testing.

5.1.7 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.

5.2 PRIMARY EFFICACY ANALYSIS

5.2.1 Analysis of NCBRF-TIQ Conduct Problem Subscale

The NCBRF-TIQ Conduct Problem subscale score is the primary efficacy variable. To assess the effect of SPN-810 in reducing persistent serious conduct problems as measured by the conduct problem subscale of the NCBRF-TIQ after 6 weeks of maintenance treatment, the following primary efficacy analysis (Section 5.2.2) will be conducted.

5.2.2 Results of Primary Efficacy Analysis

The changes from baseline in the NCBRF-TIQ conduct problem subscale scores at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4 (Hollander M, 1999). Table 5.2.2.1 provides the primary efficacy results for overall and pairwise comparisons for NCBRF-TIQ conduct problem subscale for the ITT population. Table 5.2.2.2 provides the summary statistics for NCBEF-TIQ conduct problem subscale for the restricted ITT population.

Listing 5.2.2.1 provides NCBRF-TIQ conduct problem subscale 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 endpoints are as follows.

5.3.1 Severity of Illness (CGI-S)

The changes from baseline in the CGI-S at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.3.1.1 provides secondary efficacy results for overall and pairwise comparisons for CGI-S for the ITT population. Table 5.3.1.2 provides summary statistics for CGI-S for restricted ITT population.

Listing 5.3.1.1 provides CGI-S data for the ITT population.

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 Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.3.2.1 provides secondary efficacy results for overall and pairwise comparisons for CGI-I for the ITT population. Table 5.3.2.2 provides summary statistics for CGI-I for the restricted ITT population.

Listing 5.3.1.1 provides CGI-I data for the ITT population.

5.3.3 SNAP-IV Subscale: ADHD-Inattention

The changes from baseline in the ADHD-Inattention ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.3.3.1 provides secondary efficacy results for overall and pairwise comparisons for ADHD-Inattention for the ITT population. Table 5.3.3.2 provides summary statistics for ADHD-Inattention for the restricted ITT population.

Listing 5.3.3.1 provides ADHD-Inattention data for the ITT population.

5.3.4 SNAP-IV Subscale: ADHD-Hyperactivity/Impulsivity

The changes from baseline in the ADHD-Hyperactivity/Impulsivity ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.3.4.1 provides secondary efficacy results for overall and pairwise comparisons for ADHD-Hyperactivity/Impulsivity for the ITT population. Table 5.3.4.2 provides summary statistics for ADHD- Hyperactivity/Impulsivity for the restricted ITT population.

Listing 5.3.4.1 provides ADHD- Hyperactivity/Impulsivity data for the ITT population.

5.3.5 SNAP-IV Subscale: ADHD-Combined Scale

The changes from baseline in the ADHD-Combined Scale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.3.5.1 provides secondary efficacy results for overall and pairwise comparisons for ADHD-Combined Scale for the ITT population. Table 5.3.5.2 provides summary statistics for ADHD-Combined Scale for the restricted ITT population.

Listing 5.3.5.1 provides ADHD-Combined Scale data for the ITT population.

5.4 EXPLORATORY ANALYSES

5.4.1 SNAP-IV: ODD Subscale

The changes from baseline in the ODD subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.1.1 provides exploratory analysis results for overall and pairwise comparisons for ODD subscale for the ITT population. Table 5.4.1.2 provides summary statistics for ODD subscale for the restricted ITT population.

Listing 5.4.1.1 provides ODD subscale data for the ITT population.

5.4.2 The NCBRF-TIQ Subscales

5.4.2.1 NCBRF-TIQ: Positive Social Subscale

The changes from baseline in the positive social subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.1.1 provides exploratory analysis results for overall and pairwise comparisons for positive social subscale for the ITT population. Table 5.4.2.1.2 provides summary statistics for positive social subscale for the restricted ITT population.

Listing 5.4.2.1.1 provides positive social subscale data for the ITT population.

5.4.2.2 NCBRF-TIQ: Overly Sensitive Subscale

The changes from baseline in the overly sensitive subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.2.1 provides exploratory analysis results for overall and pairwise comparisons for overly sensitive subscale for the ITT population. Table 5.4.2.2.2 provides summary statistics for overly sensitive subscale for the restricted ITT population.

Listing 5.4.2.2.1 provides overly sensitive subscale data for the ITT population.

