STATISTICAL ANALYSIS PLAN

Open-Label Extension Study to Evaluate the Long-Term Safety of Molindone Hydrochloride Extended-Release Tablets for the Treatment of Impulsive Aggression in Pediatric and Adolescent Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment

Protocol 810P304

Protocol Version and Date:	Version 5.0, 22FEB2019
Study Drug:	SPN-810
Phase:	Phase 3
Sponsor:	Supernus Pharmaceuticals, Inc. [redacted]
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STATISTICAL ANALYIS PLAN APPROVAL SIGNATURE PAGE

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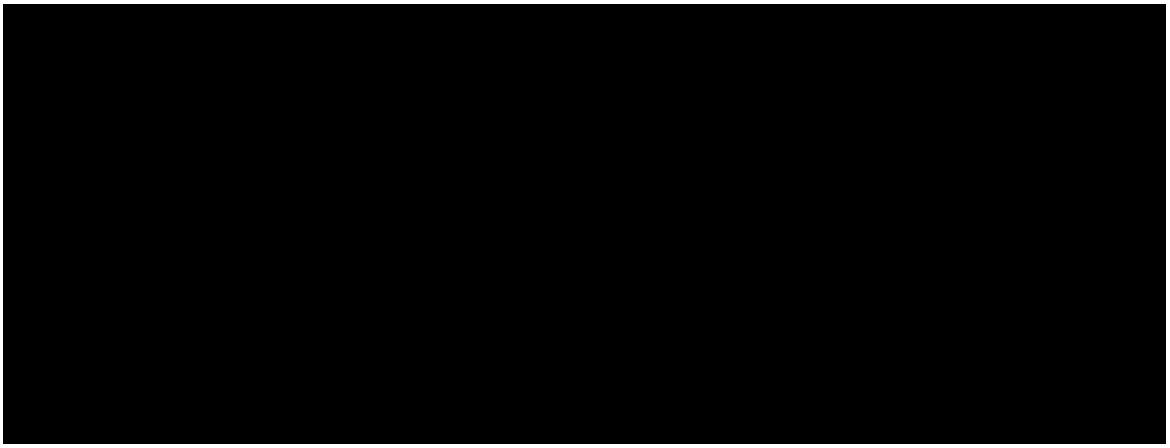

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention Deficit/Hyperactivity Disorder
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CGI-I	Clinical Global Impression – Improvement Scale
CGI-S	Clinical Global Impression – Severity Scale
C-SSRS	Columbia Suicide Severity Rating Scale
CFB	Change from baseline
CRF	Case report form
ECG	Electrocardiogram
EOS	End of Study
EPS	Extrapyramidal Symptoms
IA	Impulsive aggression
IPD	Important protocol deviation
MedDRA	Medical dictionary for regulatory activities
OLE	Open label extension
PD	Parental Distress or Parent Domain
PN	Preferred name
PSI	Parenting Stress Index
PT	Preferred term
QT	QT interval
QTcF	QT interval corrected using Fridericia's method
R-MOAS	Retrospective-Modified Overt Aggression Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIPA	Stress Index for Parents of Adolescents
SM	Study medication
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO-DD	World health organization drug dictionary

1. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are listed in **Table 1**.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Safety Objective (Primary): Long-term safety on the use of SPN-810 as a treatment for impulsive aggression (IA) in subjects (6-17 years of age) with Attention Deficit/Hyperactivity Disorder (ADHD) when taken in conjunction with standard ADHD treatment only after satisfactory participation in a preceding double-blind study (810P301, 810P302, 810P503 or 810P204).	1. Adverse Events 2. Extrapyramidal Symptoms (EPS) scales (Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale) 3. Clinical Laboratory Tests (Hematology, Chemistry, Insulin, Prolactin and Urinalysis) 4. Concomitant Medications 5. Vital signs, Standardized BMI, Physical Examination and ECG (12-lead) 6. Columbia Suicide Severity Rating Scale (C-SSRS)
Efficacy Objective (Secondary): Long-term efficacy on the use of SPN-810 as a treatment for impulsive aggression (IA) in subjects (6-17 years of age) with ADHD when taken in conjunction with standard ADHD treatment.	1. Change from Baseline (CFB) in Retrospective-Modified Overt Aggression Scale (R-MOAS) at each scheduled visit 2. Clinical Global Impression – Improvement Scale (CGI-I) at each scheduled visit 3. CFB in Clinical Global Impression – Severity Scale (CGI-S) at each scheduled visit
Quality of Life Objective (Exploratory): Long-term quality of life on the use of SPN-810 as a treatment for impulsive aggression (IA) in subjects (6-17 years of age) with ADHD when taken in conjunction with standard ADHD treatment.	1. CFB in Child Health Questionnaire Parent Form 28-item (CHQ-PF28) at each scheduled visit 2. CFB in Parenting Stress Index – Short Form (PSI-4-SF) or Stress Index for Parents of Adolescents (SIPA) at each scheduled visit 3. Socio-demographics Characteristics

