STATISTICAL ANALYSIS PLAN

Protocol Title	Exploratory Neuroimaging Study to Evaluate the Effect on Brain Activity of SPN-810 for Impulsive Aggression (IA) in Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment
Protocol Number	810P204
Protocol Version	V3.0
Protocol Date:	12 Apr 2019
Investigational Medicinal Product:	Molindone Hydrochloride Extended-Release Tablets (SPN-810)
Indication:	Treatment of Impulsive Aggression (IA) in subjects with Attention-Deficit/Hyperactivity Disorder (ADHD) in conjunction with standard ADHD treatment
Study Phase	2
IND Number	106,515
Sponsor	Supernus Pharmaceuticals, Inc. [redacted]
SAP Version	1.0
Date	10 Mar 2020

SIGNATURE PA

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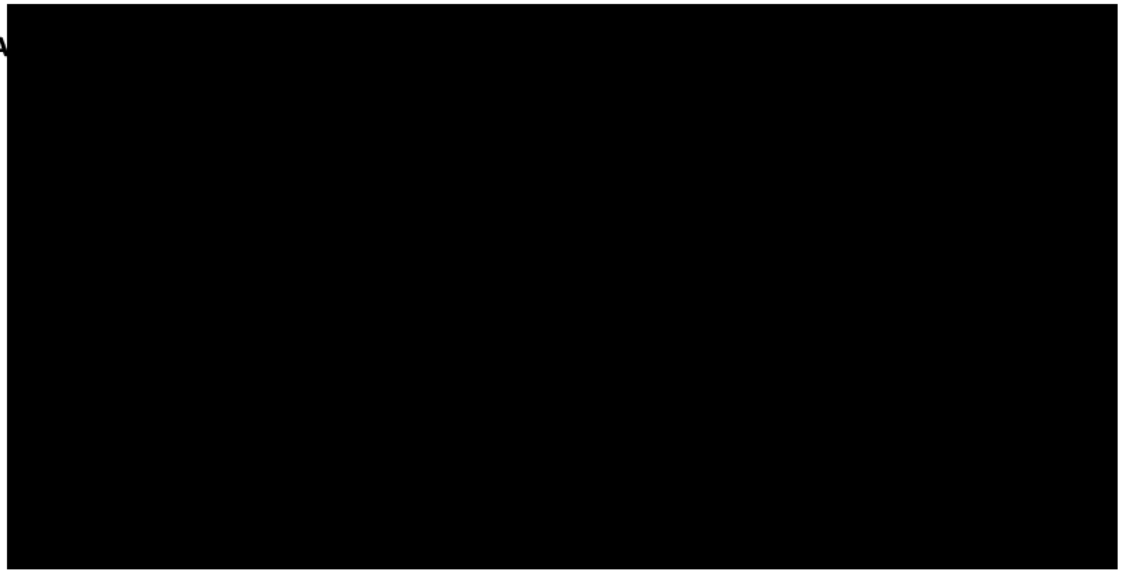
Approved by



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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of the data. This SAP covers the planned analyses of all data collected on the eCRFs, and will identify handling of data issues. The statistical analysis plan presented in this document will supersede the statistical analysis methods described in the clinical protocol. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report. This SAP is based on the clinical study protocol 810P204, version 3.0, dated 12 Apr 2019 and its associated electronic case report forms (eCRF).

2 STUDY OBJECTIVES

The primary objective is to evaluate the effect of SPN-810 treatment on brain activity in subjects aged 8-12 years with ADHD and IA using functional Magnetic Resonance Imaging (fMRI).

Secondary objectives are to evaluate the effect of SPN-810 treatment on:

- The functional connectivity between brain regions using resting-state fMRI (rs-fMRI)
- The concentration of neurotransmitters glutamate and gamma-aminobutyric acid (GABA) using Magnetic Resonance Spectroscopy (MRS)
- Safety of SPN-810

Tertiary objectives are to evaluate the following:

- Pharmacokinetics (PK) of Molindone
- Effect of SPN-810 treatment on the Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I) scores
- Effect of SPN-810 on the Retrospective-Modified Overt Aggression Scale (R-MOAS) score.