5.4.2.3 NCBRF-TIQ: Oppositional Behavior Subscale

The changes from baseline in the oppositional behavior subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.3.1 provides exploratory analysis results for overall and pairwise comparisons for oppositional behavior subscale for the ITT population. Table 5.4.2.3.2 provides summary statistics for oppositional behavior subscale for the restricted ITT population.

Listing 5.4.2.3.1 provides oppositional behavior subscale data for the ITT population.

5.4.2.4 NCBRF-TIQ: Hyperactivity Subscale

The changes from baseline in the hyperactivity subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.4.1 provides exploratory analysis results for overall and pairwise comparisons for hyperactivity subscale for the ITT population. Table 5.4.2.4.2 provides summary statistics for hyperactivity subscale for the restricted ITT population.

Listing 5.4.2.4.1 provides hyperactivity subscale data for the ITT population.

5.4.2.5 NCBRF-TIQ: Inattention Subscale

The changes from baseline in the inattention subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.5.1 provides exploratory analysis results for overall and pairwise comparisons for inattention subscale for the ITT population. Table 5.4.2.5.2 provides summary statistics for inattention subscale for the restricted ITT population.

Listing 5.4.2.5.1 provides inattention subscale data for the ITT population.

5.4.2.6 NCBRF-TIQ: Withdrawal/Dysphoria Subscale

The changes from baseline in the withdrawal/dysphoria subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons

of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.6.1 provides exploratory analysis results for overall and pairwise comparisons for withdrawal/dysphoria subscale for the ITT population. Table 5.4.2.6.2 provides summary statistics for withdrawal/dysphoria subscale for the restricted ITT population.

Listing 5.4.2.6.1 provides withdrawal/dysphoria subscale data for the ITT population.

5.4.2.7 NCBRF-TIQ: Disruptive Behavior Disorder (DBD) Subscale

The changes from baseline in the DBD subscale ratings at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.7.1 provides exploratory analysis results for overall and pairwise comparisons for DBD subscale for the ITT population. Table 5.4.2.7.2 provides summary statistics for DBD subscale for the restricted ITT population.

Listing 5.4.2.7.1 provides DBD subscale data for the ITT population.

5.4.2.8 NCBRF-TIQ: ADHD-Total Score

The changes from baseline in the ADHD-Total Score at each post-baseline visit and endpoint will be compared among treatment groups using Kruskal-Wallis test (for the overall comparisons) and Wilcoxon rank-sum test (for the pairwise comparisons of Treatment 1 vs. Treatment 2, Treatment 2 vs. Treatment 3, and Treatment 3 vs. Treatment 4) for the ITT population. The Hodges-Lehmann estimators and associated 95% confidence intervals will be calculated for the median differences between Treatment 1 and Treatment 2, Treatment 2 and Treatment 3, and Treatment 3 and Treatment 4. Table 5.4.2.8.1 provides exploratory analysis results for overall and pairwise comparisons for ADHD-Total Score for the ITT population. Table 5.4.2.8.2 provides summary statistics for ADHD-Total Score for the restricted ITT population.

Listing 5.4.2.8.1 provides ADHD-Total Score data for the ITT population.

5.5 SENSITIVITY ANALYSIS

As a sensitivity analysis, the changes from baseline in the NCBRF-TIQ conduct problem subscale scores at each post-baseline visit and endpoint will be compared among treatment groups using analysis of covariance (ANCOVA) with treatment and weight group as the main factors and the baseline value as the covariate. Table 5.5.1 provides the sensitivity analysis results for NCBRF-TIQ conduct problem subscale for the ITT population.

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), as well as by the Simpson-Angus scale, the Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (AIMS).

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 6.1.1).

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.

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 6.1.1.1 will provide overall incidence of AEs for the Safety population. Table 6.1.1.2 will provide an incidence summary of AEs by System Organ Class, and Preferred Term for the Safety population.

Table 6.1.1.3 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 6.1.1.4 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 (6.1.1.1 - 6.1.1.4) will be presented for the demographic/baseline variables listed below:

Sex – Tables 6.1.2.1 - 6.1.2.4
Race – Tables 6.1.2.5 - 6.1.2.8
Ethnicity – Tables 6.1.2.9 - 6.1.2.12
Weight (<30kg and ≥ 30kg) – Tables 6.1.2.13 - 6.1.2.16.

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 6.1.3.1 through 6.1.3.5).

