STATISTICAL ANALYSIS PLAN

An Open-Label, Single-Group Study to Evaluate the Efficacy and Safety of SPN-820 in Adults with Major Depressive Disorder

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Alternative Drug Name:	SPN-820
Phase:	Phase 2
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 Phone 301.838.2500
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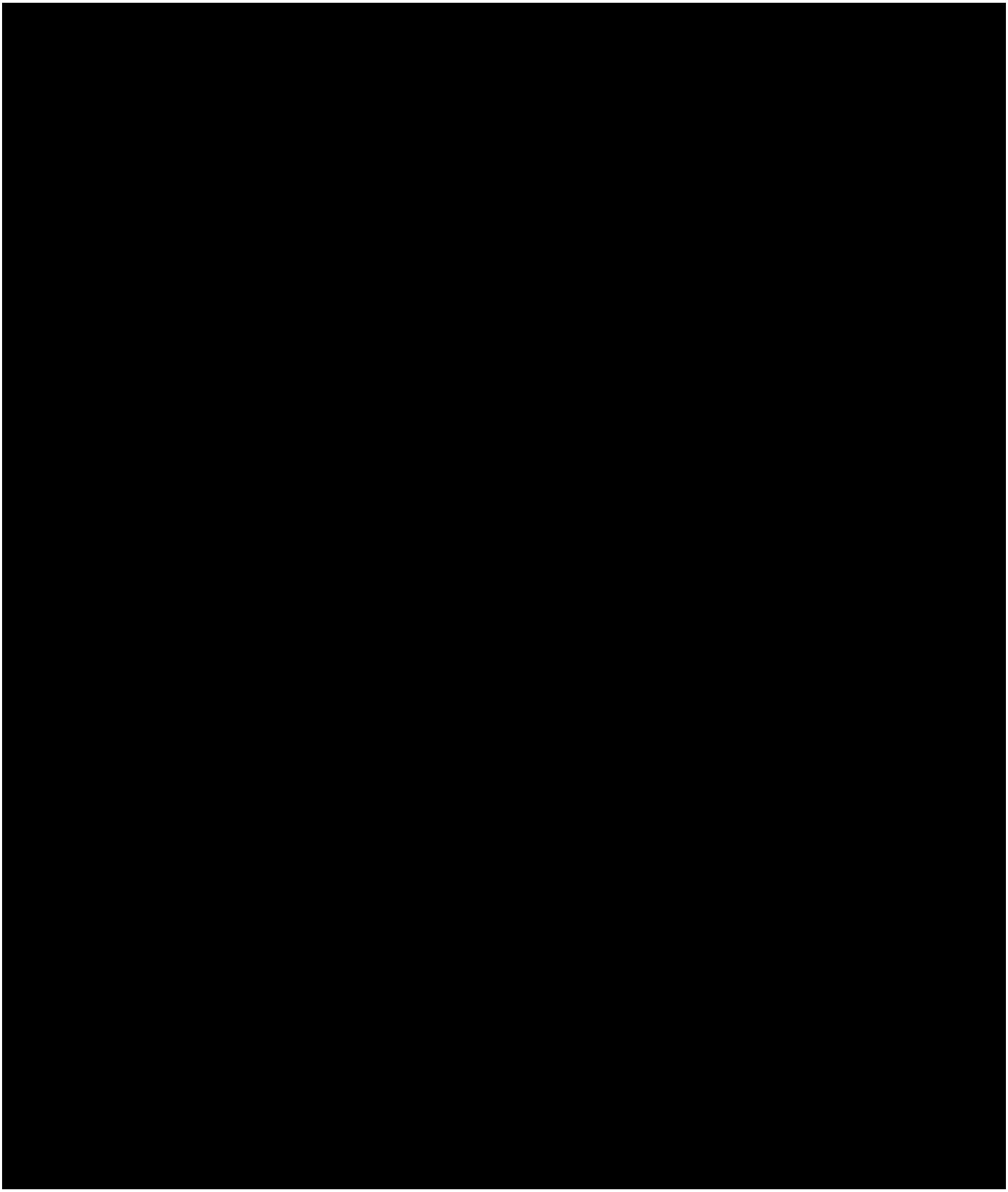

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VERSION HISTORY

Version	Section	Description of Change	Rationale
1.0	NA	Original Version	NA

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADT	Antidepressant Therapy
ATC	Anatomical Therapeutic Chemical
BDNF	Brain-Derived Neurotrophic Factor
BLQ	Below Limit of Quantification
BMI	Body Mass Index
BPRS	The Brief Psychiatric Rating Scale
CADSS	Clinician Administered Dissociative State Scale
CGI-S	Clinical Global Impression – Severity of Illness
C_{max}	Maximum Observed Concentration
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	Trough plasma concentration (Concentration at the end of dosing interval)
CFB	Change from Baseline
CI	Confidence Interval
CNV	Clinically Notable Values
eCRF	Electronic Case Report Form
CV%	Coefficient of variation expressed as a percentage
ECG	Electrocardiogram
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
HAM-D6	Hamilton Depression Rating Scale-6 Items
IPD	Important Protocol Deviation
LLOQ	Lower Limit of Quantification
MADRS	Montgomery–Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDD	Major Depressive Disorder
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term