3 ENDPOINTS

Primary Endpoint is the change in the whole brain in BOLD fMRI contrast in response to the PSAP task from Baseline (Visit 2) to Visit 5.

Secondary Endpoints are:

- Change in functional connectivity as reflected in the Fisher's Z-transformation of correlation coefficients between brain regions during rs-fMRI from Baseline (Visit 2) to Visit 5.
- Change in the concentrations of neurotransmitters GABA and glutamate in the anterior cingulate cortex (ACC) from Baseline (Visit 2) to Visit 5 as determined by MR spectroscopy.
- Safety endpoints:
    1) Adverse events.
    2) Safety scales (Simpson-Angus Scale, Barnes Akathisia Rating Scale [BARS], and Abnormal Involuntary Movement Scale [AIMS]).
    3) Clinical laboratory tests (hematology, chemistry, and urinalysis).

4) Vital signs.
5) Electrocardiograms (ECGs).
6) Columbia-Suicide Severity Rating Scale (C-SSRS).

[redacted]

4 STUDY DESIGN

This is a multi-center, double-blind, randomized (1:1), placebo-controlled, parallel-group, 2-arm study.

The study will screen approximately 40 male and female subjects, aged 8-12 years inclusive, with ADHD and IA, to achieve an approximate enrollment of 30 subjects.

This study consists of 3 phases: Pre-Treatment, Treatment, and Conversion/Taper.

The Pre-Treatment Phase comprises of Screening and a Baseline MRI Visit for a total duration of up to 30 days. Following Screening (Visit 1), eligible subjects will proceed to the Baseline MRI visit (Visit 2) at the Imaging Center, where the brain MRI scans will be performed. At Visit 3, eligible subjects will be randomized to study medication or placebo.

Eligible subjects will follow a dose-titration schedule with initial dosing at [redacted] approximately every 2 days until the target dose (36 mg/day) is reached. The final dose will be maintained for 2 weeks (Maintenance period) during which time subjects will return for PK sampling (Visit 4) prior to receiving the final MRI scan at the Imaging Center (Visit 5). At the intervening visit during the maintenance phase (Visit 4), subjects will be given the option to taper down/discontinue study medication or convert to an ongoing OLE study (810P304) upon completion of the current study and will receive the blinded taper or the conversion study medication kit. Subjects will return to the study site for a final EOS visit (Visit 6), after completing the 1-week Taper or Conversion phases. Subjects who choose to convert into the ongoing OLE (SPN-810 304) will enter the study at a dose of 18 mg/day SPN-810.

This study is designed to use fMRI in conjunction with the PSAP aggression task. MR imaging parameters for the PSAP Task were optimized in the non-interventional 810P204a study that was conducted by the Sponsor in typically developing children 8-12 years of age.

5 ANALYSIS VARIABLES

5.1 *Primary Variables*

The primary analysis variable will be the treatment effect of SPN-810 on the change in BOLD fMRI contrast associated with the aggressive response from Baseline (Visit 2) to Visit 5 measured in subjects with ADHD and IA participating in the PSAP aggression Task.

Briefly, the primary endpoint is the change in brain activity measured by a change in BOLD response in brain regions during provocation or during the aggressive response relative to the monetary response at baseline and following 4 weeks treatment with SPN-810, compared to placebo.

Behavioral data may allow calculation of the aggressive score, defined as the number of Option 2 presses (aggressive response) divided by the total number of button presses and the number of provocations received.

5.2 ***Secondary Variables***

5.2.1 *Functional Connectivity*

Resting-state data will be used to generate maps of functional connectivity within brain networks and/or ROI and will be stored in a correlation matrix. To investigate brain networks, a seed to whole brain correlation map may be used to investigate changes in network connectivity. All correlation coefficients will be converted to a z-score using Fisher's Z-transformation to normalize values.

