COVER PAGE – STATISTICAL ANALYSIS PLAN (SAP)

Protocol Number:	812P311
Title:	An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder
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STATISTICAL ANALYSIS PLAN

Study 812P311

An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder

Name of Test Drug:	SPN-812 ER
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Ave Rockville, MD 20850 United States
Prepared by:	Supernus Pharmaceuticals, Inc.
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DOCUMENT HISTORY

See Appendix A: Document History

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ABBREVIATIONS

Abbreviation	Definition
AAQoL	Adult ADHD Quality of Life
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	adverse event
AESI	adverse events of special interest
AISRS	ADHD Investigator Symptom Rating Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Version
BUN	blood urea nitrogen
CBC	complete blood count
CFB	change from baseline
CGI-I	Clinical Global Impressions Scale – Improvement
CGI-S	Clinical Global Impressions Scale – Severity of Illness
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
EOS	end of study
ER	extended-release
FSH	follicle stimulating hormone
GAD	generalized anxiety disorder
HCT	hematocrit
LLT	lower level term
mmol/L	millimoles per liter
msec	millisecond
MedDRA	Medical Dictionary for Regulatory Affairs

Abbreviation	Definition
N/A	not available
OLE	open-label extension
PCS	potentially clinically significant
PE	physical examination
PN	preferred name
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDQ	Symptoms of Depression Questionnaire
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cells

1 INTRODUCTION

Study 812P311 is an open-label extension (OLE), long-term, multicenter, flexible-dose study of SPN-812 in adults diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD). Up to 366 subjects will be enrolled. Subjects who have completed Study 812P306 (a randomized, double-blind, placebo-controlled study of SPN-812 for the treatment of ADHD) will be eligible for enrollment into Study 812P311. Interest and suitability will be ascertained at the last 1 to 2 visits of 812P306 to allow immediate enrollment into Study 812P311 for subjects who complete Study 812P306

2 DATA CONVENTIONS FOR ANALYSIS

The Safety Population is defined as all subjects who are enrolled and receive at least one dose of SPN-812 during the OLE study.

Safety will be assessed from data based on the analysis of adverse events (AE), potentially clinically significant (PCS) laboratory evaluations, abnormal liver enzymes and liver function tests, abnormal vital signs, electrocardiogram (ECG) results, Columbia Suicide Severity Rating Scale (C-SSRS) and caffeine intake. Subject disposition (including reasons for premature terminations), subject demographics, physical assessment, and exposure to study drug will also be presented.

2.1 Disposition of Subjects and Withdrawals

Subject disposition summary will be presented for the Safety Population. Disposition will include tabulations of the number and percentage of subjects in each of the following categories:

- Subjects dosed
- Subjects completed study
- Subjects early discontinued

The primary reason for early discontinuation will be summarized. The reason for early discontinuation may include any of the following:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Withdrawal of consent by subject
- Lack of efficacy
- Investigator’s decision
- Misuse or abuse of study drug

- Study terminated by sponsor
- Other

2.2 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be listed and summarized.

2.3 Demographic Characteristics

Demographic characteristics include:

- Age (18-44, 45-65)
- Sex (male, female)
- Race
- Ethnicity (Hispanic, Non-Hispanic)
- Height
- Weight
- Body mass index (BMI)

The number and percent of subjects reporting various medical histories, grouped by Medical Dictionary of Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) will be analyzed. Medical history will be coded using MedDRA Version 22.1 This analysis will be conducted for the Safety Population.

Alcohol, tobacco, and substance use collected at screening will be listed. Subject training module data will also be listed.

2.4 Study Drug Exposure

Study drug exposure is collected as both actual and planned dose and duration of exposure to SPN-812.

