STATISTICAL ANALYSIS PLAN

Protocol Title	Assessment of Efficacy and Safety of SPN-810 for the Treatment of Impulsive Aggression (IA) in Adolescent Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment
Protocol Number	810P503
Protocol Version	V5.0
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Study Drug	Molindone Hydrochloride Extended-Release Tablets (SPN-810)
Study Phase	3
IND Number	106,515
Indication	Treatment of Impulsive Aggression in subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in conjunction with standard ADHD treatment
Sponsor	Supernus Pharmaceuticals, Inc. [redacted]
SAP Version	Final
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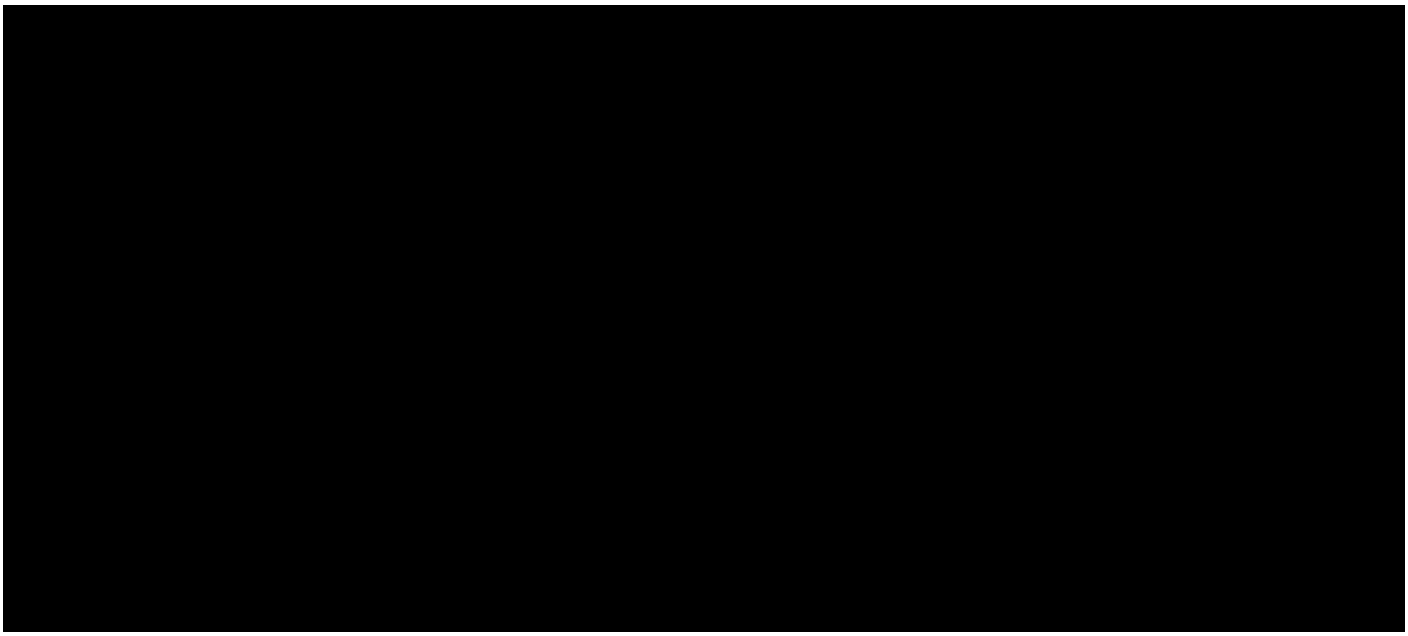

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LIST OF ABBREVIATIONS AND TABLE

ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse Event
CGI-S	Clinical Global Impression – Severity of Illness
CGI-I	Clinical Global Impression – Global Improvement
CHQ-PF28	Child Health Questionnaire Parent Form 28 item
C-SSRS	Columbia Suicide Severity Rating Scale
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
R-MOAS	Retrospective Modified Overt Aggression Scale
SAE	Serious Adverse Event
SIPA	Stress Index for Parents of Adolescents
SM	Study Medication
SNAP-IV	Swanson, Nolan and Pelham-IV