2. STUDY DESCRIPTION

2.1. Study Design

Study 810P304 is a multicenter, open-label, extension study aimed to assess safety of SPN-810 in the treatment of impulsive aggression (IA) in patients aged 6-17 years with Attention Deficit/Hyperactivity Disorder (ADHD) taken in conjunction with standard ADHD treatment. The study has three phases: Optimization, Maintenance, and Taper.

All subjects who complete the randomized, double-blind portion of Studies 810P301, 810P302, 810P503 or 810P204 will have the option to participate in the open label extension (OLE) study, 810P304, in which all subjects will receive active Study Medication (SM) treatment. Subjects who choose to participate in the OLE will receive blinded conversion medication kits at Visit 6 of the previous SPN-810 double-blind randomization study (810P301, 810P302) or at Visit 4 for subjects completing the 810P204 study. Subjects, who have completed the 810P503 study and, chose to participate in this study, will receive the blinded conversion card at Visit 7.

2.2. Schedule of Visits and Study Procedures

The Schedule of Events and Assessments for the study is shown in Appendix **9.1**.

2.3. Study Treatments

Molindone Hydrochloride Extended-Release (SPN-810) tablet dosage forms of 3 [redacted] are available. SM is to be administered orally twice daily with or without food. Once treatment on the previous clinical study is complete and consent obtained for Study 810P304, the Investigator will initiate the subjects at [redacted] (6-12 years of age from Studies 810P301, 810P302 and 810P204) [redacted] (12-17 years of age from 810P503), and may gradually adjust the dose of SPN-810 between [redacted] for up to 60 months. For subjects with body weight ≥ 30 kg and not fully responding to [redacted] doses, the Investigator may gradually increase the dose of SPN-810 up to [redacted]. At the end of the maintenance phase, the subject will be tapered off study medication over a period of 2-weeks.

The maximum duration of the study is up to 60 months or until market availability.

- Optimization Phase: 8 weeks
- Maintenance Phase: initial period of 6 months, with the option for additional periods of 6 months each
- Taper Phase: 2 weeks

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

3.1. General Statistical Methods

All statistical analysis will be performed using SAS version 9.4 or higher.

All data summaries will be presented by the optimized dose group (<18 mg/day; 18-<24 mg/day, 24-<36 mg/day or 36-54 mg/day) and overall. The optimized dose is defined as the first maintenance dose (at visit 5) for subjects entering maintenance period; otherwise using the end of study (EOS) dose for subjects discontinued prior to maintenance period.

Continuous variables will be summarized descriptively using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.

Categorical variables will be summarized descriptively using counts and percentages. However, the number of patients with missing data will be excluded from the denominator for the percentage calculation. When the denominator for the percentage is different from the number of subjects in the treatment column header, the denominator will be clearly specified in the table or in a footnote for the table.

Individual subject data will be listed by subject ID. Unscheduled measurements (unless defined as baseline) will be excluded from summary tables but will be included in data listings. For assessments that are repeated or unscheduled, unless otherwise specified, the non-missing values from the first assessment will be used for generating summary statistics.

3.2. Definitions and Derivations

The general definitions and derivations are listed in **Table 2**.