Q1	First Quartile
Q3	Third Quartile
QTc	QT Interval Corrected for Heart Rate
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Method
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SM	Study Medication
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
T_{max}	Time to Reach Maximum Observed Concentration (C_{max})
WHO-DD	World Health Organization Drug Dictionary

1. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and other efficacy endpoints are described in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: To evaluate the efficacy of SPN-820 administered once every 3 days for a 7-day treatment period in adults with major depressive disorder (MDD).	**Primary Efficacy Endpoint:** • Change from baseline (CFB) to each time point in the Hamilton Depression Rating Scale-6 Items (HAM-D_6) total score. **Secondary Efficacy Endpoints:** • CFB to each time point in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score. • CFB to each time point in the Clinical Global Impression – Severity of Illness (CGI-S) total score. • Proportion of subjects achieving a ≥50% reduction from baseline in the MADRS total score. • Proportion of subjects in remission (MADRS total score ≤10) at each time point. • Percentage of subjects with a CGI-S score of 1 or 2 at each time point.
Secondary Objectives: 1. To evaluate the safety and tolerability of SPN-820 administered once every 3 days for a 7-day treatment period in adults with MDD. 2. To characterize the pharmacokinetics (PK) of SPN-820 and its metabolite M8 in plasma after multiple administrations of SPN-820.	**Safety Endpoints:** • Treatment-emergent adverse events (TEAEs). • Clinical safety laboratory test results. • Vital sign measurements including orthostatic blood pressure and pulse rate. • Body weight. • Electrocardiography (ECG) findings. • Physical examination findings. • Suicidal ideation and behavior as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) score. • Dissociative symptomatology as measured by Clinician Administered Dissociative State Scale (CADSS) score. • Psychopathology severity as measured by Brief Psychiatric Rating Scale Positive Subscale (BPRS+) score. [redacted]

Objectives	Endpoints
	• [redacted]
Exploratory Objective: To characterize the effect of SPN-820 on brain-derived neurotrophic factor (BDNF) concentrations.	**Exploratory Endpoint:** • CFB to each time point for BDNF concentrations.

2. STUDY DESCRIPTION

2.1. Study Design

This is an open-label study of SPN-820 administered orally once every 3 days for a 7-day treatment period in adult subjects with major depressive disorder (MDD). The study consists of a 28-day screening period, a 10-day evaluation period (clinic and home), and a safety follow-up phone call approximately 5 (+2) days after the last administration of study medication (SM). The total study duration from the screening visit to completion of the safety follow-up phone call is up to 40 days.

2.2. Schedule of Visits and Study Procedures

The Schedule of Events and Assessments for the study is shown in Section 1.1.

2.3. Study Treatment

SM will be administered orally in the clinic once every 3 days for a 7-day treatment period. SM should be administered in the morning, approximately 3 hours after breakfast.

Subjects will receive a single dose of SPN-820 2400 mg as six 400 mg capsules on days 1, 4, and 7.

Subjects who cannot tolerate SPN-820 2400 mg should be discontinued from the study at the discretion of the Investigator.

Subject will not receive SM on days 2, 3, 5, 6, 8, 9, or 10.

2.4. Randomization

Not applicable.

2.5. Blinding

Not applicable.

2.6. Sample Size

Approximately 50 subjects will be enrolled to achieve about 40 subjects completing the study. This sample size is based on clinical judgement without a formal, statistical power calculation.

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 will be summarized for the SPN-820 treatment group.

Continuous variables will be summarized descriptively using number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

Categorical variables will be summarized descriptively using counts and percentages. When the denominator for the percentage is different from the number of subjects in the treatment column header of a summary table, the denominator will be specified in a footnote for the table.

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

3.2. Definitions and Derivations

The definitions and derivations are shown in Table 2.

Table 2: Definitions and Derivations

Terminology	Definition
Baseline	Unless specified otherwise, baseline is the last non-missing assessment collected before the first dose of SM (Day 1).
Study Day	Day 1 is defined as the date of the first dose of study medication. For visits prior to Day 1, Study Day is calculated as (Event date – Day 1). For visits after Day 1, Study Day is calculated as (Event date – Day 1 + 1).
Screened Subjects	Subjects who have provided signed informed consent.

3.3. Analysis Population

The full analysis set (FAS) includes all subjects who receive at least one dose of SM, and have a baseline and at least one post-baseline measurement of HAM-D_6.

The Safety Population includes all subjects who receive at least one dose of SM.

[redacted].

The Pharmacodynamics (PD) Population includes all subjects who receive at least one dose of SM and have a baseline and at least one valid post-baseline BDNF concentration.

3.4. Data Pooling

Data from all sites will be pooled together for all analyses unless otherwise specified.

3.5. Adjustments for Covariates

Not Applicable.

3.6. Hypotheses

Not Applicable.

3.7. Multiplicity Adjustments

Not Applicable.

3.8. Subgroups

No subgroup analyses are planned.

3.9. Handling of Missing Data

3.9.1. Missing Efficacy Endpoints

Missing efficacy endpoints will not be imputed. Efficacy endpoints will be summarized on an observed-case basis.

3.9.2. Missing Dates for Adverse Events and Concomitant Medication

Missing dates for adverse events (AEs) and concomitant medications will be imputed according to the rules in Table 3.