2.5 Efficacy Data

1) The adult ADHD Investigator Symptom Rating Scale (AISRS) was developed to better measure the presence and severity of ADHD symptoms based on DSM-IV diagnostic criteria in adult subjects[7]. It is a semi-structured clinical interview with suggested prompts for each item to improve inter-rater reliability. The scale consists of 18 items that directly correspond to the 18 symptoms of ADHD and are further subdivided into 2 subscales: Inattention (9 items) and Hyperactivity/Impulsivity (9 items). During the interview with the subject, the clinician/investigator rates the frequency and severity of each symptom on a 4-point Likert-type scale, where 0 = None, 1 = Mild, 2 = Moderate,

and 3 = Severe, with a maximum total score of 54 points and maximum subscale scores of 27 points each.

2) The Clinical Global Impressions 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 the administration of SPN-812. The Clinical Global Impression – Severity of Illness (CGI-S) is a single item clinician rating of clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with subjects with ADHD. The Clinical Global Impression – Improvement Scale (CGI-I) is an assessment of how much the subject's illness has improved or worsened relative to a baseline state prior to treatment. Both CGI-S and CGI-I are rated on a 7-point scale of 1 to 7 with 7 being "extremely ill" or "very much worse", respectively. Successful therapy is indicated by a lower overall score in subsequent testing.

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

4) 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.

5) Generalized Anxiety Disorder 7 scale (GAD-7) is a self-reported 7-item questionnaire for screening and measuring the severity of generalized anxiety disorder[9]. The GAD-7 measures the severity of various symptoms of generalized anxiety disorder over the past 2 weeks according to reported response categories with assigned points. The subject scores each GAD-7 item on 4-point Likert scale, where 0 = Not at all, 1 = Several days, 2 = More than half the days, and 3 = Nearly every day. GAD-7 total scores range from 0 to 21, where a total score of 1 to 4 = None/Minimal anxiety, 5 to 9 = Mild anxiety, 10 to 14 = Moderate anxiety, and ≥15 = Severe anxiety.

6) The BRIEF-A is a standardized 75-item rating scale in 9 scales and 2 summary index scales that assesses aspects of executive function and problems with self-regulation from the perspective of the individual. The subject rates each item on a 3-point Likert scale (Never, Sometimes, or Often) based on their experiences within the last month. Higher scores indicate poorer executive function. The Global Executive composite (GEC) raw score is the sum the Behavioral Regulation Index (BRI) raw score and Metacognition Index (MI) raw score. The BRI raw score is the sum of raw scores of subscales Inhibit, Shift, Emotional Control, and Self-Monitor scales. To calculate the MI raw score, sum the raw scores obtained for the Initiate, Working Memory, Plan/Organize, Task Monitor; and Organization of Materials scales. Raw GEC scores, BRI, MI, and their component subscale (individual scales) will be converted to T-scores using Appendix A of the BRIEF-A Professional Manual[10], and the change from baseline in T-scores will be calculated.

7) The Symptoms of Depression Questionnaire (SDQ) is a 44-item, self-reported depression scale, designed to measure the severity of symptoms of depression that inquires about an extensive number of depressive symptoms. The subject self-rates/scores each item on a 6-point scale (1 to 6) as it pertains to the past month. Each item is rated based on a subject's perception of what is normal for the individual (score = 2), what is better than normal (score = 1), and what is worse than normal (scores = 3 to 6). SDQ subscales are as follows: SDQ-1 subscale includes items related to lassitude, mood, and cognitive functioning; SDQ-2 subscale includes items related to anxiety, agitation, irritability, and anger; SDQ-3 subscale includes items related to suicidal ideation; SDQ-4 subscale assesses disruptions in sleep quality; and SDQ-5 subscale includes items on changes in appetite and weight.
8) Adult ADHD Quality of Life (AAQoL) is a 29-item questionnaire that measures how ADHD has impacted the subject's quality of life over the past 2 weeks. The AAQoL includes 4 subscales: life productivity, psychological health, relationships, and life outlook. The subject rates/scores each item on a 5-point Likert scale, where 1 = Not at all/Never, 2 = A little/Rarely, 3 = Somewhat/Sometimes, 4 = A lot/Often, and 5 = Extremely/Very often. For subscale calculations, items are transformed such that a score of 1 = 0, 2 = 25, 3 = 50, 4 = 75, and 5 = 100 and then the sum of these transformed subscale items is averaged by the number of items.