Table 2: Definitions and Derivations

Terminology	Definition
Safety Baseline	Safety baseline is the last visit in double blinded studies (810P301, 810P302, 810P503 and 810P204), which is visit 1 in 810P304.
Efficacy Baseline (R-MOAS and CGI-S assessments)	Efficacy baseline is defined as the last non-missing value collected prior to the first dose of the SM in the double-blind studies (810P301, 810P302, 810P503 and 810P204).
Study Day	Day 1 is defined as the date of safety baseline. For visits prior to safety baseline, Study Day is calculated as (Visit Date – safety baseline). For visits after study safety baseline, Study Day is calculated as (Visit Date – safety baseline +1).

3.3. Analysis Populations

The enrolled subjects consist of all subjects from any of the preceding double-blind studies (810P301, 810P302, 810P503 and 810P204) and meet the eligibility requirements.

The Safety Population includes all subjects who have signed Informed Consent/Assent forms and received at least 1 dose of SM in the 810P304 study.

The Safety Population will be used for all safety, efficacy and quality of life data analyses.

3.4. Visit Windows

Data from scheduled visits will be analyzed. Visits will be analyzed as scheduled. Unscheduled measurements will be excluded from the descriptive statistics and statistical analyses but will be included in listings.

3.5. Data Pooling

Data from all sites will be pooled together for all analyses.

3.6. Handling of Missing Data

No missing data imputation will be performed. For efficacy variables, if any item is missing, the subscale and summary score will be set to missing.

4. STUDY SUBJECTS AND EXPOSURE

4.1. Subjects Disposition

Subject disposition will be summarized descriptively by the optimized dose group and overall including the following categories:

- Number of subjects enrolled.
- Number of subjects in the Safety population
- Number (%) of subject who completed the study
- Number (%) of subjects who discontinued from the study
- Primary reasons of discontinuation may include any of the following:
  - Withdrawal by subject
  - Withdrawal by parent/guardian
  - Lost to follow-up
  - Adverse event
  - Physician decision
  - Lack of efficacy
  - Protocol violation
  - Other

4.2. Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. An important protocol deviation (IPD) is defined as a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Potential IPDs may include, but are not limited to:

- Non-compliance with any scheduled study visit
- Non-compliance with study treatment
- Disallowed concomitant medications
- Non-compliance with study inclusion or exclusion criteria
- Non-compliance with study assessment procedures

IPDs will be provided in subject data listings.

4.3. Demographic and Baseline Characteristics

The summaries of demographic data and baseline characteristics will be provided for the Safety Populations. Subject demographic data (age, sex, race, and ethnicity) will be summarized descriptively by the optimized dose group and overall.

4.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities MedDRA version 18.1. The number and percent of subjects reporting various medical, family, and psychiatric histories, grouped by system organ class (SOC) and preferred term (PT), will be summarized for the Safety Population descriptively by the optimized dose group and overall.

4.5. Prior and Concomitant Medication

Prior and Concomitant medications will be coded using WHO DRUG Global version March 2019, and will be summarized descriptively by the fourth level anatomical therapeutic chemical (ATC) classification and Preferred Name (PN), using counts and percentages for the Safety Population by the optimized dose group and overall. ATC fourth (ACT4) level is for the chemical, pharmacological or therapeutic subgroup.

4.6. Study Treatment Exposure and Compliance

Duration of treatment exposure will be calculated for each subject by taking the difference between the date of last dose minus the date of baseline, plus 1 (date of last dose – date of baseline +1). Duration of treatment exposure will be summarized descriptively by the optimized dose group and overall.

Duration of treatment exposure will also be summarized by duration category (i.e., 0 to <3, 3 to <6, 6 to <9, 9 to <12, 12 to <15, 15 to <18, 18 to <21 21 to < 24, 24 to < 30, 30 to <36, 36 to <42, 42 to <48, 48 to <54, 54 to < 60, >= 60 months) using descriptive statistics.

