Statistical Analysis Plan

An Open-label, Flexibly-dosed, Multicenter, Extension Study of Dasotraline to Evaluate Long-term Safety and Tolerability in Adults with Binge-eating Disorder

DASOTRALINE (SEP-225289)

Protocol SEP360-322

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AN OPEN-LABEL, FLEXIBLY-DOSED, MULTICENTER, EXTENSION STUDY OF DASOTRALINE TO EVALUATE LONG-TERM SAFETY AND TOLERABILITY IN ADULTS WITH BINGE-EATING DISORDER

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List of Abbreviations and Definition of Terms

Abbreviation	Full Form
AE	Adverse event
ALT	Alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	Aspartate aminotransferase
BDRM	Blind Data Review Meeting
BE-CGI-S	Binge-eating Clinical Global Impression-Severity
BED	Binge eating disorder
BMI	Body mass index
BSN	Baseline
BUN	Blood urea nitrogen
CI	Confidence interval
CRF	Case report form
C-SSRS	Columbia-suicide severity rating scale
CSSA	Cocaine Selective Severity Assessment
DAS	Dasotraline
DB	Double-blind
DBL	Database lock
DEAE	Discontinuation-emergent adverse event
DESS	Discontinuation-Emergent Signs and Symptoms
DSMB	Data and Safety Monitoring
ECG	Electrocardiogram
EDC	Electronic data capture
EDE-Q	Eating Disorder Examination Questionnaire
EDE-Q7	Eating Disorder Examination Questionnaire Brief Version
EDE-QM	Eating Disorder Examination Questionnaire Modified
EOS	End of Study
EOT	End of treatment
FDA	U.S. Food and Drug Administration
HAM-A	Hamilton Anxiety Rating Scale
HDL	High-density lipoprotein (cholesterol)
HR	Heart rate
ICF	Informed consent form
LDL	Low-density lipoprotein (cholesterol)
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale

Abbreviation	Full Form
MALV	Markedly Abnormal Laboratory Values
MAVS	Markedly Abnormal Vital Signs
MCS	Mental Component Summary
NDA	New Drug Application
OL	Open Label
PCS	Physical Component Summary
PK	Pharmacokinetic(s)
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RR	RR interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Sheehan disability Scale
SF-12	Medical Outcomes Study 12-Item Short Form
SIGH-A	Structured Interview Guide for the HAM-A
SIGMA	Structured Interview Guide for the MADRS
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cells

1. Introduction

This statistical analysis plan (SAP) contains the definitions of analysis populations, derived variables, and statistical methods for the analyses of efficacy and safety data from study Dasotraline SEP360-322 for subjects continued from core studies SEP360-221 or SEP360-321.

Study completion status of the two core studies is given below: both studies were completed. Study SEP360-221 clinical database was locked on Nov 15, 2016 and study SEP360-321 clinical database was locked on June 25, 2018.

One full interim analysis was planned to support regulatory filing of New Drug Application (NDA) submission for binge eating disorder (BED). The interim analysis was conducted per data snapshot with data cut date of Aug 31, 2018. In total there are two separate and independent data analyses for study SEP 360-322, one for the interim analysis and the other for final analysis. The final database lock will occur when the study is completed and a subsequent final analysis of study SEP 360-322 will be performed.

This SAP is developed based on the version of the study protocol with Amendment 3.0 dated June 13, 2017. It outlines analyses to be conducted for the final database lock for data collected through the withdrawal period. A separate SAP for the interim analysis was prepared and finalized prior to data snapshot for the interim data cut.

If additional analyses are required to supplement the planned analyses described in this SAP after the final database lock, they may be performed and will be identified and documented in Clinical Study Report (CSR).

2. Study Objectives

2.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of flexibly-dosed dasotraline (4, 6, or 8 mg/day) in adults with BED who have completed a prior dasotraline study in BED by:

- The incidence of AEs, discontinuations due to AEs, and serious AEs (SAEs)
- The frequency and severity of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)
- Changes in 12-lead electrocardiograms (ECGs), vital signs, body weight, body mass index (BMI), and clinical laboratory results

2.2. Secondary Objective

The secondary objects are:

- To assess potential withdrawal effects of dasotraline using the following assessments (administered during the withdrawal period):
  - Cocaine Selective Severity Assessment (CSSA)
  - Discontinuation-Emergent Signs and Symptoms (DESS) Scale
  - Symptoms of anxiety utilizing the Hamilton Anxiety Rating Scale (HAM-A)
  - Symptoms of depression utilizing the Montgomery-Asberg Depression Rating Scale (MADRS)
- To assess the abuse potential of dasotraline utilizing a comprehensive abuse potential monitoring plan (APMP)
- To evaluate the long-term effectiveness of flexibly-dosed dasotraline in the treatment of adults with BED as measured by the following:
  - Eating Disorder Examination Questionnaire (EDE-Q) modified
  - Binge-eating Clinical Global Impressions - Severity (BE-CGI-S)
  - Sheehan Disability Scale (SDS)
- To assess subject-reported health status using the Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12) (SF-12 collected only for subjects enrolling in this study after completing core study SEP360-221).

3. Study Design

This is a Phase 3, 12-month, multicenter, open-label, flexibly-dosed, safety study in adults with BED. This study is projected to enroll approximately 500 subjects based on the number of subjects expected to complete treatment in the core studies (ie, SEP 360-221 or SEP360-321).

Informed consent is obtained from all subjects after all procedures from the core study have been completed and before any study procedures unique to this study are performed. Safety and tolerability is monitored throughout the study by AE reports, physical and neurological examinations, 12-lead ECG, vital signs, body weight, BMI, clinical laboratories (hematology, chemistry, urinalysis, hemoglobin A1c, and lipid panel), and C-SSRS. Effectiveness will be evaluated using the BE-CGI-S, EDE-Q modified, and SDS. Subject-reported health status will be assessed using the SF-12 (subjects from Study SEP360-221 only). Assessment of potential withdrawal effects of dasotraline will be conducted via administration of the CSSA, DESS, HAM-A, and MADRS at the end of treatment and during the 3-week study medication withdrawal period.

A comprehensive Abuse Potential Monitoring Plan (APMP, see Protocol Section 24) for dasotraline designed to detect potential abuse of the compound and to more closely monitor AEs consistent with the known pharmacology for dasotraline will be implemented.

An independent Data and Safety Monitoring Board (DSMB) reviews safety data including data on adverse events (AEs) and serious adverse events (SAEs) at regular intervals.

Subjects self-administers study drug on an outpatient basis for 12 months, once a day at approximately the same time each morning with or without food, including on the days when clinic visits occur. Subjects meeting all inclusion and no exclusion criteria start taking open-label study drug on Day 1, the morning following the open-label (OL) Baseline visit (ie, Week 12 visit in the core study).