To look at connectivity between ROIs, seed to seed correlation values will be calculated. All correlation coefficients will be converted to a z-score using Fisher's Z-transformation to normalize values. In addition, the relevant variables for the correlation matrices will be calculated by Northwestern University.

5.2.2 *GABA and Glutamate Brain Concentrations*

The concentrations of neurotransmitters Glu and GABA will be achieved during the MRS scan and evaluated in the anterior cingulate cortex (ACC).

5.3 ***Safety Variables***

Safety assessments will focused on adverse event (AE) occurrences (including its severity, relationship to study drug, SAE (Yes/No), and, action taken, and outcome), laboratory tests (e.g. Hematology, Chemistry, Urinalysis, urine drug test, and urine pregnancy test), vital signs, height/weight measurements, medical history, physical examinations, ECGs and special safety tests including Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involunt***a***ry Movement Scale (AIMS), and Columbia-Suicide Severity Rating Scale (C-SSRS).

5.4 ***Tertiary Variables***

The tertiary variables include the following:

1) The pharmacokinetic variables of interest will include (1) Apparent clearance (CL/F); (2) Apparent volume of distribution (V/F) of Molindone in the study population.

2) Clinical Global Impression scales [Severity of illness (CGI-S) and global improvement (CGI-I)] will be evaluated. Both scales will be rated on a scale of 1 to 7 with 7 being "extremely ill" (CGI-S) or "very much worse" (CGI-I) respectively. They will be administered at Visit 1 (CGI-S only), Visit 4 and 6.

3) Retrospective-Modified Overt Aggression Scale (R-MOAS) was developed to gauge the severity of aggressive behavior (Blader et al., 2009). Parents rate the frequency over the past week of 16 aggressive behaviors in 4 areas: verbal aggression; physical aggression toward others; aggression toward oneself; and destruction or hostile misuse of property. Numeric weighting amplifies the seriousness of more harmful behaviors in the total score. The R-MOAS will be administered at Visit 1, Visit 4, and Visit 6.

5.5 *Other Special Tests*

Other special tests will be administered in the clinic as per Schedule of Events in the protocol. They are MINI-KID, Vitiello Aggression Scale, and Edinburgh Handedness Inventory.

6 STATISTICAL METHODS

6.1 *General Notions*

The primary and secondary endpoint data (Section 7.4 and 7.5) were handled and analyzed by Todd Parrish, Ph.D., Department of Radiology, Northwestern University, Chicago, IL 60611. All other data were analyzed at Supernus using SAS version 9.

Tabular summaries of the data collected during the study will provide a general description of the subjects studied and an overview on brain functioning, GABA and Glu levels, and safety results by study treatment group. Due to early termination of the study, all statistical analyses will be descriptive without any hypothesis testing. Continuous variables will be summarized using descriptive statistics [number of subjects, mean, standard deviation (SD), median, and minimum and maximum]. Categorical (nominal) variables will be summarized by reporting the frequency and percentage of subjects in each category.

In addition, subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, will be provided. Analysis processing will be performed before the database is released. Any deviation from the statistical plan will be documented and described in the final report.

6.2 *Handling of Dropout or Missing Data*

No imputation will be implemented.

7 STATISTICAL ANALYSIS

7.1 *Analysis Populations*

The population of "all enrolled subjects" consists of all those screened subjects who meet the requirements for study participation and have completed the imaging procedures prior to randomization. The following populations will be analyzed:

Randomized Population: The population of "all randomized subjects" consists of all those enrolled subjects who complete the Baseline Period including imaging scans, meet the inclusion/exclusion criteria and are randomized.

Safety Population: includes all subjects randomized and who received at least 1 dose of study drug.

Completed Population: includes all subjects randomized, who have baseline imaging scans (including the anatomical scan) and post-treatment imaging scans.