Percentage compliance will be calculated as the following:

$$\left(\frac{\sum_{i=start\ visit}^{last\ visit-1}(Dose\ in\ mg\ dispensed\ at\ visit_i - Dose\ in\ mg\ returned\ at\ visit_{i+1})}{\left(\sum_{i=start\ visit}^{last\ visit-1}(Y_i\ \times \#\ of\ days\ from\ visit_i\ to\ visit_{i+1})\right)}\right) \times 100$$

Where i=index of visits within a given period (e.g., titration, maintenance, and overall)*;* Y_i= Dose in mg that the subject was instructed to take daily between visits.

Descriptive statistics for SM compliance along with the number and percent of subjects belonging to compliance categories (<80%, 80-120%, and >120%) will be provided.

5. SAFETY ANALYSES

The assessment of overall safety and tolerability will be based on adverse events, laboratory values, vital signs, body size (Height/Weight/BMI), ECGs, physical examinations, Barnes Akathisia Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS), and Columbia Suicide Severity Rating Scale (C-SSRS).

5.1. Adverse Events

All adverse events (AEs) will be coded using the MedDRA Version 18.1. All AEs reported in this study are considered treatment-emergent adverse events (TEAEs).

The incidence of TEAEs (number and percent of subjects) will be summarized by System Organ Class (SOC), preferred term (PT), and by the optimized dose group and overall. A subject with multiple occurrences of an AE will be counted only once in the AE category per SOC and PT for summary tables.

Based on the investigator's determination, the severity of TEAEs will be classified as mild, moderate or severe. For summaries by severity, a patient experiencing multiple AE in the same preferred term with different intensities will only be counted once with the maximum severity. If severity is missing, then the maximum severity will be assumed for the analysis (i.e., severity = severe).

The relationship between the study medication and a TEAE is determined by the investigator and will be classified as unrelated (i.e., unlikely related and not related) or related (possibly related and definitely related). TEAEs with missing relatedness will be counted as definitely related. For summaries by relationship, a patient experiencing multiple AE in the same preferred term with different relationship will only be counted once with the most related occurrence.

The summary of TEAE will include incidence rates (number and percent of subjects) who had at least one TEAE, treatment related TEAE, serious TEAE, TEAE leading to death, TEAE by maximum severity, treatment related TEAE, treatment related SAE, and TEAE of special interest.

In addition to the overview of TEAE summary, the following TEAE summary tables will be provided:

- Number and Percent of Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Number and Percent of Subjects with Common (≥ 5% in Any Treatment Group) Treatment-Emergent Adverse Events by Preferred Term
- Number and Percent of Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity

- Number and Percent of Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Medication

- Number and Percent of Subjects with Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

- Number and Percent of subjects with Treatment-Emergent Adverse Events Leading to Withdrawal of Study Medication by System Organ Class and Preferred Term

- Number and Percent of Subjects with Treatment-Emergent Adverse Events of special interest by System Organ Class and Preferred Term
  Note: Adverse events of special interest (AESI) are collected and flagged on eCRF.

- Listing of Deaths
  A data listing of death will be provided. If no death occurred, a blank listing with "No subject died on this study." will be presented.

Listing will be provided for AEs.

5.2. Laboratory Data

Laboratory data will be collected following the event schedule in Appendix **9.1**. Data summaries and listings will be provided in International System of Units (SI). All laboratory data will be listed.

Laboratory assessment values of the form of "< x, ≤ x" (i.e., below the lower limit of quantification) or "> x, ≥x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics. For listings, however, the original ranges (i.e., "< x, ≤ x" or "> x, ≥x") as stated in the database will be presented.

5.2.1. Absolute Value and Change from Baseline

Absolute values and change from baseline (CFB) in hematology, chemistry, and urinalysis continuous variables will be summarized descriptively at each scheduled visit by the optimized dose group and overall. Insulin and Prolactin will be summarized at each scheduled visit by sex and by the optimized dose group and overall.

For visit-based summary tables, in the event of repeat assessments within visit window, the first non-missing value will be used in the tabulations. Results from unscheduled visits will not be included in this summary.

All laboratory data including repeated values and results from unscheduled visits will be provided in data listings with indication of higher or lower than the associated normal range of each laboratory test.