Table 3: Missing Date Imputation for Adverse Event or Concomitant Medication

Missing Date Pattern	Imputation Rule
Partial Start Date	• Missing day only: Impute the first dose date if (1) the year and the month of the event start date are identical to those of the first dose date and (2) the event end date is not prior to the first dose date; otherwise, impute the first day of the month. • Missing month only: Impute the first dose month if (1) the year of the event start date is identical to the year of the first dose date and (2) the event end date is not prior to the first dose date; otherwise, impute January. • Missing month and day: Impute the first dose date if (1) the year of the event start date is identical to the year of the first dose

Missing Date Pattern	Imputation Rule
	date and (2) the event end date is not prior to the first dose date; otherwise, impute 1st January.
Partial End Date	• Missing day only: Impute the last day of the month or the last study date, whichever is earlier. • Missing month only: Impute December or the month of the last study date, whichever is earlier. • Missing month and day: Impute 31st December or the last study date, whichever is earlier.
Missing Year or Completely Missing Date	No Imputation will be done.

3.10. Visit Windows

Unless otherwise specified, data will not be analyzed using visit windows; instead, nominal visits will be used. Deviations from protocol-specified visit windows will be recorded and displayed in data listings.

3.11. Interim Analyses

No interim analyses are planned.

4. STUDY SUBJECT AND EXPOSURE

4.1. Subjects Disposition

Subject disposition will be summarized descriptively using the number and percentage.

The disposition table will include the following categories:

- Number of subjects screened.
- Number of subjects in the specified population (i.e., Safety, FAS, PK and PD)
- Number (%) of subject who completed the study in the specified population
- Number (%) of subject who discontinued the study as well as the primary discontinuation reasons as recorded in the eCRF in the specified population

Inclusion and exclusion criteria met/not met and reasons for screen failures will be summarized in a separate table. A listing of subject disposition will be provided.

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:

- Subjects who received the study treatment but are later found not to have met all the inclusion criteria or met any of the exclusion criteria
- Subjects who received concomitant medications that were prohibited as described in Protocol Section 5.7

Occurrence of any of these and other events may be considered as potential IPDs. However, these events should be categorized as IPDs only if they could potentially affect interpretation of study results. Prior to the database lock, potential IPDs identified in the clinical database and/or recorded in the site deviation log will be reviewed for the determination of IPDs. All protocol deviations will be provided in subject data listings.

4.3. Demographic and Baseline Characteristics

Subject demographics and characteristics will be summarized descriptively using the Safety Population. Demographic includes age in years, age group (18-45, 46-65), sex, race, and ethnicity. Baseline characteristics includes height, weight, body mass index (BMI), and other pre-dosed baseline efficacy measurements (i.e. HAM-D_6, MADRS, and CGI-S total scores).

4.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version v26.1. 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 descriptively using the Safety Population. The table will be sorted by descending frequency of SOC and then PT within SOC. All medical and psychiatric history will be listed.

4.5. Prior and Concomitant Medications

Prior and concomitant medications and antidepressant therapy (ADT) will be coded using WHO DRUG Global version SEP2023 with anatomical therapeutic chemical (ATC) classification and Preferred Name (PN). ATC fourth (ATC4) level is for the chemical, pharmacological or therapeutic subgroup. If a ATC4 level classification is not available for a coded term, the lowest available ATC level code will be substituted.

If a medication starts prior to the first dose and continues after the first dose, it will be considered both prior and concomitant. Prior and concomitant medications as well as ATDs will be summarized by ATC and PN, and also listed by subject ID using the Safety Population.

4.6. Study Treatment Exposure

Duration of exposure for each subject is defined as:

- Duration of Treatment Exposure = date of last dose – date of first dose + 1.

The number (%) of subjects been dosed at each visit and the duration of exposure (days) will be summarized descriptively. A listing of treatment exposure will also be provided.

5. EFFICACY ANALYSES

All efficacy data will be summarized descriptively using the FAS and listed using the Safety Population.

5.1. Primary Efficacy Endpoint

The Hamilton depression rating scale is one of the most widely used clinician-administered depression scales. The original version contains 17 items related to symptoms of depression over the past week developed for hospital inpatients. The HAM-D_6, a subscale version with 6 items derived from the 17 items of the original scale, offers sensitivity for measuring severity of detecting improvement of depression comparable to other more complex versions. Five of the 6 items (Depressed Mood, Work and Activities, Feeling of Guilt, Anxiety Psychic, and Retardation) are scored on a scale of 0 to 4, and 1 item (Somatic Symptoms General) is scored on a scale of 0 to 2, for a possible total score of 0 to 22. If any item score is missing, the total score will not be calculated. A total score ranging 0-4 indicates that the subject is in the normal range (no depression), a score ranging 5-8 indicates “mild depression”, 9-12 indicates “moderate depression”, and 13-22 indicates “severe depression”.

CFB in the HAM-D_6 total score will be analyzed descriptively at each time point using the FAS.