The total daily dose remains between 4 mg/day and 8 mg/day for the 12-month treatment period. Dasotraline is dosed at 4 mg/day for the first 2 weeks of the study. At the Week 2 visit, the dose may be increased to 6 mg/day. Thereafter the dose may be increased or decreased by 2 mg/day, as necessary for effectiveness or tolerability reasons at the discretion of the investigator. A minimum of 8 days is required between dose increases. Dose decreases may be made at less than 8 day intervals, at the investigator's discretion, for reasons of safety or tolerability. If, in the judgment of the investigator, the subject does not tolerate the minimum required dose (4 mg/day), he or she is discontinued from the study. All changes in study drug dose begins the morning after the visit at which the dose change decision is made and using the new package of study drug.

The study consists of a baseline visit, 12-month open-label treatment period, and 3-week study drug withdrawal period as shown in the Study Schematic (protocol section 7.1 Figure 1). During the treatment period, subjects will return to the clinic at the end of 2 and 4 weeks for clinical evaluation and thereafter will return to the clinic once every 4 weeks during the treatment period

for scheduled visits. At the approximate midpoint between the scheduled monthly visits (ie, 14 ± 2 days after a visit), the site staff will contact the subject via telephone, text, or email in order to monitor for SAEs, AEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration, and upcoming visits. If necessary, an unscheduled visit can be arranged.

Subjects attend weekly visits during the 3-week study drug withdrawal period. Assessment of potential withdrawal effects of dasotraline will be conducted via administration of the CSSA, DESS, HAM-A, and MADRS at the end of treatment. Subjects will undergo assessments every other day and weekly as follows: The CSSA and DESS will be completed every other day during the 3-week study medication withdrawal period. Clinical site staff will call the subject every other day, beginning the second day after the last dose of study drug, unless a clinic visit is scheduled for that day. Phone contacts may be made up to 3 times per day if the clinical site staff are unable to contact the subject on the first 2 attempts. If the subject cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the missed CSSA and DESS, in addition to the current day's CSSA and DESS, as necessary. Clinical site staff will record the responses in the subject's source information and in the case report form (CRF) with the contact date and time. The CSSA, DESS, HAM-A, and MADRS also will be administered at each weekly visit during the withdrawal period.

A window of ± 1 day is allowed for each weekly clinic visit and telephone call during the study medication withdrawal period.

After the last withdrawal period visit, all subjects will be referred for follow-up care as determined by the investigator.

The schedule of assessments for this study is in Attachment 9.1; also see protocol Section 11.5 for study visits and assessments detail.

3.1. Determination of Sample Size

Subjects who complete the double-blind treatment period of the core study, sign the consent, and meet all entry criteria are included in this study. The double-blind core study SEP360-221 planned to randomize approximately 300 subjects and the double-blind core study SEP360-321 planned to randomize approximately 480 subjects. It is estimated that approximately 500 subjects are eligible for enrollment in this study based on the number of subjects expected to complete treatment in the core studies.

3.2. Randomization, Stratification and Blinding

This is an open-label extension study, therefore randomization and blinding is not employed.

4. Changes in Planned Analyses

There is not any change made in this SAP from the analyses planned in the protocol.

5. Effectiveness and Safety Variables

5.1. Effectiveness Variables

5.1.1. Binge-eating Clinical Global Impression-Severity (BE-CGI-S)

The BE-CGI-S is a single value, clinician-rated assessment of illness severity, and 7-point scale with range from 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects. A higher score is associated with greater illness severity.

BE-CGI-S score is collected at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/EOT in the open-label treatment period, and at Weeks 53, 54 and 55/EOS for subjects who enter the withdrawal period.

5.1.2. Eating Disorder Examination Questionnaire (EDE-Q) modified and Comparison with EDE-Q and EDE-Q Brief Version (EDE-Q7)

The Eating Disorder Examination Questionnaire (EDE-Q) is a self-report version of the eating disorder examination (EDE) (Fairburn-1994). Like the EDE, the EDE-Q measures eating-disorder psychopathology in the past 28 days and over longer intervals for diagnostic items. EDE-Q generates two types of data. First, it provides frequency data (ie, numerical data) on key behavioral features of eating disorders in term of number of episodes of the behavior and in some instance number of days which behavior has occurred; Second, they provide ratings (ie, categorical data), 4 subscale scores, and an EDE-Q global score reflecting the severity of aspects of the psychopathology of eating disorders. The 4 subscale scores are Restraint, Eating Concern, Shape Concern, and Weight Concern. Severity rating ranges 0- 6, where 0 represents absence of the feature and 6 represents an extreme degree. Frequency ratings range from 0 to 6 where 0=’No days’ or absence of the feature, 6=’every day’.

Both the Eating Disorder Examination Questionnaire Brief Version (EDE-Q7) and EDE-Q modified are shorter versions of the EDE-Q.

EDE-Q7 comprises 7 items to generate a global score and 3 subscale scores (Restraint, Shape Concern, and Weight Concern). The EDE-Q7 along with 3 items (see below) to assess binge eating, including the number of binge eating days, is referred to as the EDE-Q modified and is used in this study.

- **Item 4:** Over the past 28 days, how many **times** have you eaten what other people would regard as an **unusually large amount of food** (given the circumstances)?
- **Item 5:** On how many of these times did you have a sense of having lost control over your eating (at the time that you were eating)?
- **Item 6:** Over the past 28 days, on how many **DAYS** have such episodes of overeating occurred (i.e., you have eaten an unusually large amount of food **and** have had a sense of loss of control at the time)?

See Table 1 below for definition of rating data for EDE-Q, EDE-Q7, EDE-Q modified, and their relationship. Table 2 provides the definition of frequency data for EDE-Q, EDE-Q modified, and their mapping relationship.