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1 INTRODUCTION

The study is a randomized, double-blind, multicenter, placebo-controlled, flexible-dose (36, 45 or 54 mg/day), 2-arm, (1:1) parallel group study to evaluate the safety and efficacy of SPN-810 (molindone extended release tablets) for reducing impulsive aggression in adolescents (12-17 years of age) with ADHD as an adjunctive treatment to an approved ADHD medication.

2 STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy and safety of flexible doses of SPN-810 (36 to 54 mg/day) in the improvement of IA behaviors in adolescents diagnosed with ADHD when taken in conjunction with standard ADHD treatment.

The key secondary objectives, additional secondary objectives and exploratory objectives are to assess the effect of SPN-810 on the key secondary endpoints, additional secondary endpoints and safety endpoints described below.

3 STUDY ENDPOINTS

3.1 Primary efficacy endpoint

The primary efficacy endpoint is the percent change (PCH_T) in the frequency (unweighted score) of IA behaviors per 7 days in the Treatment Phase (titration + maintenance) relative to the Baseline period calculated over the number of days with non-missing IA diary data.

3.2 Key Secondary Endpoints

The key secondary endpoints include the following:

1. Investigator-rated Clinical Global Impression – Severity Scale (CGI-S)
2. Retrospective Overt Modified Aggression Scale (R-MOAS)
3. Percent of children whose IA behaviors were remitted at the end of the study measured by R-MOAS score ≤ 10.

3.3 Additional Secondary Endpoints

The additional secondary endpoints include the following:

1. Investigator-rated Clinical Global Improvement (CGI-I) scale.
2. Caregiver-rated CGI-I scale.
3. Caregiver-rated CGI-S scale.
4. Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) rating scale
5. Child Health Questionnaire Parent Form 28 (CHQ-PF28) rating scale
6. Stress Index for Parents of Adolescents (SIPA) rating scale

3.4 Safety Endpoints

1. Incidence of Adverse Events
2. Incident of Extrapyramidal Symptoms (EPS)

3. Clinical laboratory evaluations
4. Vital signs and ECG
5. Suicidal symptoms (C-SSRS)
6. Infrequent behaviors

4 STUDY METHODS

4.1 Study Design

This study is a randomized, double-blind, multicenter, placebo-controlled, flexible-dose (36, 45 or 54 mg/day), 2-arm, (1:1) parallel group study to evaluate the safety and efficacy of SPN-810 (molindone extended release tablets) for reducing impulsive aggression in adolescents (12-17 years of age) with ADHD as an adjunctive treatment to an approved ADHD medication.

Schedule of Visits and Procedures.

All subjects who are consented are required to follow the protocol procedures regardless of the number of doses of SM taken. The Schedule of Visits and Procedures are presented in Table 1.

Table 1 Schedule of Events and Assessments

Phase	Pre-Treatment		Treatment					Conversion/Taper
Period	Screening	Baseline	Titration		Maintenance			
VISIT NUMBER	1	2	3	4	5	6	7	8 (EOS)
DAY	-45	-15	1	15	22	29	36	46
WINDOW (DAYS)	≤45d prior to Visit 3	≥15d prior to Visit 3	14d±2d from Visit 2	14d±2d from Visit 3	21d±2d from Visit 3	28d±2d from Visit 3	7d±2d from Visit 6	10d±1d from Visit 7
Informed Consent/Assent[a]	X[b]							
R-MOAS Scale	X	X	X	X	X	X	X	X
MINI-KID & Vitiello Aggression Scales	X							
Medical History	X		X[c]					
Demographics	X							
Physical Examination & ECG (12-lead)	X						X	
Inclusion/Exclusion Criteria	X		X[d]					
Randomization			X[b]					
Urine Drug Screen	X	X	X	X	X	X	X	X
Pregnancy Test[e]	X[f]	X	X	X	X	X	X	X
Diary Training & Distribution or Evaluation		X	X[g]	X	X	X	X	
Vital Signs[h]	X		X	X	X	X	X	X
Weight, Height, BMI	X		X			X		X
Hematology/Chemistry/Urinalysis	X		X				X	X
PK Blood Sampling[i]					X	X		
PGx sampling[l]	X							

a. Written consent must be obtained prior to performing any study-related procedure.