5.2. Secondary Efficacy Endpoints

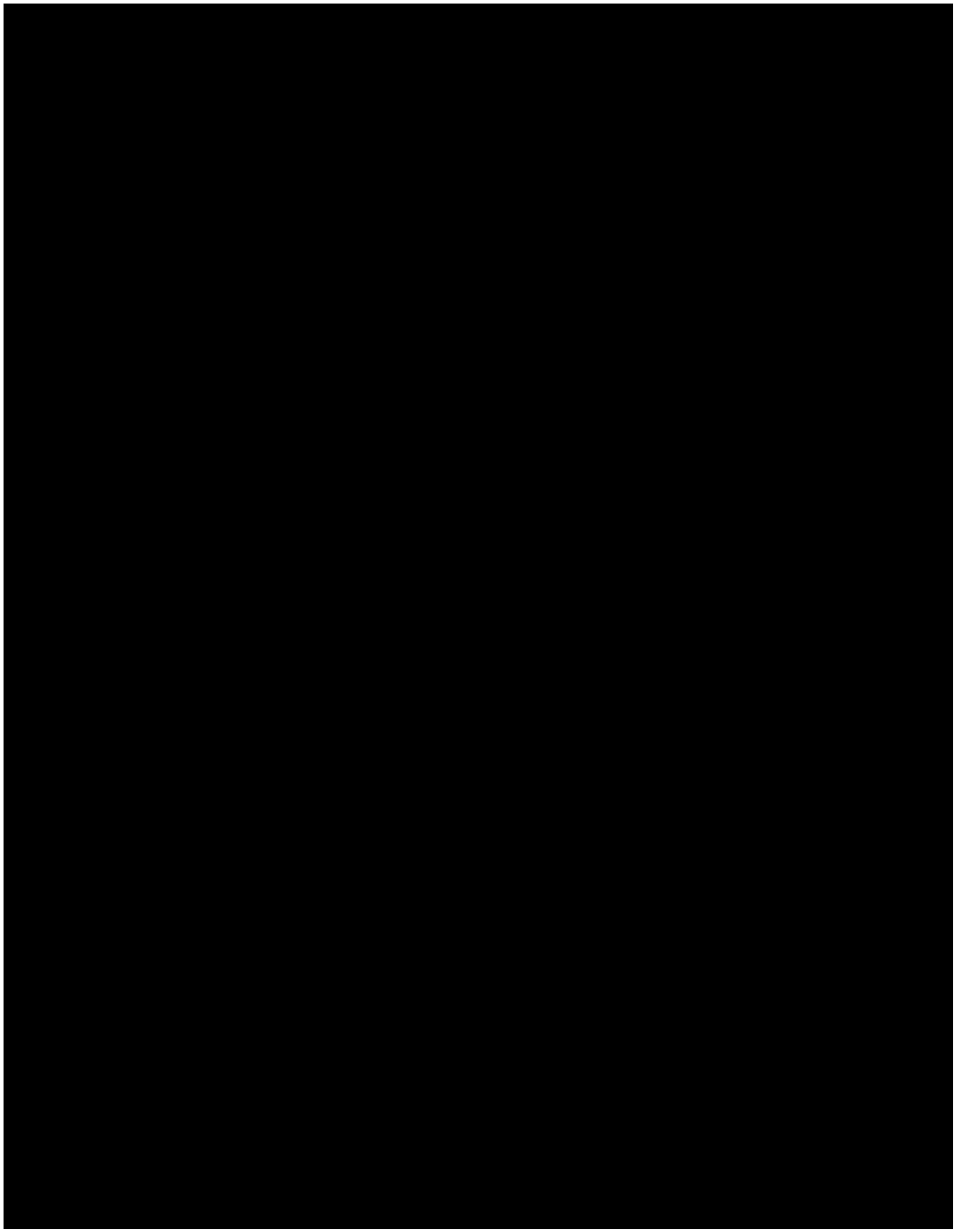
The MADRS is a 10-item investigator-rated diagnostic questionnaire used to measure the severity of depressive episodes in subjects with mood disorders and is designed to be sensitive to changes brought on by treatment. Each question is scored from 0 to 6, the sum of the 10 subtests score will yield a total score ranging from 0 to 60. If any item score is missing, the total score will not be calculated. A total score ranging from 0 to 6 indicates that the subject is in the normal range (no depression), a score ranging from 7 to 19 indicates “mild depression”, 20 to 34 indicates “moderate depression”, and 35 to 60 indicates “severe depression”.

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

CFB to each time point in the MADRS total score and CGI-S score will be analyzed using descriptive statistics.

Percent reduction, defined as 100×(postbaseline–baseline)/baseline, in MADRS total score will be derived for each subject.

The n (%) of responders (i.e., subjects with ≥50% reduction in MADRS total score), the n (%) of subjects in remission (i.e., subjects with MADRS total score ≤10) and the n (%) of subjects with a CGI-S score of 1 or 2 will be summarized at each scheduled time point.



7. PHARMACODYNAMICS ANALYSES

Concentrations below the lower limit of quantitation (<LLOQ) will be treated as zero. Concentrations above the upper limit of quantitation (>ULOQ) will use the value of ULOQ.

To measure BDNF concentrations, additional 2 blood samples will be collected at clinic visits on days 1, 4 and 7, as follows:

- pre-dose (within 60 minutes of SM administration).
- 4 hours (±30 minutes) following SM administration.

One additional blood sample will be collected at the clinic visit on Day 10, as follows:

- 72 hours (±60 minutes) following the last SM administration on Day 7.

The PD analysis is an exploratory analysis and will be performed using the PD population.