Table 1: Rating Data of EDE-Q, EDE-Q7, and EDE-Q modified Items

EDE-Q Modified Item	EDE-Q7 Item	EDE-Q Item	Abbreviated Content	Subscale
1	**1**	**1**	**Restraint over eating**	Restraint
		2	Avoidance of eating	
2	**2**	**3**	**Food avoidance**	
3	**3**	**4**	**Dietary Rules**	
		5	Empty stomach	
		7	Preoccupation with food, eating or calories	Eating Concern
		9	Fear of losing control over eating	
		19	Eating in secret	
		21	Social eating	
		20	Guilt about eating	
		6	Flat stomach	Shape Concern
		8	Preoccupation with shape or weight	
8	**5**	**23**	**Importance of shape**	
		10	Fear of weight gain	
10	**7**	**26**	**Dissatisfaction with shape**	
		27	Discomfort seeing body	
		28	Avoidance of exposure	
		11	Feelings of fatness	
7	**4**	**22**	**Importance of weight**	Weight Concern
		24	Reaction to prescribed weighing	
		8	Preoccupation with shape or weight	
9	**6**	**25**	**Dissatisfaction with weight**	
		12	Desire to lose weight	

Reference: Fairburn C.G., 2014, EDE Edition 17.D, Cognitive Behavior Therapy and Eating Disorders[1]

Table 2: Frequency Data of EDE-Q and EDE-Q modified Items

EDE-Q Modified Item	EDE-Q Item	Abbreviated Content
4	13	Times of unusually large amount of food
5	14	Times of having lost control eating
6	15	Days of overeating episodes
	16	Times of having made of sick for controlling shape or weight
	17	Times of having taken laxatives for controlling shape or weight
	18	Times of having exercised in a "driven" or "compulsive" for controlling shape or weight

For EDE-Q, EDE-Q Modified, and EDE-Q7, the subscale scores are calculated as average of the corresponding individual scores. If any individual score of the subscale is missing, the corresponding subscale score will be set as missing and no imputation will be done. An EDE-Q global score is calculated as average of 4 EDE-Q subscale scores, an EDE-Q7 global score is calculated as average of 3 EDE-Q7 subscale scores, and an EDE-Q Modified global score is calculated as average of 3 EDE-Q Modified subscale scores. The EDE-Q global score, EDE-Q modified global score, and EDE-Q7 global score will be missing if any of corresponding subscale scores is missing. For EDE-Q, EDE-Q modified, and EDE-Q7, higher scores on the global score and subscale scores indicate greater levels of symptomatology; the global scores and subscale scores of EDE-Q Modified and EDE-Q7 are equivalent.

EDE-Q, EDE-Q7, and EDE-Q modified are all designed to collect the data in the past 28 days.

For subjects continued from study SEP360-221, EDE-Q modified is collected at open label baseline visit; for subjects continued from study SEP360-321, EDE-Q modified is carried over from W12/EOT visit in study SEP360-321. In addition, EDE-Q modified is collected at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/EOT in the open-label treatment period.

5.1.3. Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS) is to assess functional impairment in 3 domains: (1) work/school; (2) social life; and (3) home life. The subject rates the extent to which work/school, social life and home life have been impaired by his/her symptoms on a 10-point anchored visual analog scale (VAS). The subject's responses for each domain are rated on the following scale: 0 = not at all; 1-3 = mildly; 4-6 = moderately; 7-9 =markedly; 10 = extremely. The 3 items can be combined into a single global measure of impairment (SDS total score) that ranges from 0 (unimpaired) to 30 (highly impaired). If any of the 3 SDS subscale scores is missing at a visit, the SDS total score for that visit is also missing. A higher subscale score and total score are associated with greater illness severity.

SDS is collected at Weeks 12, 24, 36, 52/EOT in treatment period, and at Week 55/EOS for subjects who enter the withdrawal period.

5.2. Patient-Reported Outcome (PRO)

5.2.1. 12-Item Short Form Health Survey (SF-12)

The SF-12 is a 12-item self-report questionnaire. The survey captures physical and mental health. There are 8 subscales including: Physical functioning, Role-physical, Bodily pain, General health, Vitality, Social Functioning, Role-emotional, Mental health. The responses are reported on a 3 or 5 point Likert scale, depending on the question. The SF-12 uses two items each to estimate scores for four of the eight health concepts (physical functioning, role-physical, role-emotional, and mental health). Scores for the remaining four health concepts (bodily pain, general health, vitality, and social functioning) are estimated using one item each. Physical Component Summary (PCS) and Mental Component Summary (MCS) are computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health.

SF-12 data will be provided by Optum. For details of data derivation, see Attachment 9.2.

For subjects who continued from study SEP360-221 only, the SF-12 is collected at Weeks 12, 24, 36 and 52/EOT and at Week 55/EOS for subjects who enter the withdrawal period. SF-12 is not collected for subjects who continue from study SEP360-321.

5.3. Safety Assessment

The safety assessments/endpoints are

- adverse event (AE) reports, including the incidence of overall AEs, serious AEs (SAEs), and AEs (or SAEs) leading to discontinuations
- Clinical laboratory evaluations (serum chemistry, hematology, and urinalysis)
- Clinical evaluations (vital signs including orthostatic effects, and 12-lead ECGs)
- body weight and body mass index (BMI)
- concomitant medication reports
- physical examinations
- Columbia – Suicide Severity Rating Scale (C-SSRS)

The following safety measurements will also be collected to assess the occurrence of symptoms of withdrawal from dasotraline:

- Cocaine Selective Severity Assessment (CSSA)
- Discontinuation-Emergent Signs and Symptoms (DESS) Scale
- Symptoms of anxiety utilizing the HAM-A

- Symptoms of depression utilizing the MADRS

5.3.1. Columbia – Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an instrument designed to systematically assess and track suicidal behavior and suicidal ideation throughout the trial. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The C-SSRS includes the following four sections: Suicidal Ideation, Ideation Intensity, Suicidal Behavior and Actual Suicide Attempts. The C-SSRS is administered by a trained rater at the site.

Severity of suicidal ideation is rated on a 6-point scale from 0=’No ideation present’ to 5=’Active ideation with plan and intent’. A score of 4 or 5 on this scale indicates serious suicidal ideation. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional. Suicidal ideation score is defined as the most severe suicidal ideation score (1-5 on the CSSRS) present at the assessment; assign a score of 0 if no ideation is present. The ideation intensity total score is calculated as summation of the five items from the Ideation Intensity scale: frequency, duration, controllability, deterrents, and reasons for ideation. If one or more of these 5 items are missing at a visit, no imputation will be made and the corresponding ideation intensity total score will be set as missing. Items corresponding to frequency and duration are each rated on a scale from 1 to 5 and items corresponding to controllability, deterrents, and reasons for ideation are each rated on a scale from 0 to 5. If the patient did not endorse any suicidal ideation, set the intensity rating to 0. Thus, the possible range for the intensity total score is 0 to 25.

Suicidal behavior is collected as presence/absence of actual attempts, non-suicidal self-injurious behavior, interrupted attempts, aborted attempts, preparatory acts or behavior, and any suicidal behavior. In addition, the number of actual attempts, interrupted attempts, and aborted attempts is captured. Any attempt will be defined as suicidal behavior.

The lethality associated with actual attempts is rated on a 6-point scale from 0=’No physical damage or very minor physical damage’ to 5=’Death’. Potential lethality of attempts is rated on a 3-point scale from 0=’Behavior not likely to result in injury’ to 2=’Behavior likely to result in death despite available medical care’.

For all study visits, the “Since Last Visit” version of the C-SSRS is administered.
C-SSRS is collected at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/EOT in the open-label treatment period, and at Weeks 53, 54 and 55/EOS for subjects who enter the withdrawal period.