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, Chemistry, and Urinalysis tests. Tables 6.2.1 through 6.2.4 will provide summaries for Hematology and Chemistry respectively and associated shift tables. Listings 6.2.1 through 6.2.4 will provide by-patient listing for hematology, chemistry, urinalysis, 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 6.3.1 provides the summary table for vital signs, heights, weights and BMI.

Individual listings will also be provided for these parameters (Listing 6.3.1).

6.4 ECG RESULTS

Table 6.4.1 provides overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant). Table 6.4.2 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 6.4.3 presents the ECG Shift Table from Baseline to Post-Baseline Visits for qualitative ECG parameters.

Table 6.4.4 provides the number and percentage of subjects with any QTcF value >= 450 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 of >= 30 – 59 msec as well as >= 60 msec over all assessments made during the study as well as by visit and treatment group.

Listing 6.4.1 provides ECG Findings.

6.5 PHYSICAL EXAMINATION

Findings from the physical examinations will be summarized through 2 by 2 shift tables that, for each system or area examined, compare the normal/abnormal finding at screening to the normal/abnormal finding at the Final Visit. Table 6.5.1 gives the results of physical examination.

Listing 6.5.1 provides physical examination findings.

6.6 CONCOMITANT MEDICATIONS

A table (Table 6.6.1) summarizing frequencies of current use of concomitant medications will be presented for the safety population and its treatment group subsets.

Listing 6.6.1 provides the details of concomitant medications, and will summarize medications by WHO ATC and include information on dosage, route of administration, frequency, dates, and indication.

6.7 OTHER SAFETY ANALYSES FOR EXTRAPYRAMIDAL SYMPTOMS (EPS)

6.7.1 Simpson-Angus Scale (SAS)

Listing 6.7.1.1 provides subject-wise SAS scores for each visit. The occurrence of neurological side effects will be assessed by looking at the changes in scores from baseline to post-baseline visits.

For each item on the SAS scale, the number (and percentage) of subjects with a worse score at any post-baseline visit, compared to baseline, will be presented in Table 6.7.1.1.

6.7.2 Barnes Akathisia Scale (BAS)

Listing 6.7.2.1 provides subject-wise BAS scores for each visit. The occurrence of neurological side effects will be assessed by looking at the changes in scores from baseline to post-baseline visits.

For each item on the BAS scale, the number (and percentage) of subjects with a worse score at any post-baseline visit, compared to baseline, will be presented in Table 6.7.2.1.

6.7.3 Abnormal Involuntary Movement Scale (AIMS)

Listing 6.7.3.1 provides subject-wise AIMS scores for each visit. The occurrence of neurological side effects will be assessed by looking at the changes in scores from baseline to post-baseline visits.

For each item on the AIMS scale, the number (and percentage) of subjects with a worse score at any post-baseline visit, compared to baseline, will be presented in Table 6.7.3.1.

7. DATA SAFETY MONITORING BOARD (DSMB)

A Data Safety Monitoring Board (DSMB) will monitor the conduct and safety of the study on a quarterly basis. Appendix 13.2 and 13.3 respectively contain the DSMB reports for the two meetings.

8. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Describe any changes to statistical methods section in the protocol before database lock. Provide the reasons for the changes. Some changes may require an amendment to 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.

8. PROGRAMMING SPECIFICATIONS

All summary tables, data listings, figures and other statistical output will be produced with the SAS system (version 9.2) 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.

8.1 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 (1.12 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.

8.1.1 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, weight category at baseline, center number, subject number, visit, 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.

8.1.2 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 TESS 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

8.1.3 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.: 810P201
```

and the following Footer:

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

8.2 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 displayed using the ISO 8601 format as required for Clinical Data Interchange Standards Consortium (CDISC) standards. Dates will be presented as DDMMMYYYY and time values will be presented as HH:MM:SS or HH:MM.

8.3 CODING LISTS

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

Data	Coding list / Version
Adverse events	MedDRA / Version 11.1
Medication names	WHO Drug Dictionary/ December 2008

9. SUMMARY TABLES, DATA LISTINGS AND FIGURES (TLFS)

Shells of summary tables and data listings 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. There are no shells for figures.

10. REFERENCES

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11. FINAL VERSION REVISION HISTORY

Date of Revision	Author	Summary of Change(s) From Final Version 1.0

12. APPENDICES

12.1 APPENDIX I: DATA REVIEW MEETING MINUTES

12.2 APPENDIX II: REPORT TO THE FIRST MEETING OF THE DSMB

12.3 APPENDIX III: REPORT TO THE SECOND MEETING OF THE DSMB