The change and percent change from baseline in BDNF concentrations at each time point will be analyzed descriptively. The mean (±SD) over time for the change and percent change from baseline will be displayed graphically. The relationship between the change and the percent changes from baseline in BDNF and the efficacy endpoints (e.g., HAM-D_6 and MADRS Total score) or plasma SPN-820 concentrations will be explored graphically using the data from the above time points. Because no PK blood samples were taken on Day 10, the BDNF data on Day 10 will not be used in the exploration of the relationship with plasma concentrations.

8. SAFETY

The assessment of overall safety and tolerability will be based on adverse events, laboratory values, vital signs and weight, ECGs, physical examinations, C-SSRS, CADSS, and BPRS+ using the safety population.

8.1. Adverse Events

All adverse events (AEs) will be coded using the MedDRA v26.1. The MedDRA version used for reporting will be specified in the footnote of the applicable output.

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the date of the first dose of study medication, or that worsened in severity following the first dose of study medication. Any event that is present at baseline but worsens in severity will be determined by the Investigator and entered in the CRF as new AE. Thus, all eCRF-collected AEs that occurred on or after the date of the first dose of study medication are TEAEs.

Based on the Investigator's determination, the severity of TEAEs will be classified as mild, moderate or severe. For summaries by severity, a subject experiencing multiple AEs 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 subject experiencing multiple AEs in the same preferred term with different relationship will only be counted once with the most related occurrence.

An overview of TEAE will include summaries of number and percent of subjects who had at least one TEAE, Treatment-emergent serious AE (SAE), Treatment-emergent SAEs related to SM, TEAE leading to death, TEAE by maximum severity, TEAE by relationship, and TEAE leading to withdrawal of study medication.

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

- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Most Common (≥ 5%) Treatment-Emergent Adverse Events by Preferred Term
- Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity
- Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Medication
- Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events Leading to Withdrawal of Study Medication by System Organ Class and Preferred Term

- 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.

A subject with multiple occurrences of an AE will be counted only once in the AE category per SOC and PT for summary tables. The sorting will be based on the decreasing frequency.

Listing will be provided for all AEs, SAE, and TEAE Leading to Withdrawal of Study Medication.

8.2. Laboratory

Laboratory data will be collected according to the schedule in Section 11.1. Different local laboratories may have different normal (reference) ranges and units for each of the laboratory tests (parameters). Thus, all numerical laboratory values will be converted to the International System of Units (SI) and then normalized to a standard set of reference ranges as described by Chuang-Stein (1992 and 2001). The normalization process will be performed separately by each of the laboratory parameters as described in Section 11.2. These normalized data will be used for summary statistics. All data summaries and listings will be provided in SI.

Numerical laboratory values reported in a special form (e.g., $<x$, $\leq x$, $>x$, or $\geq x$) will be derived as a numerical value, x, for summary statistics. However, the originally reported values in the special form (i.e., $<x$, $\leq x$, $>x$, or $\geq x$) will be presented in data listings.

8.2.1. Absolute Value and Change from Baseline

Absolute values and CFB in haematology, serum chemistry and urinalysis variables will be summarized descriptively by visit.

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 used in summary statistics but will be included in data listings.

8.2.2. Shift in Laboratory Values

Compared to the original reference range, each laboratory test value will be classified as low, normal, high or missing. Shift tables of laboratory data from baseline will be summarized using number and percentage of subjects by visit.

The shift from baseline to the worst post-baseline laboratory values will also be presented. The worst post-baseline value is defined as the highest or the lowest value (for some parameters may be applicable in both directions) among all post-baseline values collected at any time from all (scheduled and unscheduled) visits.

8.2.3. Clinically Notable Values of Laboratory

Values of laboratory tests are considered clinically notable values (CNV) if they meet the selected criteria in Section 11.3. The number and percentage of subjects with post-baseline CNV will be summarized by overall. For each individual laboratory parameter, the denominator of the percentage includes all subjects who have a non-CNV (or including missing) at baseline and at least one post-baseline assessment (including unscheduled visit) for that parameter. And the numerator of the percentage is the number of subjects who are included in the denominator and

have a CNV at post-baseline for that parameter. A supportive listing of subjects with any CNVs will be provided.

Number and percent of subjects who meet Hy's Law criteria (ALT or AST >3×ULN, along with total bilirubin >2×ULN and a non-elevated ALP <2×ULN, where ULN denotes the upper limit of the normal range) will be summarized.

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 reference range of each laboratory test.

8.3. Vital Signs

8.3.1. Absolute Value and Change from Baseline

The CFB in vital sign variables will be calculated for each post-baseline visit. The postural change in blood pressure and pulse rate from sitting to standing will be calculated for each visit. The analyses of vital signs will be summarized descriptively in the same manner as described in Section 8.2.1.

8.3.2. Shift in Vital Signs

The shift analyses of vital signs will be performed in the same manner as described in Section 8.2.2. Vital sign normal ranges are presented in Section 11.4.

8.3.3. Clinically Notable Values of Vital Signs

The number and percentage of subjects meeting the criteria of clinically notable values specified in Section 11.5 will be summarized by overall. For each individual vital sign parameter, the denominator of the percentage includes all subjects who had a baseline and at least one post-baseline assessment (including unscheduled visit) for that parameter. And the numerator of the percentage is the number of subjects who are included in the denominator and have a CNV at post-baseline for that parameter.