5.3. Vital Signs and Body Size (Height/Weight/BMI)

5.3.1. Absolute Value and Change from Baseline

CFB in vital sign and body size (Height/Weight/BMI) variables will be calculated for each scheduled post-dose visit. The analyses will be the same as described in Section **5.2.1**.

5.4. Electrocardiogram

5.4.1. Absolute Value and Change from Baseline

CFB in Electrocardiogram (ECG) variables will be calculated for each scheduled post-dose visit. The analyses will be the same as described in Section **5.2.1**.

5.4.2. Clinically Notable ECG

The clinically notable QT interval corrected for Fridericia's method (QTcF) are presented in appendix **9.2**. The number and percentage of subjects with potentially post-baseline Clinically Notable Value(CNV) will be summarized by optimized dose group and overall. The denominator includes all subjects with non-CNV baseline and at least one post-baseline assessment (including unscheduled visit) and the numerator is the number of subjects with non-CNV baseline and CNV at post-baseline.

5.5. Physical Examination

Data listing will be provided.

5.6. Extrapyramidal Symptoms (EPS)

Absolute value and CFB of each item in each of EPS scales will be analyzed descriptively at each scheduled visit by the optimized dose group and overall. Data listings will be provided.

5.6.1. Simpson-Augus 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 3 items measuring glabella tap, tremor and salivation, respectively.

5.6.2. 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.

5.6.3. 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.

5.7. Columbia Suicide Severity Rating Scales (C-SSRS)

Suicidal ideation: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions on the C-SSRS.

Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions on the C-SSRS.

Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions on the C-SSRS.

The number and percentage of subjects will be presented at each visit by the optimized dose group and overall for suicidal ideation, suicidal behavior, and suicidal ideation or behavior.

The data listing will be provided.

6. EFFICACY ANALYSES

Absolute value and CFB (if applicable) of efficacy endpoints will be analyzed descriptively at each scheduled visit by the optimized dose group and overall using the Safety Population, unless otherwise specified.

6.1. Retrospective-Modified Overt Aggression Scale (R-MOAS)

The Retrospective-Modified Overt Aggression Scale (R-MOAS) was developed to gauge the severity of aggressive behavior. Parents rate the frequency over the past week of 16 aggressive behaviors in four areas: verbal aggression (VE); physical aggression toward others (PH); aggression toward oneself (PR); and destruction or hostile misuse of property (SE).

VE, PH, PR, SE subdomain scores and total score will be collected on eCRF and no derivation is needed.

6.2. Clinical Global Impression - Severity (CGI-S)

The CGI-S is evaluated on a 7-point scale, where 1 = Normal, not at all ill, asymptomatic, 2 = Borderline Ill, 3 = Mildly Ill, 4 = Moderately Ill, 5 = Markedly Ill, 6 = Severely Ill, and 7 = Extremely Ill.

6.3. Clinical Global Impression - Improvement (CGI-I)

The CGI-I is evaluated on a 7-point scale where 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, and 7 = Very much worse. The CGI-I results will be summarized using the absolute value (i.e., no CFB).

There are caregiver and investigator CGI-I assessments.

7. EXPLORATORY ANALYSES

Absolute value and CFB (if applicable) of quality of life continuous variables will be analyzed descriptively at each scheduled visit by the optimized dose group and overall, unless otherwise specified. The quality of life categorical variables will be analyzed using count and percentage at each scheduled visit by the optimized dose group and overall, unless otherwise specified.

7.1. The Child Health Questionnaire Parent Form 28-item (CHQ-PF28)

The recorded score on CRF needs to be transformed in 0-100 range before calculating subscales and summary scores.

Item	Recorded Score on CRF	Final Raw Score	Transformed Score
1.1; 5.2; 9.4	1	5	((Final Raw Score -1)/4) * 100
	2	4.4	
	3	3.4	
	4	2.2	
	5	1	
2.1a-2.1c; 3.1; 3.2; 9.2a-9.2b	1	1	((Final Raw Score -1)/3) * 100
	2	2	
	3	3	
	4	4	
4.1	1	6	((Final Raw Score -1)/5) * 100
	2	5	
	3	4	
	4	3	
	5	2	
	6	1	
5.1a-5.1c; 6.1a-6.1c; 8.1a-8.1c; 9.3a-9.3b	1	1	((Final Raw Score -1)/4) * 100
	2	2	
	3	3	
	4	4	
	5	5	
7.1a-7.1c; 8.2; 9.1a-9.1b	1	5	((Final Raw Score -1)/4) * 100
	2	4	
	3	3	
	4	2	
	5	1	

The physical functioning summary score (PHS) and psychosocial health summary score (PSS) are calculated in three steps.