   Life productivity scores come from items 1, 2, 3, 4, 5, 11, 22, 23, 24, 25 and 26 and the values are reversed, i.e., a score of 1 becomes a score of 5, a score of 2 becomes a score of 4, a score of 3 remains a 3, and so on. This is then transformed and averaged as stated above.

   Psychological health scores come from items 6, 7, 8, 13, 20 and 21 and the values are reversed, i.e., a score of 1 becomes a score of 5, a score of 2 becomes a score of 4, a score of 3 remains a 3, and so on. This is then transformed and averaged as stated above.

   Relationships scores come from items 9, 10, 12, 18 and 19. This is then transformed and averaged as stated above.

   Life outlook scores come from items 14, 15, 16, 17, 27, 28 and 29. This is then transformed and averaged as stated above.

2.6 Safety Data

2.6.1 Adverse Events

All AEs will be coded using MedDRA Version 22.1 for consistency with the Study 812P306 AE analyses. Study-level Lower Level Terms (LLT) will be assigned to the corresponding PT and SOC in MedDRA Version 22.1.

2.6.2 Prior and Concomitant Medications

A concomitant treatment refers to all treatment, including concomitant therapies as well as herbal treatments, vitamins, behavioral treatment, and non-pharmacological treatment, such as psychotherapy, taken between the dates of the first dose of study drug and the end of the subject's participation in the study (Visit 22/EOS), inclusive.

Treatments that started prior to the first dose of study drug are considered prior treatments whether or not they were stopped prior to the first dose of study drug. Any treatment starting on or after the first dose of study drug will be considered as concomitant. If a treatment starts prior to the first dose of study drug and continues after the first dose of study drug, the medication will be considered both prior and concomitant.

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD Enhanced version September 2019), Anatomical Therapeutic Chemical (ATC) level 4 for ATC class and level 5 (clinical substance) for preferred name (PN).

2.6.3 Laboratory Evaluations

Laboratory tests will include hematology, serum chemistry, and urinalysis. Values will be presented using the international system of units (SI).

Hematology:

Hematology parameters will include complete blood count (CBC), white blood cell count with differential, platelet count, red blood cell (RBC) count, hemoglobin, and hematocrit.

Serum Chemistry:

Serum chemistry parameters will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bicarbonate, bilirubin (direct), bilirubin (total), blood urea/blood urea nitrogen (BUN), calcium, chloride, creatinine, phosphate, potassium, sodium, total protein, and glucose.

Urinalysis:

Urinalysis parameters will include bilirubin, glucose, ketones, nitrites, occult blood, pH, protein, specific gravity, urobilinogen, and WBCs.

Other:

Serology, follicle stimulating hormone (FSH), serum drug screen results, standard urine drug screen results, point of care urine drug screen results, and pregnancy test results will be listed separately.

2.6.4 Vital Signs

Vital signs data will include weight (kg), BMI (kg/m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute) and temperature (°C). Blood pressure and heart rate measurements taken in the standing and the seated position will be analyzed.

2.6.5 Electrocardiogram

The ECG parameters to be summarized include heart rate, PR interval (msec), QRS interval (msec), QT interval (msec), and QT interval corrected for heart rate using Fridericia's (QTcF) correction formula.

3 STATISTICAL METHODS

3.1 General Methods

Premier Research, the designated CRO, will perform all statistical analysis using SAS version 9.4 or higher. Premier Research will be responsible for creating table, listing, and figure reports by SAS programming and delivering the reports, as well as the programs, to Supernus at study completion.

All analyses will be based on subjects who received any amount of study drug in Study 812P311. This will be referred to as the Safety Population. Since subjects received variable dosing in this study, all subject data will be summarized together under All SPN-812.

For categorical variables, summary statistics will include the number and percentage of subjects within each category (with a category for missing data). Percentages will be based on the total number of subjects with non-missing data. For continuous variables, summary statistics will include the number of non-missing observations, mean, standard deviation (SD), median, and interquartile range (Q1, Q3), minimum, maximum.