Columbia Suicide Severity Rating Scale (CSSRS)	X		X	X	X	X	X	X
Caregiver and Investigator CGI-S	X[j]		X	X	X	X	X	
Caregiver and Investigator CGI-I				X	X	X	X	
SNAP-IV, CHQ-PF28, SIPA			X				X	
Infrequent Behaviors Checklist		X[k]	X	X	X	X	X	
Simpson-Angus, Barnes & AIMS			X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Drug Dispensation			X[b]	X	X	X	X	
Drug Return and Compliance				X	X	X	X	X
Diary Return								X

b. Subject number will be assigned via [redacted].
c. Assess for any clinically significant change in Medical History since screening.
d. Confirm inclusion/exclusion criteria.
e. Urine pregnancy test will be performed for all female subjects. Prior to the administration of the first dose of SM subjects will have to be tested as negative to continue in the study. If Visit 1 and Visit 2 occur on the same day then both urine and serum pregnancy tests must be performed.
f. Serum pregnancy test will be performed at Screening for all female subjects.
g. Diary compliance must be at least 70% (minimum of 11 days out of 15) to qualify for randomization.
h. Heart Rate (HR), blood pressure (BP), temperature, and respiratory rate will be measured.
i. PK blood samples will be obtained over two visits
j. Only the Investigator-rated CGI-S will be completed at Screening; Caregiver and Investigator-rated CGI-S will be collected at randomization and every visit thereafter.
k. The checklist will be recorded on a paper source and entered on EDC only at Visit 2.
l. Optional

4.2 Sample Size and Power Consideration

Assuming a mean difference of 15 between SPN-810 dose group and placebo with a common standard deviation of 35, a sample of 93 subjects per arm will yield 80 % power to detect a non-zero difference between the median of SPN-810 treatment group and the placebo group using the Wilcoxon rank-sum test with a 2-sided significance level α=0.05.

5 STATISTICAL METHODS and ANALYSES

5.1 General Considerations

Because SPN-810 did not show efficacy for the Treatment of Impulsive Aggression in the two previous Double-Blind Studies (810P301 and 810P302), the conduct of this study (810P503) was halted. Therefore, the analysis will be limited to the primary, key secondary endpoints and safety data, which will include adverse events (AEs), Extrapyramidal Symptoms (EPS), Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale, clinical laboratory evaluations, vital signs, suicidal symptoms (C-SSRS) and ECG results.

All descriptive statistical analyses will be performed using SAS (Version 9.4), unless otherwise noted and will be presented by treatment groups (Placebo, SPN-810).

Continuous variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum, and maximum.

Categorical variable summaries will include the frequency and percentage of subjects who are in the category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified. The denominator for by visit displays will be the number of subjects in the relevant study population with non-missing data at each study visit.

In general, the baseline value for a variable is defined as the last observation prior to the first dose of double-blind study medication, ideally Visit 3, but including the screening value, if necessary.

All data will be presented in Listings.

5.2 Analysis Population

The population of “all enrolled subjects” consists of all those screened subjects who meet the requirements for study participation and are entered in the Baseline period of the study. The population of “all randomized subjects” consists of all those enrolled subjects who complete the Baseline Period, meet the inclusion/exclusion criteria and are randomized via the [redacted]. The safety population will include all subjects who received at least 1 dose of study drug and has at least one post-baseline safety assessment.