- Step1: z-score standardizations.

Subscale	**Sum of Transformed Score**	**Formulas for z-score standardizations**
Physical Functioning (PF)	2.1a–2.1c	PF_Z=(PF - 90.8525408) / 16.3826344
Role/Social Limitations - Physical (RP)	3.2	RP_Z=(RP - 91.4951246) / 18.9079749
General Health Perceptions (GH)	8.1a-8.1c,1.1	GH_Z=(GH - 66.6958379) / 19.3564297
Bodily Pain/Discomfort (BP)	4.1	BP_Z=(BP - 78.6833515) / 20.7355708
Role/Social Limitations - Emotional/Behavior (REB)	3.1	REB_Z=(REB - 90.4013015) / 19.5067502
Parental Impact - Time (PT)	9.2a-9.2b	PT_Z=(PT - 83.8816188) / 20.2901603
Parental Impact - Emotional (PE)	9.1a-9.1b	PE_Z=(PE - 73.9788476) / 21.406013
Self-Esteem (SE)	7.1a-7.1c	SE_Z=(SE - 79.2555314) / 17.8308361
Mental Health (MH)	6.1a–6.1c	MH_Z=(MH - 77.2595806) / 13.6861999
Behavior (BE)	5.1a-5.1c,5.2	BE_Z=(BE - 72.3086051) / 17.1447913
Family Activities (FA)	9.3a-9.3b	NA
Global Health (GGH)	1.1	NA
Global Behavior (GBE)	5.2	NA
Family Cohesion (FC)	9.4	NA
Change in Health (CH)	8.2	NA

- Step 2. PHS_raw and PSS_raw scores

PHS_raw = (PF_Z * .37138) + (RP_Z * .34493) + (BP_Z * .27883) + (GH_Z * .29460) + (REB_Z *-.01178) + (PT_Z * .09113) + (PE_Z * .06063) + (SE_Z * -.09480) + (MH_Z * -.08263)+ (BE_Z * -.12675)

PSS_raw = (PF_Z * -.09243) + (RP_Z * -.06973) + (BP_Z * -.05514) + (GH_Z * -.05547) + (REB_Z* .21155) + (PT_Z * .16944) + (PE_Z * .19823) + (SE_Z * .24792) + (MH_Z * .25335) + (BE_Z * .27911)

- Step 3. Transformation of PHS_raw and PSS-raw

PHS = 50 + (PHS_raw * 10)

PSS = 50 + (PSS_raw * 10)

Note: More details can be found in the Child Health Questionnaire (CHQ) Scoring and Interpretation Manual (HealthActCHQ).

Subscales, PHS and PSS will be analyzed descriptively by the optimized dose group and overall and by visit.

7.2. The Parenting Stress Index – Short Form (PSI-4-SF)

The PSI-4-SF is for 6-12 years of age only.

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

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

- Parental Distress (PD) = Sum responses items 1-12
- Parental-Child Dysfunctional Interaction (P-CDI) = Sum responses items 13-24
- Difficult Child (DC) = Sum responses items 25-36
- Total Stress Score (TS) = PD + P-CDI + DC

PD, P-CDI, DC and TS will be analyzed descriptively.

7.3. Stress Index for Parents of Adolescents (SIPA)

The SIPA is for 13-17 years of age only.

The SIPA includes 112 items. The first 90 items are divided in three major domains and 8 subscales showing in the table below. They use a 5-point rating scale ranging from Strongly Disagree (5) to Strongly Agree (1): 1=SD (Strongly Disagree), 2=DA (Disagree), 3=NS (Not Sure), 4=A (Agree), and 5=SA (Strongly Agree).