5.3.2. Withdrawal Assessment for Physical Dependence and Withdrawal Symptoms

Subjects who either are early terminated in the open-label treatment period or complete the 52-week open-label treatment period need to complete the study medication withdrawal period assessments and visits.

Assessment of potential withdrawal effects will be conducted via administration of the CSSA, DESS, HAM-A and MADRS at Week 52/EOT, then at Weeks 53, 54, and 55/EOS during the 3-week study medication withdrawal period. The CSSA and DESS will also be completed during the 3-week study medication withdrawal period on non-clinic visit days. Clinical site staff will call the subject every other day during the study medication withdrawal period, beginning the second day after the last dose of study drug, unless a clinic visit is scheduled for that day. Clinical site staff will record the responses in the subject's source information and in the CRF with the contact date and time. A window of ± 1 day is allowed for each weekly clinic visit and telephone call. If the subject cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the missed CSSA and DESS, in addition to the current day's CSSA and DESS.

5.3.2.1. Cocaine Selective Severity Assessment (CSSA)

The CSSA is a clinician-administered scale designed to evaluate withdrawal signs and symptoms related to stimulants over the past 24 hours. Included in the CSSA are those symptoms most often associated with early cocaine abstinence, including change in appetite, depression, fatigue, anhedonia, anxiety, irritability, sleep disturbance, and inability to concentrate, paranoia, carbohydrate craving, bradycardia, and suicidality. The CSSA scale contains 18 items. All items except item 14, are scored 0 to 7 according to instructions generally with 0 = no symptoms and 7 = maximum score on any individual item. Item 14 is scored 0 to 8 with 0 = no symptoms and 8 = maximum score. The score for each question will be summed to compute a total score ranging from 0 to 127 with higher score indicates severe withdrawal signs and symptoms. If the response to any question is missing, the total score will be missing.

The CSSA is collected at Week 52/EOT, and Weeks 53, 54 and 55/EOS for subjects who enter the withdrawal period.

5.3.2.2. Discontinuation-Emergent Signs and Symptoms (DESS) Scale

The DESS Scale is a clinician-rated instrument of 43 items used to evaluate signs and symptoms associated with discontinuation or interruption of monoamine reuptake inhibitor treatment. Each of the 43 signs and symptoms is assessed and placed in one of the following categories: new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged, and symptom not present. Each sign and symptom that is placed in the category new symptom or in the category old symptom but worse receives 1 point. All other categories receive 0 points. The total DESS score is the sum of the number of points, which corresponds to the number of

symptoms rated as either a new symptom or as an old symptom but worse. The score ranges from 0 to 43, where higher scores indicate more discontinuation-emergent signs and symptoms.

The DESS is collected at Week 52/EOT, and Weeks 53, 54 and 55/EOS for subjects who enter the withdrawal period.

5.3.2.3. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated assessment of the subject's level of depression. This scale contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6, with higher scores indicating increased depressive symptoms. The score for each question will be summed to compute a total score ranging from 0 to 60. If the response to any question is missing, the total score will be missing.

The MADRS is collected at Weeks 24, 52/EOT, and Weeks 53, 54 and 55/EOS for subjects who enter the withdrawal period.

5.3.2.4. Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a rating scale developed to quantify the severity of anxiety symptomatology. It consists of 14 items, each defined by a series of symptoms. The 14 items are: anxious mood, tension, fears, insomnia, intellectual, depressed mood, somatic (muscular), somatic (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior at interview. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe/disabling). The score for each question are summed to compute a total score ranging from 0 to 56. If the response to any question is missing, the total score is missing. A higher score is associated with a greater degree of anxiety. A score of $\geq$ 14 has been suggested to indicate clinically significant anxiety.

The HAM-A is collected at Weeks 24, 52/EOT, and Weeks 53, 54 and 55/EOS for subjects who enter the withdrawal period.

6. Statistical Methods

6.1. General Analysis Definition

6.1.1. Analysis Period and Study Day

Two scopes of data for a subject are considered in this study. Each scope of data consists of a specific portion (subset) of study data for the subject.

6.1.1.1. Open-Label Treatment Period (On Treatment)

The day of the 1st dose date in the extension study will be denoted as study Day 1. All measurements at each visit will be assigned a study day relative to this date. All data collected on/after Day 1 for subjects previously randomized to placebo group in core study or on/after the extension baseline visit for subjects previously randomized to dasotraline groups and up to Week 52, including the End-of-treatment/Early Withdrawal visit, will be considered within the open-label treatment phase. That is to say, the start of the open-label treatment period is defined as Day 1 for subjects previously randomized to placebo group and the OL Baseline visit date for subjects previously randomized to dasotraline groups; the end of the open-label treatment phase is defined as the maximum of the last date of administration of study medication and the withdrawal/ completion date.

The start and end of open-label treatment period are given below:

- **Start of treatment period** =

  = Date of the first study medication administration for subjects previously randomized to placebo group

  = Date of the OL Baseline visit for subjects previously randomized to dasotraline;

- **End of treatment period** = maximum of the last date of administration of study medication and the withdrawal/ completion date (ie, Week 52/EOT visit date).

Each subject's assessment at each visit in pre-treatment and treatment period will be assigned a study day with respect to the first dose date in the extension study.

- Study Day = Assessment date − the first dose date in the extension study + 1; if assessment date ≥ the first dose date in the extension study
- Study Day = Assessment date − the first dose date in the extension study; if assessment date < the first dose date in the extension study

6.1.1.2. Withdrawal Period (Off Treatment)

The withdrawal period will begin with immediately after the last study dose. Study day relative to the last study dose date will be denoted as Day 0. The end of the withdrawal period is defined as the maximum of last study visit (scheduled or unscheduled) and last phone contact after the

last study dose. If the last study dose date is missing or 'unconfirmed' (eg, lost follow-up subjects), start and end days relative to the last study dose will be set as missing.

Each subject's assessment at each visit (site or phone contact) in the withdrawal period will be assigned a study day with respect to start date of the withdrawal period (ie, the last study dose date).

- Study Day = Assessment date − the last dose date if assessment date ≥ the last dose date in the extension study

6.1.1.3. Overall Study Period

Overall study period is defined as a combination of the open-label treatment period and withdrawal period. See Table 3 below for summary of definition of all analysis periods and study day used for this study.