8.4. Weight

8.4.1. Absolute Value and Change from Baseline

The CFB in body weights will be calculated for each post-baseline visit. The analyses of body weights will be summarized descriptively in the same manner as described in Section 8.2.1.

8.5. Electrocardiogram

8.5.1. Absolute Value and Change from Baseline

The CFB in electrocardiogram (ECG) variables will be calculated for each post-baseline visit. The analyses of ECG will be summarized descriptively in the same manner as described in Section 8.2.1.

8.5.2. Shift in ECG

The shift analyses of ECG will be performed in the same manner as described in Section 8.2.2. ECG normal ranges are presented in Section 11.6.

8.5.3. Incidence of ECG

The number and percentage of subjects meeting the following criteria for any post-baseline value will be presented:

- QTcF: 450 to 480 msec (if male); 470 to 480 msec (if female); 480 to 500 msec; >500 msec
- CFB in QTcF: 30 to 60 msec; >60 msec.

8.6. Physical Examination

The number and percentage of subjects with Normal, Abnormal not Clinically Significant, Abnormal Clinically Significant and Not Done findings from CRF page will be summarized descriptively and flagged in the listings. Data listings will be provided.

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

C-SSRS includes combined suicidal ideation from 5 suicidal items (categories 1-5), combined behavior from 5 behaviors items (categories 6-10), overall suicidal ideation or behavior classification, and non-suicidal self-injurious behavior. The number and percentage of subjects with a response of "Yes" to each category of suicidal ideation and suicidal behavior will be presented by visit. The data listing for C-SSRS will be provided.

8.8. CADSS and BRPS+

The CADSS is a 23-item clinician administered scale that measures present-state dissociative symptoms. The subject then rates items on a 4-point Likert scale as follows:

a. 0 = not at all
b. 1 = mild
c. 2 = moderate
d. 3 = severe
e. 4 = extreme

The total score ranging from 0 – 92 is the sum of the 23 items.

The Brief Psychiatric Rating Scale (BPRS+) is a tool clinicians or researchers uses to measure psychiatric symptoms such as anxiety, depression, and psychoses. For the study, the version used is adapted from the original BPRS 4-item positive symptoms (BPRS+). The scale is comprised of 4 items assessing a subject's experience of psychosis, often referred as positive symptoms of Suspiciousness, Hallucinatory Behavior, Unusual Thought Content and Conceptual Disorganization. Of the 4 items assessed, the first three items are based on questions asked by the clinician to the subject, Conceptual Disorganization is a clinician rated item based on observation of subjects' behavior and speech during the assessment. Each subscale is rated on a 7-point scale ranging from 0-7 as follows:

a. 0 = not able to be assessed
b. 1 = not present
c. 2 = very mild
d. 3 = mild

e. 4 = moderate
f. 5 = moderately severe
g. 6 = severe
h. 7 = extremely severe

The total score ranging from 0-28 is the sum of the 7 items.

Descriptive statistics will be presented for CADSS total score, and BPRS+ scores by visit.

9. CHANGES FROM THE PROTOCOL

No changes to any planned analyses from the protocol.

10. REFERENCES

1. Chuang-Stein, C. Some Issues Concerning The Normalization of Laboratory Data Based on Reference Ranges. *Drug Information Journal*. 2001; 35:153-156.
2. Chuang-Stein, C. Summarizing Laboratory Data With Different Reference Ranges in Multicenter Clinical Trials. Drug Information Journal. 1992; 26:77-84.

11. APPENDIX

11.1. Schedule of Events and Assessments

Study Period	Screening	Evaluation Period							Safety/ Follow-Up (FPC[a])
		Seven-Day Treatment Period						EOS/ ET	
	Clinic	Clinic (Baseline)	Home	Clinic	Home	Clinic	Home	Clinic	Home
Visit Number	1	2	-	3	-	4	-	5	
Study Day	-28 to -1	1	2-3	4	5-6	7	8-9	10	12
Window Visit (days)									+2
Sign informed consent	X								
Review eligibility criteria	X	X							
Demographics	X								
Medical history[b]	X								
Confirm MDD diagnosis	X								
Record prior medications	X								
Confirm stable, therapeutic dose of one study-approved ADT	X								
MINI	X								
Physical examination[c]	X	X						X	
Height	X								
Body weight	X	X		X		X		X	
Calculation of body mass index	X								

Study Period	Screening	Evaluation Period							Safety/ Follow-Up (FPC[a])
		Seven-Day Treatment Period						EOS/ ET	
	Clinic	Clinic (Baseline)	Home	Clinic	Home	Clinic	Home	Clinic	Home
Visit Number	1	2	-	3	-	4	-	5	
Study Day	-28 to -1	1	2-3	4	5-6	7	8-9	10	12
Window Visit (days)									+2
Vital signs with orthostatic blood pressure and pulse rate[d]	X	X		X		X		X	
12-Lead ECG[e]	X	X		X		X		X	
Blood sample for hematology	X	X				X		X	
Blood sample for chemistry	X	X				X		X	
Blood sample for serology[f]	X								
Blood sample for FSH (post-menopausal females only)	X								
Serum pregnancy test (FOCP only)	X								
Urine sample for urinalysis	X	X				X		X	
Urine sample for urine drug screen and alcohol screen[g]	X	X		X		X		X	
Urine sample for pregnancy test (FOCP only)		X		X		X		X	
HAM-D_6	X	X	X[h]	X	X[h]	X	X[h]	X	
MADRS	X	X		X		X		X	
CGI-S	X	X		X		X		X	