3.2 Baseline Values

For all safety assessments, baseline will be defined as the last non-missing value prior to SPN-812 dosing in the 812P311 study.

For all efficacy assessments, subjects enrolled into 812P311 ≤ 7 days after their last 812P306 visit, the "baseline" efficacy assessment is defined as the assessment that subject completed at Visit 2 in 812P306 prior to the first dose of SPN-812 in 812P306. Additionally, for subjects enrolled into 812P311 > 7 days after their last 812P306 visit, the baseline efficacy assessment is defined as the assessment that was completed at Visit 1 in 812P311 prior to the first dose SPN-812 in 812P311.

All post-baseline assessments are defined as any assessments that were completed after the first dose of SPN-812 in the 812P311 study.

3.3 Handling of Missing Data

There will be no imputation made for missing data points and hence, only observed data will be used for analyses.

3.4 Computing Environment

All descriptive statistical analyses will be performed using SAS (Version 9.4), unless otherwise noted.

4 ANALYSES

4.1 Subject Disposition

The number and percentage of subjects that were dosed, completed the study, or discontinued early will be displayed. Reasons for early discontinuation will be tabulated.

4.2 Demographic Characteristics

Descriptive statistics for demographic characteristics will be calculated for all continuous variables and frequencies and percentages will be presented for categorical variables.

4.3 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, descriptive statistics, and by age group (18 to 44, 45 to 65, and overall). The categories for duration of exposure are: 0 to <13, 13 to <26, 26 to <39, 39 to < 52, 52 to < 65, 65 to < 78, 78 to < 91, 91 to <104, 104 to < 117, 117 to < 130, 130 to < 144, and 144 or more weeks. The actual average daily dose (0 to ≤200, 200 to ≤300, 300 to ≤400, 400 to ≤500, and > 500 mg/day) will be summarized by duration of exposure categories and by age group. Descriptive statistics for planned dose (n, mean, SD, median, min, max, and Q1, Q3) will be summarized by visit and by age group. The actual average daily dose is calculated as dispensed SPN-812 in mg minus returned SPN-812 in mg divided by days taken SPN-812 across all available visits.

4.4 Efficacy Analyses

For the analyses of change from baseline of 812P311 efficacy variables (e.g., descriptive statistics), a subject must have both a valid baseline assessment and at least 1 valid post-baseline assessment to be included in the analyses.

Analysis of efficacy will include:

1) The Change from baseline (CFB) in the AISRS total score will be summarized using descriptive statistics by visit.
2) The CFB in the CGI-S score will be summarized using descriptive statistics by visit.
3) The CGI-S will be dichotomized at each visit: CGI-S will be classified as 'responder' if the score is 1 or 2 and 'non-responder' if the score is 3 to 7. The number and percentage of CGI-S responders will be presented by visit.
4) The CGI-I will be summarized using descriptive statistics by visit.
5) The CGI-I will be dichotomized at each visit: CGI-I will be classified as 'responder' if the score is 1 or 2 and 'non-responder' if the score is 3 to 7. The number and percentage of CGI-I responders will be presented by visit.
6) The CFB in the GAD-7 total score will be summarized using descriptive statistics by visit.
7) The CFB in the AISRS Inattention subscale score and Hyperactivity/Impulsivity subscale scores will be summarized using descriptive statistics by visit
8) The AISRS 50% responder rate: A 50% responder rate is defined as the percentage of subjects with ≥ 50% reduction in AISRS total score from baseline at each visit, where % reduction =100*(AISRS total score - Baseline AISRS total score)/ Baseline AISRS total score.
9) The AISRS 30% responder rate: A 30% responder rate is defined as the percentage of subjects with ≥ 30% reduction in AISRS total score from baseline at each visit, where % reduction =100*(AISRS total score - Baseline AISRS total score)/ Baseline AISRS total score.
10) The CFB in the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) Global Executive Composite (GEC) T-score will be summarized using descriptive statistics by visit.
11) The CFB in the BRIEF-A T-score by BRI, MI and their subscales will be summarized using descriptive statistics by visit.
12) The CFB in the Symptoms of Depression Questionnaire (SDQ) total score will be summarized using descriptive statistics by visit.
13) The CFB in the SDQ subscale scores will be summarized using descriptive statistics by visit.
14) The CFB in the Adult ADHD Quality of Life (AAQoL) total score will be summarized using descriptive statistics by visit.
15) The CFB in the AAQoL subscale scores will be summarized using descriptive statistics by visit.