Note: Items 2, 3, 4, 5, 9, 10, 15, 25, 28, 34, 40, 45, 49, 54, 66, 69, 74, 81, 83, 85, 87, and 88 are rated from Strongly Disagree (5) to Strongly Agree (1). To be consistent with other items, they have to be reversed (1→5, 2→4, 3→3, 4→2, and 5→1) prior to calculating subscales and domains.

Domain	Subscale	Sum of Items
Adolescent Domain (AD)	Moodiness/Emotional Lability (MEL)	10 items (1, 6, 11, 16, 21, 26, 31, 36, 41, 46)
	Social Isolation/ Withdrawal (ISO)	10 items (2, 7, 12, 17, 22, 27, 32, 37, 42, 47)
	Delinquency/Antisocial (DEL)	10 items (3, 8, 13, 18, 23, 28, 33, 38, 43, 48)
	Failure to Achieve or Persevere (ACH)	10 items (4, 9, 14, 19, 24, 29, 34, 39, 44, 49)
Parent Domain (PD)	Life Restrictions (LFR)	10 items (51, 52, 55, 56, 59, 63, 67, 71, 75, 79)
	Relationship with Spouse/Partner (REL)	9 items (60, 64, 68, 72, 73, 76, 77, 80, 81)
	Social Alienation (SOC)	7 items (53, 54, 57, 58, 61, 65, 69);
	Incompetence/Guilt (INC)	8 items (62, 66, 70, 74, 78, 82, 86, 90)
Adolescent-Parent Relationship Domain (APRD)		16 items (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 83, 84, 85, 87, 88, and 89)

- AD = MEL + ISO + DEL+ACH
- PD = LFR + REL + SOC + INC
- Total Parenting Stress (TPS) = AD + PD + APRD

The Life Stressors (LS) Scale includes the last 22 items (Items 91-112) with responses of 1=Yes and 0=No.

- Life Stressors (LS) = Sum last 22 items (Items 91-112)

TPS, each domain, each subscale, and LS scale will be analyzed descriptively by the optimized dose group and overall and by visit.

7.4. Socio-demographic Characteristics

Socio-demographic variables include the number of siblings in the study, siblings with IA, caregiver's age and gender, living situation, marital status, household income and education level.

The socio-demographic characteristics variables will be analyzed descriptively by the optimized dose group and overall.

8. CHANGE FROM THE PROTOCL

Drug compliance in section 4.6 calculation was changed to use dose in mg instead of tablet because different tablet (ie. [redacted] tablet) could be distributed in the same visit and patient can take them interchangeably.

9. APPENDICES

9.1. Schedule of Events and Procedures

		Treatment					EOS
Phase	***Baseline*[a]**	***Optimization***			***Maintenance***		***Taper***
Visit Number	**EOS Visit[a]/ Visit 1**	**Visit 2 (Week 2)**	**Visit 3 (Week 4)**	**Visit 4 (Week 8)**	**[b]Visits 5 (Mo 3), 7, 9, 11, 13, 15, 17, 19, 21, and 23 (Mo 57)**	**[b]Visits 6 (Mo 6), 8, 10, 12, 14, 16, 18, 20, 22, and 24 (Mo 60)**	**Visit 25**
Window (Days)		**2 weeks ±1 week from Visit 1**	**2 weeks ±1 week from Visit 2**	**4 weeks ±1 week from Visit 3**	**Visit 5 will occur 4 weeks ±1 week from Visit 4**	**Visit 6 will occur 3 months ± 1 week from Visit 5**	
Informed Consent/Assent[c]	X						
Physical Examination	X					X	X
ECG	X				X	X	X
Inclusion/Exclusion Criteria	X						
Socio-demographic Information	X						
Urine Drug Screen	X				X	X	X
Urine Pregnancy Test[d]	X[a]	X	X	X	X	X	X
Home urine pregnancy follow-up (call)[b]					X	X	
Vital Signs[e]	X[a]	X	X	X	X	X	X
Weight, Height and BMI	X[a]	X	X	X	X	X	X