Study Period	Screening	Evaluation Period							Safety/ Follow-Up (FPC[a])
		Seven-Day Treatment Period						EOS/ ET	
	Clinic	Clinic (Baseline)	Home	Clinic	Home	Clinic	Home	Clinic	Home
Visit Number	1	2	-	3	-	4	-	5	
Study Day	-28 to -1	1	2-3	4	5-6	7	8-9	10	12
Window Visit (days)									+2
C-SSRS (Screening/Baseline Version)	X								
C-SSRS (Since Last Visit Version)		X		X		X		X	X
CADSS	X	X				X		X	X
BPRS+	X	X				X		X	X
Review AEs[i]		X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X
[redacted]									
Blood sample for BDNF[j]		X		X		X		X	
SM administered[k]		X[i]		X[i]		X[i]			
Medication adherence diary[l]	X	X	X	X	X	X	X	X	
ADT[m]	←								→

ADT=antidepressant therapy; AE=adverse event; BDNF=brain-derived neurotrophic factor; BPRS+=Brief Psychiatric Rating Scale Positive Subscale; CADSS=Clinician Administered Dissociative State Scale; CGI-S=Clinical Global Impression – Severity of Illness; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiography; EOS=End of Study; ET=Early Termination; FOCP=females of childbearing potential; FPC=Follow-Up Phone Call; FSH=follicle-stimulating hormone; HAM-D_6=Hamilton Depression Rating Scale-6 Items; MADRS=Montgomery–Åsberg Depression Rating Scale; MDD=major depressive disorder; MINI=Mini International Neuropsychiatric Review[redacted]; SM=study medication
Note: An attempt will be made to have the same qualified rater administer the same scales (efficacy) throughout the study for each subject. Administration of the HAM-D_6 and MADRS will be performed by 2 different raters.

a. The follow-up assessments will be performed through a safety follow-up phone call. The safety follow-up phone call will occur approximately 5 days after the last administration of SM.
b. AEs reported during screening will be recorded as part of the subject's medical history.
c. A complete physical examination will be performed at screening and baseline visits; a brief physical examination will be performed at EOS/ET.
d. Vital signs measurements include orthostatic blood pressure/pulse rate, respiratory rate, and oral temperature. Orthostatic blood pressure and pulse rate should be measured after the subject has been sitting for 5 minutes and again within 3 minutes of subject standing.
e. ECGs should be performed prior to blood draws.
f. Serology tests include human immunodeficiency 1/2 antigen/antibody, hepatitis B surface antigen, and hepatitis C virus antibody.
g. A standard urine drug screen will be performed at screening and point-of-care urine drug screen together with the breathalyzer will be performed at baseline (day 1) and all post-baseline clinic visits (days 4, 7, and 10).
h. On days 2, 3, 5, 6, 8, and 9, the HAM-D_6 questionnaire will be administered remotely by telephone.
i. SAEs will be captured from the time of ICF signing, and AEs will be captured following the first administration of SM and continue through the FPC.
j. Seven total blood samples will be collected for measurement of BDNF concentrations: 3 pre-dose collections on days 1, 4 and 7; 3 post-dose collections 4 hours after SM administration on days 1, 4, and 7; and 1 collection on day 10.
k. Subjects will take their SM in the clinic.
l. Subjects will receive a paper ADT adherence diary at screening and document the day and time of each dose of their ADT throughout the study. Subjects will bring their ADT adherence diaries to each clinic visit for review of subject compliance.
m. ADT will not be provided by the Sponsor. Subject's ADT will have started and have been stable for at least 4 weeks prior to screening and will continue through the safety follow-up phone call.

11.2. Clinical Laboratory Normalization

If normal values of laboratory parameters were provided from different local laboratories with inconsistent units and normal ranges, all numerical values will be converted to the conventional units and normalized to a standard set of reference/normal ranges as described by Chuang-Stein (1992 and 2001). The normalization process will be performed separately by each of the laboratory parameters.

For numerical laboratory values, the normalized values will be proportional to the ratio of the widths of reference ranges and aligned with the corresponding lower limits. For example, let (L_S, U_S) denote the standard reference range and let (L_A, U_A) represents the reference range from a local Laboratory A. Let φ denote the laboratory value provided from Laboratory A, which is needed to be normalized. The normalized value, φ_S, can be derived from the formula,

$$\varphi_S = L_S + \beta \times (\varphi - L_A),$$

where $\beta = (U_S - L_S) / (U_A - L_A)$ equals the ratio of the widths of the reference ranges.
If the normalized value, φ_S, becomes negative, the value will be replaced by zero. If one, say the lower, of the limits of a reference range is missing then the missing limit will be imputed according to the ratio of the limits from one of the closest reference ranges provided in this study. For example, let L_M denote the missing lower limits from Laboratory B. Its corresponding higher limit, U_B, is found to be closest to the upper limit, U_C from Laboratory C among all the reference upper limits in the study. Then, L_B will be imputed by the formula,