5.3 Subject Disposition

The number and percentage of subjects who were enrolled, dosed, completed, or early discontinued will be displayed. Reasons for early discontinuation will include:

- Adverse event
- Lost to follow-up
- Investigator decision
- Administrative reason
- Failure to follow required study procedures
- Withdrawal by subject and other.

5.4 Protocol Deviations

Protocol deviations will be presented in listings. Protocol deviations 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

5.5 Demographic Characteristics

Descriptive statistics for Age, Baseline Height, Weight, and BMI will be presented using n, mean, STD, Min and Max. Frequencies and percentages will be presented for Race, Ethnicity and Sex.

5.6 Study Drug Exposure

Duration of exposure in days will be calculated from the first and last dates of the study drug administration. The duration of exposure will be calculated as date of last dose minus date of first dose + 1. Duration of exposure (days) will be summarized by categories and descriptive statistics. The categories for duration of exposure are Weeks 1-2 (Titration period), Weeks 3-5 (Maintenance Period).

5.7 Handling of Missing Data

There will be no substitutions made for missing data points. The number of missing values will be presented in the analysis tabulations, as applicable, but without a percentage.

6 EFFICACY ANALYSES

The efficacy analysis will be based on the safety population for subjects who have sufficient baseline and post baseline IA diary to calculate percent change as defined below.

6.1 Primary efficacy endpoint

The primary efficacy endpoint, percent change (PCH_T) in the frequency (unweighted score) of IA behaviors per 7 days, will be calculated as $PCH_T = 100*(T - B)/B$, where T and B are IA behavior frequencies per 7 days during the Treatment Phase (titration + maintenance periods) and Baseline period, respectively. The IA behavior frequency per 7 days is defined as (SUM/DAY) x 7, where SUM is the total of the 15 IA behaviors reported in IA diary, and DAY

is the number of days with non-missing IA score in the IA diary during the specified study period.

PCH_T will be summarized by treatment groups as described for continuous variables in Section 5.1. Individual subject listings supporting the summary will be presented.

6.2 Key Secondary Endpoints

The absolute and change from baseline for CGI-S and R-MOAS will be summarized by treatment groups and visit using descriptive statistics for continuous variables as described Section 5.1.

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.

The percentage of subjects with remission of R-MOAS ≤ 10 will be summarized by treatment groups and visit using descriptive statistics for categorical variables as described Section 5.1.

Individual subject listings supporting the summaries will be presented.

6.3 Additional Secondary Endpoints

The absolute value of investigator-rated Clinical Global Improvement (CGI-I) scale, Caregiver-rated CGI-I scale and Caregiver-rated CGI-S scale will be summarized the same way as for CGI-S described in the above Section.

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 absolute Caregiver-rated CGI-S scale score and change from baseline will be summarized the same as for CGI-S as described above.

With respect to CHQ-PF28, z-score will be derived and be summarized by treatment group at visit 1 and 7. The recorded score needs to be transformed in 0-100 range before calculating subscales and summary scores.

CHQ-PF28 Questionnaire Item	Recorded on CRF	Final Raw	Transformed Score
1.1; 5.2; 9.4	1	5	((Final -1)/4) * 100
	2	4.4	
	3	3	
	4	2.2	
	5	1	
2.1a-2.1c; 3.1;	1	1	((Final -1)/3) * 100
	2	2	

3.2; 9.2	3	3	
	4	4	
4.1	1	6	((Final -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 -1)/4) * 100
	2	2	
	3	3	
	4	4	
	5	5	
7.1a-7.1c; 8.2; 9.1a-9.1b	1	5	((Final -1)/4) * 100
	2	4	
	3	3	
	4	2	
	5	1	

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

- Step1: z-score standardizations.