PK population: includes all subjects in the safety population who had at least 1 PK sample drawn which had a quantifiable concentration of Molindone.

7.2 *Disposition, Demographic and Baseline Characteristics, Protocol Deviations*

Subject disposition, reason for discontinuation from the study (randomized population), demographic characteristics (completed population), major protocol deviations during the study (completed population), medical history (safety population), and concomitant medications (safety population) will be reported in the summary tables. The prior and concomitant medications will be coded using WHO

Drug Dictionary (WHODD, March 1 2019 B3 format) for PT and Anatomical Therapeutic Chemistry classification.

7.3 *Study Medication Exposure and Compliance*

Duration of treatment exposure is defined as the total number of days a subject is exposed to study treatment. This will be calculated for each subject by taking the difference between the date of last dose *minus* the date of the first dose *plus* 1 (date of last dose – date of first dose +1). Duration of treatment exposure will be summarized using descriptive statistics.

Percent of study medication (SM) compliance will be calculated as:

$$SM\ Compliance\ (\%) = 100 * (D - R)/[4 * (\mathrm{D}_L - \mathrm{D}_F + 1)]$$

Where D=number of tablets dispensed, R=number of tablets returned,

D_L=date of last dose, and D_F=date of first dose

The SM compliance will be summarized as both categorical variable (<80%, 80-120%, and >120%) and a continuous variable using descriptive statistics.

Summaries of treatment exposure and compliance will be presented separately for the Titration period only, Maintenance period only, and Titration and Maintenance Combined.

7.4 *Primary Endpoint Analysis*

The primary endpoint will be analyzed by assessing the difference in the change of BOLD fMRI contrast related to the aggressive response in the PSAP Task from baseline (Visit 2) to the end of treatment (Visit 5) in each treatment group. The completed population will be used for the primary endpoint analyses.

7.4.1 *Imaging Analysis*

All functional imaging data will be analyzed using statistical parametric mapping software SPM12 package (Wellcome Trust Centre for Neuroimaging, Institute of Neurology; London, UK), Analysis of Functional Neuroimages (AFNI, NIH, USA) and software developed in-house at Dr. Parrish's lab, by Dr. Lana Kaiser, and at Supernus. Additional software that may be used includes FSL (Oxford, Cambridge, UK), Freesurfer (MGH, USA), and Matlab (MathWorks, USA). While performing the PSAP Task, neuronal activation is anticipated in the ACC, ventromedial PFC, amygdala, insular regions, and ventral striatum including nucleus accumbens, etc. Therefore these ROIs will be emphasized on the imaging analysis.

7.4.1.1 PSAP Task

For the PSAP Task data, the analyses will be mainly descriptive and will be assessed as the change in BOLD fMRI contrast associated with the aggressive response at baseline and post-treatment. The primary endpoint may be analyzed (depending on the data availability) by assessing the mean, SD, median, minimum and maximum of the BOLD signal change related to aggression for each treatment group (SPN-810 36 mg group and placebo) and study visit (baseline and Visit 5).

7.5 *Secondary Endpoint Analyses*

The secondary endpoint analyses will be based on the completed population.

7.5.1 *Functional Connectivity (Resting State fMRI)*

The secondary endpoints for functional connectivity will be the actual z-score, converted from the Fisher's Z-transformation of correlation coefficients, acquired during the rs-fMRI at Baseline (Visit 2) and Visit 5.

The analyses of the resting state data will be exploratory and informative of the connectivity between ROIs of the aggression network. Correlation matrices representing functional connectivity in the aggression network for each resting state scan will be generated at Visit 2 (baseline) and at Visit 5. The correlation values will be converted to a z-score (Fisher's Z-transformation). The descriptive analyses will be performed to assess the z-scores by treatment group (SPN-810 36 mg group and placebo) and visit (baseline and Visit 5).