$$L_B = L_C \times (U_B / U_C),$$

where L_C denotes the lower limit from Laboratory C. For cases where only the upper limits are missing (i.e., the lower ones are non-missing), same imputation process will be performed. For cases where both limits of a reference range are missing, the missing upper and lower limits will be imputed nu the largest upper and lowest limit among all the observed reference ranges, respectively.Because WBS differentials consist of five different type (neutrophils, lymphocytes, monocytes,
eosinophils, and basophils), the normalized differentials in percentages need to be adjusted so they add up to 100%. Let the five-part differentials be denoted by WD_k (k = 1, 2, 3, 4 5), respectively. The adjusted differential, WD_k^* in percentages, will be derived by the formula

$$WD_k^* = \{WD_k / (WD_1 + WD_2 + WD_3 + WD_4 + WD_5)\} \times 100\%,$$

where k = 1, 2, 3, 4, 5.

Similarly, the normalized differentials in absolute counts need to be adjusted to the total WBC count. Let the five-part differentials in absolute counts be denoted by aWD_k (k = 1, 2, 3, 4 5), respectively. The adjusted differential, aWD_k^* in absolute counts, will be derived by the formula

$$aWD_k^* = \{aWDk / (aWD_1 + aWD_2 + aWD_3 + aWD_4 + aWD_5)\} \times WBC,$$

where k = 1, 2, 3, 4, 5 and WBC denotes the total WBC count.

11.3. Criteria for Clinically Notable Laboratory Values

Table 5: Criteria for Clinically Notable Laboratory Values

LBCAT	LBTEST	Sex	LBUNIT	Low	High
Hematology	Basophils		10^9 cell/L	0	0.5
Hematology	Eosinophils		10^9 cell/L	0	1.5
Hematology	Hematocrit (HCT) -Female	Female	LLN or ULN	0.667	1.5
Hematology	Hematocrit (HCT) - Male	Male	LLN or ULN	0.667	1.5
Hematology	Hemoglobin	Female	g/L	80	
Hematology	Hemoglobin Change from Baseline	Female	g/L	20	
Hematology	Hemoglobin	Male	g/L	120	
Hematology	Hemoglobin Change from Baseline	Male	g/L	30	
Hematology	Lymphocytes		10^9 cell/L	0.5	20
Hematology	Monocytes		10^9 cell/L	0	1.2
Hematology	Neutrophils		10^9 cell/L	1.5	
Hematology	Platelet count		10^9 cell/L	75	
Hematology	White blood cells (WBC)		10^9 cell/L	2	100
Serum Chemistry	Alanine aminotransferase (ALT)		ULN		5
Serum Chemistry	Albumin		g/L	20	
Serum Chemistry	Aspartate aminotransferase (AST)		ULN		5
Serum Chemistry	Alkaline Phosphatase (ALP)		ULN		5
Serum Chemistry	Bilirubin		ULN		3
Serum Chemistry	Blood urea nitrogen (BUN)		mg/dL	5	28
Serum Chemistry	Calcium		mmol/L	2	2.9
Serum Chemistry	Chloride		LLN or ULN	0.8	1.2
Serum Chemistry	Creatinine		ULN		3
Serum Chemistry	Glucose - non-fasting		mg/dL	55	180
Serum Chemistry	Glucose - fasting		LLN or ULN	0.7	3
Serum Chemistry	Potassium		mmol/L	3	6
Serum Chemistry	Protein, total		g/L	39	101
Serum Chemistry	Sodium		mmol/L	125	155
Urine	Blood			1+	
Urine	Glucose			1+	
Urine	Protein			2+	

11.4. Normal Range for Vital Sign

Table 6: Vital Sign Normal Ranges

Parameter	Low	High
Body Mass Index (kg/m^2)	18	35
Temperature (°C)	35	37.8
Diastolic blood pressure (mmHg)	60	90
Systolic blood pressure (mmHg)	90	140
Heart rate (bpm)	50	100
Respiration rate (breaths/min)	10	25
Pulse rate (bpm)	50	100

11.5. Criteria for Clinically Notable Vital Sign Values

Table 7: Clinically Notable Vital Sign Values

Parameter	Criteria
Sitting Systolic Blood Pressure	≤90 and/or ≥180 mmHg Change from baseline of ≥20
Sitting Diastolic Blood Pressure	≤50 and/or ≥105 mmHg Change from baseline of ≥15
Sitting Heart Rate	≤50 and/or ≥120 bpm Change from baseline ≥30
Standing Systolic Blood Pressure	≤90 and/or ≥180 mmHg Change from baseline of ≥20
Standing Diastolic Blood Pressure	≤50 and/or ≥105 mmHg Change from baseline of ≥15
Standing Heart Rate	≤50 and/or ≥120 bpm Change from baseline ≥30
Change from sitting to standing at same Assessment in SBP	≥20 mm Hg
Change from sitting to standing at same Assessment in DBP	≥10 mm Hg

11.6. Normal Range for ECG

Table 8: ECG Normal Ranges

Parameter	Low	High
Heart Rate (beats/min)	50	100
PR Interval (msec)	120	220
QRS Duration (msec)		
Male	80	130
Female	70	120
QT (msec)		
Male	340	450
Female	340	460
QTcF (msec)		
Male	350	450
Female	350	470