Subscale	**Sum of items**	**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 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

Transformed physical (PHS) = 50 + (PHS_raw * 10)

Transformed psychosocial (PSS) = 50 + (PSS_raw * 10)

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

The ratings from the SNAP-IV scale are grouped into the following 4 subscales:

- ADHD-Inattention (items #1-9),

- ADHD-Hyperactivity/Impulsivity (items #10-18)
- ADHD-Combined subscales (items #1-18)
- Oppositional Defiant Disorder (ODD) (items #19-26)

Each subscale score is calculated by averaging the items scores within each subscale.

The absolute and change from baseline for SNAP-IV will be summarized by treatment group at visit 7.

Stress Index for Parents of Adolescents (SIPA) rating scale includes 112 items. The first 90 items 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 (TS) = AD + PD + APRD
The last 22 items (91-112) with responses of 1=Yes and 0=No.

Life Stressors (LS) = Sum of last 22 items (Items 91-112)
TS, each domain, each subscale, and LS scale will be summarized by treatment group at visit 3 and 7 using descriptive statistics for continuous variable as described in Section 5.1.

Individual subject listings supporting the additional secondary endpoint summaries will be presented.

7 SAFETY ANALYSES

7.1 Adverse Events

AEs will be coded using MedDRA Version 18.1.

Adverse events will be categorized by MedDRA system organ class (SOC) and/or preferred term. A subject experiencing the same AE multiple times will only be counted once for that preferred term. Similarly, if a subject experiences multiple AEs within the same SOC, that subject will be counted only once for that SOC.

7.1.1 Treatment-emergent Adverse Events

Overview of Treatment-emergent adverse events (TEAEs) will be provided. The incidence of TEAEs will be summarized by MedDRA SOC, preferred term and severity. The number and percentage of subjects who experienced at least one TEAE will be tabulated by treatment group.

7.1.2 Adverse Events with Treatment Relatedness

TEAE relatedness to SM will be summarized based on derived binary values as: “Drug Related” if the relationship to SM is probably or related or “Not Related” if the relationship to SM is not related or unlikely related.

7.1.3 Serious Adverse Events

The incidences of SAEs will be presented by SOC and preferred term, and a listing of all SAEs will be presented.

7.1.4 Adverse Events Leading to Study Drug Discontinuations

The incidences of TEAEs leading to study drug discontinuation will be presented in listings by SOC and preferred term.

7.1.5 Adverse Events of Special Interest

Treatment-emerging EPS (e.g., akathisia, dystonia, Parkinsonism, tardive dyskinesia) and neuroleptic malignant syndrome are reported to the Drug Safety Contact person(s) by completing the Adverse Event of Special Interest (AESI) eCRF in EDC.
The AESIs will be presented by SOC and preferred term.

Subject listings of AEs will be presented.

7.2 Clinical Laboratory Tests

The absolute value and change from baseline to EOS for laboratory tests will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by Treatment groups, laboratory category (Chemistry, Hematology, Immunochemistry, and Urinalysis). The summary will be presented by Treatment group in for Chemistry, Hematology, Immunochemistry and Urinalysis respectively.
Subject listings of clinical laboratory data will be presented.

7.3 Vital Signs

The absolute value and change from baseline to EOS for vital signs (body temperature, heart rate, respiration rate, systolic blood pressure, weight, height, BMI and diastolic blood pressure) will be summarized using descriptive statistics for continuous variables by treatment group as described in Section 5.1. The summary will be presented by treatment groups.
Subject listings of Vital signs will be presented.

7.4 ECG

The absolute value and change from baseline to EOS for ECG parameters (heart rate, PR interval (msec), QRS interval (msec), QT interval (msec), and QT corrected for heart rate using Fridericia's (QTcF) correction formula, RR interval (msec)) will be summarized using descriptive statistics for continuous variable by treatment groups as described in Section 5.1.
Subject listings of ECGs will be presented.

7.5 C-SSRS

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

7.6 Extrapyramidal Symptoms

Extrapyramidal Symptoms collected using Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale will be summarized and listed by treatment group.