7.5.2 *GABA and Glutamate Concentrations*

The concentrations of GABA and Glu in the ACC will be obtained during MRS acquisition. The descriptive analyses will be used to examine the concentrations of GABA and Glu by treatment group and visit (pre-treatment at Visit 2 fMRI scan and post-treatment at Visit 5). The change from baseline (Visit 5 – Visit 2) in concentration of GABA and Glu will also be assessed for each treatment group.

7.6 ***Safety Analysis***

Evaluation of safety will be performed for the safety population. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and findings from the physical examinations. The occurrence of neurological side effects will be assessed by looking at any worsening in scores from Visit 1 to the end of the study visit for each of the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and AIMS. Suicidal ideation and suicidal behavior will be measured by the C-SSRS.

All summary tables related to safety analyses will use the safety population.

7.6.1 *Adverse Events*

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA V22.0). AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each group of doses. Similarly, treatment-emergent AEs will be summarized by severity and relationship separately. Verbatim description and all MedDRA level terms, including the lower-level terms, for all AEs will be contained in the subject data listings.

All AEs occurring throughout the study period will be recorded. Treatment-emergent AEs (TEAEs) will be collected starting after the baseline fMRI scan and after the first dose of study medication (after Visit 3) to the end of the study. These AEs include those that emerge after the fMRI procedures and during treatment or worsen in severity during treatment. These AEs will be tabulated, listed, and analyzed.

Separate TEAE incidence tables will be presented for the 2 treatment groups. The incidence rates for all SADRs will also be summarized as described for all TEAEs.

In addition, these same tables will be presented by treatment period (Titration, Maintenance, and combined Titration and Maintenance periods). For the combined Titration and Maintenance periods, the incidence of TEAEs will also be presented by highest severity reported and the dose of study

medication at first occurrence. Listings (and tabular summaries, if warranted) of deaths, other SAEs, and other significant TEAEs, including TEAEs resulting in treatment discontinuation, will be provided.

7.6.2 *Laboratory Values*

Clinical laboratory values will be summarized by visit and by treatment group using descriptive statistics for hematology, chemistry, and urinalysis. For quantitative laboratory parameters, both actual values and change from Baseline values will be summarized.

Laboratory test results will be assigned a low, normal, high (LNH) classification according to whether the values were below (L), within (N), or above (H) the laboratory parameters' reference ranges provided by the central laboratory. Within-treatment comparisons will be based on 3 x 3 tables (shift tables) that, for a particular laboratory test, compare the LNH classification at baseline to the LNH classification at visit. Listings of all abnormal laboratory values by subject (i.e., those with L or H classification) will be provided.

7.6.3 *Vital Signs, Height, Weight, and BMI*

Vital signs will be summarized by the visit and by treatment group using descriptive statistics. Both actual values and changes from the baseline to final visit will be summarized. Descriptive summary statistics (mean, SD, median, and range) for vital sign data, height, weight, and BMI will be evaluated.

7.6.4 *ECG Results*

Tabular summaries of the quantitative ECG parameters and the overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant) will be presented. The QT will be corrected using Fridericia's method.

ECG results will be summarized by visit and by treatment group using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding). For quantitative ECG parameters, both actual values and change from Baseline values will be summarized.

7.6.5 *Physical Examinations*

Findings from the physical examinations will be listed for each system or area examined.

7.6.6 *C-SSRS*

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

7.6.7 *Extrapyramidal Symptoms*

The occurrence of neurological side effects will be assessed by examining the observed score at each visit and change from baseline at each post-baseline (Visit 4 and Visit 6) for the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and AIMS.

7.7 ***Tertiary Variable Analysis***

7.7.1 *Pharmacokinetic Analysis*

PK analysis will not be conducted.

7.7.2 *Behavioral Scales*

Each of 3 variables (R-MOAS, CGI-I, and CGI-S) will be assessed based on the completed population. The descriptive statistics will be reported for observed value and change from baseline for each measurement at each visit for both study treatment groups.

8 **VALIDATION**

The TLFs will be checked for completeness and consistency before finalization.