Table 3: Definition of Analysis Study Period

Analysis Study Period	Start Date	End Date	Applicable Scope
Open Label Treatment Period	Day 1*	EOT [a]	Subjects previously randomized to Placebo group
	Baseline Visit Date	EOT [a]	Subjects previously randomized to Dasotraline
Withdrawal Period	Day 0 **	EOS [b]	Withdrawal Population
Overall Study Period	Day 1*	EOS [b]	Subjects previously randomized to Placebo group
	Baseline Visit Date	EOS [b]	Subjects previously randomized to Dasotraline group

Note: *: the day of the first dose of open-label study medication.
[a] : Week 52 visit/ early withdrawal visit
**: the day of the last dose of open-label study medication.
[b] : last scheduled or unscheduled (site/phone contact) visit in withdrawal period

Except for adverse event data, summaries and analyses of all data on OL treatment are based on the portion of study data that fall in the open-label treatment period. For adverse events, see Section 7.4.2 for how a study subject is considered to be on treatment during the treatment period (ie, last study medication administration + 7 days for AE or +14 days for Serious AE).

6.1.2. Visit Windows

6.1.2.1. Visit Windows for Visits in Open-Label Treatment Period

While the Time and Events Schedule of the protocol indicates the visit timing and procedures for each visit, the timing of a subject's actual visit timing may not be exactly as per the protocol indicated target day/visit window (note that the protocol does not indicate required visit windows, but rather provides clear guidance for visit timing). Consequently, for the purpose of analysis, the conventions outlined below will be used to allocate the data collected at each actual visit to a planned protocol visit by defining analysis visit windows.

The reference day is study Day 1. Definition of baseline and endpoint is provided in Sections 6.1.3 - 6.1.4.

Table 4 summarizes the analysis visit windows for all questionnaires, laboratory, weight, height, vital signs, ECG, physical and neurological examination, and other safety variables assessed at scheduled visits.

Table 4. Time Intervals for Analysis Visit Windows in Open-Label Treatment Period

Scheduled Visit (label on output in Extension study)	Target Day [a]	Time Interval (Day)
OL Baseline [b]	−1	<1
Week 2	14	1 – 21
Week 4	28	22 – 35
Week 8	56	36 - 70
Week 12	84	71 - 98
Week 16	112	99 - 126
Week 20	140	127 - 154
Week 24	168	155 - 182
Week 28	196	183 - 210
Week 32	224	211 - 238
Week 36	252	239 - 266
Week 40	280	267 - 294
Week 44	308	295 - 322
Week 48	336	323 - 350
Week 52	364	351 - EOT

[a]: Relative to the day of the 1st dose date .
[b]: Also refer Section 6.1.3 for details of definition of Baseline.

If a subject has 2 or more visits in one analysis visit window (scheduled or unscheduled), the visit closest to the target day will be used as the study visit for that analysis visit window. The other additional visit(s) in the same analysis visit window will not be included in the by-visit descriptive summary analyses. However, measurements from this/these other additional visit(s) will be included in the other safety analyses (eg, Potentially Markedly Abnormal Laboratory Values or the worst case analysis) to assure all on-treatment measurements are included. If 2 study visits occur on the same number of days from the target day within the same visit window, the later one will be considered as the study visit for that target day.

Although all (scheduled and unscheduled) visits will be allocated to an analysis visit window, only planned protocol visits for each measurement will be included in the by-visit analyses. All tables and figures presenting data by visit will present only those timepoints where the applicable assessment was scheduled to be collected, unless otherwise noted below. Unscheduled and early termination data will be included for definition of endpoint or overall assessments (eg, the worst case analysis for an assessed period). Data listings will present all data, regardless of scheduled and unscheduled visits.

6.1.2.2. Visit Window for Visits in Withdrawal Period

Visits within withdrawal period will be mapped per visit window defined in Table 5.1 below for effectiveness and safety data collected in withdrawal period except of the phone contact visits used for collecting additional CSSA and DESS information.

Table 5.1: Visit Window for Clinic Visits in Withdrawal Period

Variables to be Applied	Time Interval (Day)[a]	Target Time Point (Day)	Analysis Visit (label on output)
CSSA, DESS	–5 to 1 [(b)]	**0**	Withdrawal Baseline
	2 – 10 [(c)]	7	Withdrawal Week 1
	11 – 17[(c)]	14	Withdrawal Week 2
	18 – EOS[(c)]	21	Withdrawal Week 3
Other	–5 to 3	**0**	Withdrawal Baseline
	4 – 10	7	Withdrawal Week 1
	11 – 17	14	Withdrawal Week 2
	18 – EOS	21	Withdrawal Week 3

[a] Relative to the day of the last dose of open-label study medication
[b] per both phone contacts or clinic visits
[c] for clinic visits only.

If a subject has 2 or more visits in one analysis visit window, the visit closest to the targeted day will be used as the study visit for that analysis visit window. The other additional visit(s) will be denoted as unscheduled visit and not included in the by-visit descriptive summary analyses. However, measurements from this/these other additional visit(s) may be included in the other safety analyses to assure all off-treatment measurements are included. If 2 study visits occur the same number of days from the target day within the same visit window, the later one will be considered as the study visit for that target day.

Non-clinic phone contact visits within withdrawal period will be mapped per visit window defined in Table 5.2 below for CSSA and DESS specifically.

Table 5.2: Visit Window for Non-Clinic/Phone Contact Visits in Withdrawal Period

Variables to be Applied	Time Interval (Day)[a]	Target Time Point (Day)	Analysis Visit (label on output)
CSSA, DESS	1 – 2	**1**	Day 1-2
	3 – 4	3	Day 3-4
	5 – 6	5	Day 5-6
	7 – 8	7	Day 7-8
	9 – 10	9	Day 9-10
	11 – 12	11	Day 11-12

	13 – 14	13	Day 13-14
	15 – 16	15	Day 15-16
	17 – 18	17	Day 17-18
	19 – 20	19	Day 19-20
	21 – 22	21	Day 21-22
	23 – 24	23	Day 23-24
	25 – EOS[(b)]	25	≥ Day 25
[a] Relative to the day of the last dose of open-label study medication [b] per phone contacts visits only.			

6.1.3. Baseline

Three types of Baseline will be defined: DB Baseline, OL Baseline, and Withdrawal Baseline.

6.1.3.1. DB Baseline

DB Baseline (ie, Baseline assessment of the double-blind core studies [SEP 360-221, or SEP 360-321]) is defined as the last assessment made on or before the 1st dose of double-blind study medication as described in the SAPs of the core studies.

6.1.3.2. OL Baseline

Except for height (for all subjects), demographics (for all subjects) and EDE-Q modified (for subjects continued from SEP360-221), unless otherwise specified, based on the protocol of SEP360-322 and the schedule of assessment (Attachment 9.1), OL Baseline values are to be carried over from W12/Endpoint in the core studies. The OL Baseline is defined as the last assessment made on or before Day 1 of the extension study (ie, Baseline assessment in the open-label study [SEP 360-322] for demographic (for all subjects) and EDE-Q modified (for subjects from SEP360-221), and height at the screening and the Endpoint assessment of the double-blind studies [SEP 360-221, or SEP 360-321] (for all subjects), otherwise).