		Treatment					EOS
Phase	***Baseline*[a]**	***Optimization***			***Maintenance***		***Taper***
Visit Number	**EOS Visit[a]/ Visit 1**	**Visit 2 (Week 2)**	**Visit 3 (Week 4)**	**Visit 4 (Week 8)**	**[b]Visits 5 (Mo 3), 7, 9, 11, 13, 15, 17, 19, 21, and 23 (Mo 57)**	**[b]Visits 6 (Mo 6), 8, 10, 12, 14, 16, 18, 20, 22, and 24 (Mo 60)**	**Visit 25**
Window (Days)		**2 weeks ±1 week from Visit 1**	**2 weeks ±1 week from Visit 2**	**4 weeks ±1 week from Visit 3**	**Visit 5 will occur 4 weeks ±1 week from Visit 4**	**Visit 6 will occur 3 months ± 1 week from Visit 5**	
Blood collection for Pharmacogenomic (PGx) Testings[h]	X						
Hematology/Chemistry/Urinalysis	X[a]			X		X	X
Columbia Suicide Severity Rating Scale (CSSRS)	X[a]	X	X	X	X	X	X
Investigator CGI-S	X	X	X	X	X	X	X[f]
Caregiver and Investigator CGI-I	X	X	X	X	X	X	X[f]
R-MOAS					X	X	X[f]
CHQ-PF28					X	X	X[f]
PSI-4-SF/SIPA[i]					X	X	X[f]
Safety Scales (Simpson-Angus, Barnes, AIMS)	X[a]	X	X	X	X	X	X
Adverse Events	X[a]	X	X	X	X	X	X
Concomitant Medications	X[a]	X	X	X	X	X	X

		Treatment					EOS
Phase	***Baseline*[a]**	***Optimization***			***Maintenance***		***Taper***
Visit Number	**EOS Visit[a]/ Visit 1**	**Visit 2 (Week 2)**	**Visit 3 (Week 4)**	**Visit 4 (Week 8)**	**[b]Visits 5 (Mo 3), 7, 9, 11, 13, 15, 17, 19, 21, and 23 (Mo 57)**	**[b]Visits 6 (Mo 6), 8, 10, 12, 14, 16, 18, 20, 22, and 24 (Mo 60)**	**Visit 25**
Window (Days)		**2 weeks ±1 week from Visit 1**	**2 weeks ±1 week from Visit 2**	**4 weeks ±1 week from Visit 3**	**Visit 5 will occur 4 weeks ±1 week from Visit 4**	**Visit 6 will occur 3 months ± 1 week from Visit 5**	
Drug Dispensation & Return	X[a]	X	X	X	X	X[g]	X
Drug Compliance		X	X	X	X	X	X

a. Assessment is completed as the EOS visit in the preceding double-blind randomized study: Visit 7 (810P301 and 810P302), Visit 8 (810P503) and Visit 6 (810P204).
b. Visit 7-24 will occur 3 months ±1 week from the previous visit. At each visit, a home urine pregnancy test will be distributed to female subjects of child-bearing potential. Subjects are required to complete testing 6 weeks after each visit. The site will follow-up with a call to record the results.
c. Written consent and assent must be obtained prior to performing any 810P304 study-related procedures.
d. To be performed for females subjects or childbearing potential prior administration of first dose of SM and will have to be tested as negative for the subjects to continue in the study.
e. Heart rate (HR), blood pressure (BP), temperature, and respiratory rate (RR) will be measured.
f. Assessments will be performed only for subjects who discontinue prior the end of the study
g. Taper medication and instructions will be dispensed.
h. Participation in PGx testing is optional. PGx Testing will be performed in subjects enrolling from the following studies: 810P301, 810P302 or 810P204. Subjects already enrolled, will provide a blood sample during the next visit after this amendment is effective.
i. The SIPA scale will be administered only to subjects 13 to 17 years of age

9.2. Clinically Notable ECG

Parameter	Criteria (milliseconds)
QTcF	≤450
	>450- ≤480
	>480- ≤500
	> 500
QTcF change from baseline	≤30
	>30- ≤60
	> 60