Where appropriate, the above endpoints will be summarized descriptively (frequency count and percent) for categorical variables, and number of subjects (n), mean, SD, median, interquartile range (Q1 and Q3), minimum, and maximum for continuous variables.

4.5 Safety Analyses

Safety measures include monitoring, evaluation, and recording of all concomitant medications, and the evaluations of AEs, clinical laboratory test results, vital signs, 12-lead ECGs, C-SSRS, and the performance of physical examinations.

4.5.1 Treatment-emergent Adverse Events

AEs will be coded using MedDRA Version 22.1. All AEs will be considered as treatment-emergent adverse events (TEAEs) and included in the AE summaries.

Adverse events will be categorized by MedDRA SOC and/or PT. 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.

For displays, SOCs will be presented in alphabetical order and PTs will be sorted by decreasing incidence under each SOC.

An overview of TEAEs will be provided, this will include summaries of incidence rates (frequencies and percentages) of subjects who had at least one TEAE, serious TEAE, TEAE leading to death, TEAE by maximum severity, TEAE by relationship, TEAE leading to study drug discontinuation, related serious TEAE and Adverse Event of Special Interest (AESI).

TEAEs occurring in at least 5% of subjects will be presented by SOC and PT. TEAEs occurring in at least 5% of subjects by PT will also be presented. In addition, the incidence of TEAEs will also be summarized by MedDRA SOC, PT and maximum severity, in which subjects are counted once for each unique preferred term and each SOC under the known maximum severity at which it was experienced. If severity is unknown for all occurrences of a particular PT, it will be counted under 'severe'. The incidence of TEAEs by MedDRA SOC, PT and relationship to study drug will be produced in the same fashion.

AESIs include seizures or AEs that might represent a seizure (e.g., syncope/syncopal episode, pseudo seizure, myoclonus, severe muscle spasms). To identify the AESI, the following search terms will be used to search among the PTs as well as the verbatim terms: seizure, syncope, syncopal episode, pseudo seizure, myoclonus, and muscle spasms (that is categorized as severe only). The incidence of AESIs will be summarized by MedDRA SOC and PT. For subjects who experienced the same AESI multiple times, the event will be counted once.

4.5.2 Special Safety Categories: Death, Serious Adverse Events and Adverse Events Leading to Study Drug Discontinuation

4.5.2.1 Deaths

A listing of deaths will be presented.

4.5.2.2 Serious Adverse Events

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

4.5.2.3 Adverse Events Leading to Study Drug Discontinuation

The incidences of TEAEs leading to study drug discontinuation will be presented by SOC and PT, and a listing of AEs that led to discontinuation of study drug will be presented.

4.5.3 Laboratory Data

4.5.3.1 Potentially Clinically Significant Laboratory Values

The number and percentage of subjects with PCS values post-baseline will be summarized for the hematology and chemistry parameters defined in Table 1 and Table 2. All scheduled and unscheduled results will be included in this laboratory analysis.