As indicated in the protocol, height at the screening visit in the core studies will be carried over as OL Baseline. For operation convenience, the protocol specified that data collected at the EOT visit of the core studies are recorded in core studies only and are not to be saved in the clinical database of the extension study. Height at OL Baseline visit will be assigned a value per the corresponding Study Data Tabulation Model (SDTM) dataset of core studies directly.

Unless otherwise specified, at each study visit of study SEP 360-322, data derivation rule and missing imputation method for aggregated parameters that involves multiple individual items (eg, total score, subscale score, or composite score), are same as the corresponding ones in individual core study SAPs. DB Baseline is defined same as the Baseline in individual core study per core study SAPs. DB Baseline used in the analysis of study SEP 360-322 will be extracted from corresponding Analysis Data Model datasets (ADaM) of the core studies directly.

6.1.3.3. Withdrawal Baseline

See Section 6.1.2.2 for the definition of Withdrawal Baseline. No imputation will be made if the Withdrawal Baseline value is missing.

6.1.4. Endpoint

6.1.4.1. Endpoint

Endpoint (ie, Week 52 Endpoint) is defined as the last post-OL Baseline assessment during the open-label treatment period.

6.1.4.2. Withdrawal Endpoint

Withdrawal Endpoint is defined as the last non-missing post-withdrawal baseline assessment in the withdrawal period (regardless of clinic or non-clinic visits).

6.1.5. Aggregated Analysis Timepoint

An aggregated analysis timepoint named as 'any OL treatment period (treatment emergent)' will be derived for selected safety assessments (eg, the worst case analysis) as below.

- Any OL treatment period (treatment emergent): defined as any assessment collected in open-label treatment period (see Section 6.1.1.1).

Specifically, the aggregated analysis timepoint of any OL treatment period (treatment emergent) will be applied on the following worst-case analysis:

- Markedly Abnormal Laboratory Values (MALV) (Section 7.4.3.1, Table 6)
- Markedly Abnormal Vital Signs (MAVS) (Section 7.4.5.1, Table 9.1)
- QTc prolongation (Section 7.4.4.1, Table 7)
- ECG abnormality (Section 7.4.4.1, Table 8).
- C-SSRS (Section 7.4.7)

6.1.6. Pooling Strategy for Analysis of Centers

There will be no pooling of centers in this study.

6.1.7. Adjustments for Covariates

Not Applicable. No statistical modeling or inference will be performed, including the ones containing baseline as a covariate to adjust baseline.

6.1.8. Analysis Populations

The Safety Population: All subjects who receive at least one dose of study medication. The safety population mainly is used for the data analyses of the safety data collected through Week 52 or during the open-label treatment period.

The Withdrawal Population*:* The withdrawal population includes all subjects who receive at least one dose of study medication, and either early terminate from the study drug during the OL treatment period or complete the 52-week OL treatment period, and have at least 1 assessment after the last study drug for any evaluation. The withdrawal population is used to summarize the safety and effectiveness assessments collected in the withdrawal period. Withdrawal analysis will be presented by analysis group.

The 'Modified' Withdrawal Population*:* all subjects in the withdrawal population plus the subjects who either are early terminated during the OL treatment period or complete the 52-week OL treatment period and do not enter the withdrawal period, but the last study dose dates are at least 2 days prior to their last study visit. The modified withdrawal population will be only used for summary of adverse event data which could be retrospectively collected.

6.1.9. Analysis Group and Analysis Subgroup

For all subjects in Study 360-322, summary tables, wherever applicable, will be presented by analysis group per subject's previous participation in core studies (ie, subjects previously randomized to dasotraline, subjects previously randomized to placebo, all subjects combined) as described as below

- Pbo-Das: Subjects previously randomized to placebo in studies SEP360-221 or SEP360-321
- Das-Das: Subjects previously randomized to dasotraline group in studies SEP360-221 or SEP360-321
- All-Das: all subjects combined

For subjects continued from Study SEP360-221, analyses per selected data may be conducted as needed; summary of these analyses will be presented per subject's previous participation in study SEP360-221 as described below(hereafter, referred as 'Analysis Subgroup A'):

- Pbo-Das: previously randomized to placebo
- Das-Das: previously randomized to dasotraline 4–8 mg/day
- 221-Das: all subjects continued from study SEP360-221

For subjects continued from Study SEP360-321, analyses per selected data may be conducted as needed; summary of these analyses will be presented per subject's previous participation in study SEP360-321 as described below (hereafter, referred as 'Analysis Subgroup B**'**):

- Pbo-Das: previously randomized to placebo
- Das4-Das: previously randomized to dasotraline 4 mg/day
- Das6-Das: previously randomized to dasotraline 6 mg/day
- AllDas-Das: previously randomized to dasotraline (4 mg/day or 6 mg/day)

- 321-Das: subjects continued from study SEP360-321

Subjects in Study SEP360-322 may be further grouped and presented according to their predominant dose (alternatively, modal dose, see Section 6.1.10) and the maximum dose during the open-label treatment period as below, as needed. Hereafter, analysis subgroup based on the modal dose will be referred as 'Analysis Subgroup C' and analysis subgroup based on the maximum dose will be referred as 'Analysis Subgroup D'.

Analysis Subgroup C

- Das4: subjects with modal dose of dasotraline 4 mg/day
- Das6: subjects with modal dose of dasotraline 6 mg/day
- Das8: subjects with modal dose of dasotraline 8 mg/day
- All Das: all subjects combined

Analysis Subgroup D

- Das4: subjects with maximum dose of dasotraline 4 mg/day
- Das6: subjects with maximum dose of dasotraline 6 mg/day
- Das8: subjects with maximum dose of dasotraline 8 mg/day
- All Das: all subjects combined

For limited analyses, wherever applicable, results may be presented by modal dose group and maximum dose group as needed.

6.1.10. Average Dose, Predominant/Modal Dose, Maximum Dose

The predominant dose (or, equivalently, modal dose, used interchangeably hereafter in this document) duration in the open-label treatment period is defined as the dasotraline dose to which the subject was exposed for the greatest duration during the treatment period. If a subject has 2 or more doses with the great duration, the one with higher dosage will be selected as predominant treatment.

The average total daily dose during the open-label treatment phase will be calculated as the sum of the total daily dose divided the treatment duration (see Section 7.1.5.1). The average total daily dose during a visit period is defined in a similar way.

For any study visit , if medication kit usage information is incomplete (ie, meet one of following conditions: any dispensed medication kit at the visit has missing number of tables returned, or has missing dosing start or ending date), average total daily dose at the visit will not be derived and will be set as missing. For an assessment period that involves multiple study visits (eg, the open-label treatment period), if at some visit(s) the drug usage information is incomplete, then

the other visits with complete information of kit usage will be used to derive the average daily dose, predominant dose, and maximum dose, accordingly.

6.1.11. Handling of Dropouts or Missing Data

6.1.11.1. Unknown or Unconfirmed Last Study Dose Date

If the end date of the medication intake is unknown or 'unconfirmed' (including but not limited to, eg, subject is lost to follow-up), it will be imputed as the earlier date of the disposition date (ie, date of the last contact with subject) and 7 days from the date of the last medication kit dispensed if the last contact visit is either V1E (OL baseline), or V2E (Week 2), and 14 days from the date of the last medication kit dispensed if the last contact visit is V3E (Week 4) or after.

6.1.11.2. Composite Score

Unless otherwise specified, any individual missing item in any scale won't be imputed. When calculating a total score, subscale score, composite score, or any assessment with more than one item (e.g. EDE-Q modified global score and 3 subscale scores, SDS total score and subscale scores, MADRS total score, HAM-A total score, CSSA total score, DESS total score), if one or more items are missing at a visit, then the associated score (ie, total score or subscale score) will be set to missing.

Since a vendor generates for the SF-12, two component scores and subdomain scores using standard software, missing data is imputed by default algorithm provided by the vendor, which is provided on Attachment 9.2.

For analyses of the change from baseline for a given effectiveness parameter, only subjects who have both baseline and at least one post-baseline measurement are included.

6.1.11.3. Incomplete/Missing Dates

6.1.11.3.1. Start/End Dates for Adverse Event

Treatment-emergent adverse events (TEAEs) are those reported adverse events with an onset date on or after the first day of the open-label treatment period (See Section 6.1.1.1 for definition of the OL treatment period)), through 7 days after study drug discontinuation (14 days for serious adverse events and deaths).

A conservative approach will be used to handle the missing dates for AE onset date and end date to identify the treatment-emergent AE (ie, if the available incomplete date cannot determine treatment emergent status, the AE will be considered as a treatment-emergent AE). No imputation is to be done to calculate AE duration.

6.1.11.3.2. Start/End Dates for Prior/Concomitant Medication

Partial dates of non-study medication start/end date need to be imputed in order to classify the medications as prior or concomitant medications, or post-treatment medication (ie, medication initiated after the last dose of study medication). A conservative approach will be used to handle the incomplete date(s) for medication start/end date (ie, if the available incomplete date(s) cannot determine the concomitant relationship relative to the open-label treatment phase, the medication is considered as a concomitant medication).

6.1.12. Subgroup Analysis

For a limited number of descriptive analyses, data will be presented for analysis group by subgroup below as needed:

- Age group at OL Baseline (years): "< 40 years", "≥ 40 years"
- Gender: Male, Female
- Race: White, Non-white
- BMI at OL Baseline: Non-obese (ie, Normal & Overweight), Obese class I/II, Obese class III

6.1.13. BMI (kg/m^2)

BMI is calculated at each visit using the following formula:

BMI = weight (kg)/(height(m)*height(m))

Height is per measurement at Screening visit in core studies.

6.1.14. EDE-QM Items 4, 5, and 6

EDE-QM items 4, 5, and 6 are expected to collect numeric type of data. Due to the data fields were set as character type in clinical database, total 11 records (6 cases for item 4, 3 cases for item 5, and 2 cases for item 6), which were collected at early stage of the study, had a range type of data (ie, 1-2, 8-10 etc.) instead of a single integer value. For such cases, the higher value (ie, the worse value) are to be used in EDE-QM related summary analyses (eg, mean actual value and change from baseline). In addition, for a few records with character value of 'NO','NONE','NA', and 'N/A', zero will be used instead in terms of analysis purpose. The original data will be displayed in data listing.

6.2. Methods of Analysis

6.2.1 General Methodology

All statistical inference analyses will be performed with 2-sided tests at a significance level of 0.05, and 2-sided 95% confidence intervals (CI) will be calculated whenever appropriate. All data will be summarized by analysis group (or analysis subgroup) and visit as appropriate. All subject data will be presented in data listings by subject.

6.2.2 Statistical Hypotheses for Trial Objectives

Because of the nature of an open-labeled study, no hypotheses are planned and to be tested.

6.2.3 Interim Analysis

One interim analysis was planned to support regulatory filing of BED NDA submission and a separate SAP was developed for the interim analysis.

6.2.4 Data Monitoring

Data and Safety Monitoring Board (DSMB) meetings are planned to be held at regular intervals. Data to be presented to the DSMB are described in its charter.

7. Statistical Analyses

All analyses and summaries will be produced using SAS® version 9.3 (or higher) for windows. Unless otherwise specified, continuous variables will be summarized with descriptive statistics including: the number of observations (n), mean, standard deviation (SD), median, range (minimum and maximum values). For change from baseline, 95% CI will be calculated whenever appropriate. All categorical data will be presented using frequency counts and percentages. Shift tables will be produced for some assessments that contain counts and percentages of subjects in each cross-classification level of baseline versus post-baseline assessment. The by-visit summary of continuous and categorical data will be displayed at protocol planned visits (weeks) and endpoint. Data for unscheduled assessments will be included when determining baseline values, selecting worst result for shift analyses, and for summary of normal/abnormal values. The listings will include all enrolled subjects in the database. In general, the subject listings will be sorted by analysis group, subject number and assessment visit and date (and time, if applicable).

7.1. Subject Information

Unless otherwise specified, subject information will be presented by analysis group and analysis subgroup, as needed (see Section 6.1.9) for the safety population.

7.1.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by analysis group and analysis subgroup based on the safety population.

Baseline descriptive statistics (N, mean, SD, median, and range) of demographic characteristics will be provided by analysis group and analysis subgroup for age at study entry (in years), body weight, height, body mass index (BMI, calculated as weight (kg)/ [height (m) ^{2}]), and waist circumference.

The number and percentage of subjects in each of the following categories (and sub-categories) at baseline will also be summarized by analysis group:

- Age group: <40, ≥40 years old;
- Gender: Male, Female;
- Race: white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino;
- Baseline BMI category : Underweight/Normal (<25), Overweight (25 to <30), Obesity Class I (30 to <35), Obesity Class II (35 to <40), and Obesity Class III (≥ 40) kg/m^2;

Baseline summary statistics (N, mean, SD, median, and range) of disease characteristics will be provided by analysis group

- DB Baseline and OL Baseline of BE-CGI-S score
- DB Baseline and OL Baseline of EDE-Q modified global score and subscale scores

7.1.2. Disposition Information

Subject disposition of open-label treatment period for all enrolled subjects will be summarized by analysis group and analysis subgroup using the following categories:

- Subjects who entered the extension study;
- Subjects who entered the extension study, but not dosed;
- Subjects in the Safety population;
- Subjects in the Safety who completed the study;
- Subjects who discontinued during the treatment period.