Table 1 Hematology Potentially Clinically Significant Values

Hematology parameter	Potentially clinically significant values
Hemoglobin	Female: <85 g/L or >160 g/dL) Male: <90 g/L or >170 g/L)
Hematocrit (HCT)	Hematocrit (Female) ≤32% or >49 % Hematocrit (Male) ≤37% or >48 %
Platelet count	<125 x 10^9/L or >470 10^9/L
White blood cells (WBC)	<2.0 x 10^9/L or >12.0 10^9/L
Basophils	>0.5 x 10^9/L
Eosinophils	>1.5 x 10^9/L
Lymphocytes	<0.5 x 10^9/L or >6.0 10^9/L
Monocytes	>1.6 x 10^9/L
Neutrophils	<1.5 x 10^9/L

Table 2 Chemistry Potentially Clinically Significant Values

Chemistry parameter	Potentially clinically significant values
Alanine aminotransferase (ALT)	>3 x upper limit of normal (ULN)
Albumin	<22 g/L or >65 g/L
Aspartate aminotransferase (AST)	>3 x ULN
Alkaline Phosphatase (ALP)	>3 x ULN
Bilirubin	>2 x ULN
Blood urea nitrogen (BUN)	>9.6 mmol/L
Calcium	<2.0 mmol/L or >2.75 mmol/L
Chloride	<90 mmol/L or >120 mmol/L
Creatinine	> 1.3 mg/dL or >115 µmol/L
Potassium	<3 mmol/L or >5.8 mmol/L
Sodium	<125 mmol/L or >158 mmol/L
Protein	<45 g/L
Glucose	non-fasting < 2.2 mmol/L or >8.9 mmol/L

Abnormally low or high laboratory results based on the laboratory normal ranges will be presented in a data listing.

4.5.3.2 Abnormal Liver Enzymes and Liver Function Values

Summaries of abnormal liver enzymes and liver function tests post-baseline will be presented for ALT, AST, Direct Bilirubin, Total Bilirubin, and ALP. All scheduled and unscheduled results will be included in these analyses.

4.5.4 Vital Signs

The number and percentage of subjects with abnormally low or high vital sign values post-baseline based on the normal ranges defined in Table 3 will be presented. All scheduled and unscheduled results will be included in this analysis.

Table 3 Vital Signs Normal Ranges

Measurement	Normal Range
Body mass index	18 – 35 kg/m^2
Temperature	95-100 °F (35-37.8 °C)
Diastolic blood pressure	60 – 90 mmHg
Systolic blood pressure	90 – 140 mmHg
Heart rate	50 – 100 bpm
Respiration rate	10 – 25 breaths per minute

A listing of subjects with abnormalities in vital sign parameters will be presented.

4.5.5 ECG Data

Twelve-lead ECGs will be collected. Descriptive summaries will be presented for heart rate (bpm), PR interval (msec), QRS duration (msec), uncorrected QT interval (msec), and QTcF (msec).

Normal, abnormal but not clinically significant, and abnormal and clinically significant ECG investigator interpretation results will be summarized and flagged in the listings.

The number and percentage of subjects with post-baseline abnormally low or high values for heart rate, PR interval, and QRS duration based on the normal ranges defined in Table 4 will be presented.

Table 4 ECG Normal Ranges

Parameter	Low	High
Heart Rate (beats/min)	45	120
PR Interval (msec)	120	220
QRS Duration (msec	80	130

Additionally, the number and percentage of subjects with actual QT and QTcF values ≤450 msec, 450 msec to ≤480 msec, 480 to ≤ 500 msec, >500 msec and with changes from baseline ≤30 msec, 30 msec to ≤60 msec, and >60 msec will be presented.

All ECG results will be displayed in the data listings.

4.5.6 C-SSRS Data

C-SSRS outcomes will be summarized and listed. The number and percentages of subjects with a response of "Yes" at any visit by categories for suicidal ideation only, suicidal behavior only, suicidality (ideation and behavior combined) items, and non-suicidal self-injurious behavior will be presented.

4.5.7 Caffeine Intake

Weekly caffeine intake will be summarized by consumption category. Weekly caffeine consumption categories include no caffeine intake, 0 to <250 mg, 250 to ≤500 mg, 500 to ≤750 mg, 750 to ≤1000 mg, 1000 to ≤1250 mg, 1250 to ≤1500 mg, 1500 to ≤1750 mg, 1750 to ≤2000 mg, and ≥2000 mg.

4.5.8 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately by ATC Class Level 4 and PN.

5 TABLES AND LISTINGS

For table, listing, and figure mock shells, see Appendix B: TLF Shells.

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