Subject disposition of withdrawal period for subjects in withdrawal population will be summarized by analysis group and analysis subgroup as below:

- Subjects in withdrawal population;
- Subjects who completed the withdrawal period;
- Subjects who discontinued during the withdrawal period.

For subjects who are consented and discontinue from the study, the corresponding reasons for discontinuation will be summarized.

Kaplan-Meier plot of the time to early discontinuation will be presented by analysis group and subgroup.

7.1.3. Treatment Compliance

At each post OL-baseline (Weeks 2 – 52) visit, prior to dispensing study medication, previously dispensed study medication will be retrieved and assessed by tablet count. Compliance in the open-label treatment phase will be calculated for each post-OL baseline visit and overall as follows:

- Percent compliance = (number of tablets taken / number of tablets should have taken) x 100.
- Number of tablets taken = number of tablets dispensed – number of tablets returned.
- Number of tablets should have taken = (number of tablets supposed to take in a day) x (number of exposure days).
- Number of exposure days = last dose date – first dose date + 1.

For any study visit, if medication kit usage information is incomplete (ie, meet one of following conditions: any dispensed medication kit at the visit has missing number of tables returned, or has missing dosing start or ending date), compliance rate at the visit will not be derived and will be set as missing.

For an assessment period that involves multiple study visits (ie, the open-label treatment period), if at some visit(s) the drug usage information is incomplete, then the other visits with complete information of kit usage will be used to derive the compliance rate. Number and proportion of medication kits with incomplete usage information at each dispensed visit and the overall open-label treatment period will be summarized by treatment for categories below.

- incomplete kit usage of Dasotraline 4 mg kit
- incomplete kit usage of Dasotraline 6 mg kit
- incomplete kit usage of Dasotraline 8 mg kit
- incomplete kit usage of any Dasotraline kit

Specifically, for each subject, overall rate (percentage) of medication kits with incomplete usage information during the open-label treatment period will be calculated as the total number of medication kits with incomplete usage information divided by total number of medication kits dispensed in the treatment period. Summary statistics (n, mean, median, range) of overall rate of incomplete medication kit usage will be presented by treatment group.

In addition, number and percentage of subjects with at least one of incomplete medication kit usage information for each dispensed visit and the number and percentage of subjects for categories below for the overall open-label treatment period will be summarized by treatment group.

- With <=4 incomplete kit usage
  - With 1 incomplete kit usage ONLY,
  - With 2 incomplete kit usage ONLY,
  - With 3 incomplete kit usage ONLY,
  - With 4 incomplete kit usage ONLY,
- With 5-12 incomplete kit usage
- With >=13 incomplete kit usage

- Missing at 1 study visit only;
- Missing at 2 study visits only;
- Missing at 3 study visits only;

- Missing at >=4 visits

Non-compliance is defined as less than 75% or more than 125% non-missing compliance with the study medication. Subjects with missing compliance will not be classified as non-compliant.

Descriptive summary statistics (N, mean, median, and range) will be provided by analysis group for percent compliance by study visit and overall open-label treatment period. In addition, the number and percentage of subjects in the categories of the following variables will also be summarized by analysis group for open-label treatment period:

- Compliant;
- Non-compliant (<75% or >125%);
- Non-compliant: <75%;
- Non-complaint: >125%.

7.1.4. Extent of Exposure

Treatment duration is defined as the amount of elapsed time between the first and the last day that study medication was taken (inclusive). It will be calculated (in days) in terms of the difference in relative study days between the last and first dose of study medication, plus one day. See Section 6.1.11.1 for imputation rule if the end date of the medication intake is unknown or 'unconfirmed'.

Descriptive statistics (N, mean, standard deviation, median, and range) will be presented by analysis group and analysis subgroup for treatment duration. Number of subjects with duration in each of following categories (days): ≥ 1, ≥ 14, ≥ 28, ≥ 56, ≥84, ≥112, ≥140, ≥168, ≥183, ≥196, ≥252, ≥308, and ≥364; 1-13, 14-27, 28-55, 56-83, 84-111, 112-139,140-167,168-195, 196-251, 252-307, 308-363, ≥364 days will also be presented. Return of the blister card at any given visit is not a prerequisite for inclusion in exposure summary statistics if corresponding dose start and end dates are reported.

7.1.5. Study Medication and Concomitant Medications

7.1.5.1. Study Medication

Descriptive summary statistics (N, mean, median) for the mean daily dose will be provided by analysis group at each post-baseline visit, endpoint, and overall treatment period. Mean daily dose for an assessed period (eg, overall treatment period) will be calculated as the sum of the total daily dose divided by the total exposure (ie, last dose day – first dose day+1) in the assessed period.

In addition, frequency distribution of the following dose information will be summarized:

- predominant dose(ie, modal dose) during the open-label treatment period
- maximum daily dose during the open-label treatment period

See Section 6.1.10 for definition of the predominant daily dose during the OL treatment period.

In addition, frequency distribution of the all dispensed medication (regardless the kit return status) by study visit and number and percentage of subjects who have modified the dosing schedule since last visit will be summarized by visit.

Return of the blister card at any given visit is not a prerequisite for inclusion in average daily dose summary statistics or predominant dose summary statistics if corresponding dose start and end dates and amount are reported.

7.1.5.2. Concomitant Medications

Concomitant medications during the open-label treatment period (see Section 6.1.1.1) (ie, medications taken during the OL treatment period) are coded using World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) codes.

Number and percentage of subjects taking concomitant medications will be provided by level 3 ATC classification and preferred name by analysis group based on the safety population. Since medications are coded to ATC classification by indication, preferred names may appear under multiple ATC classifications. Concomitant medications started prior to and on/after the first day of the open-label treatment period will be summarized separately in a similar way.

Number and percentage of subjects taking medications after last dose of study drug will be summarized based on the withdrawal population.

Summary of concomitant usage of sleep aids

As specified in the study protocol, during the course of the study, subjects are permitted to receive sleep aids with some restrictions. The full list of sleep aids used in the study will be obtained through medical review prior to the final database lock and the definition of sleep aids is provided in Attachment 9.6. The number and percentage of subjects receiving any sleep aid during the open-label treatment period will be summarized by preferred term based on the Safety population. In addition, percentage of subjects with usage of sleep aids over time will be presented graphically by study day, where the percentage is calculated as number of subjects with usage of any sleep aid on the day divided by number of subjects remaining on the treatment period at that time point.

All medication data will be included in the prior and concomitant medication listing.

7.1.6. Psychiatric History and Medical History Prior to DB Phase of Core Study

Psychiatric history and medical history data will be extracted from the corresponding ADaM datasets of core studies directly. The number and percentage of subjects with medical pre-

condition will be summarized by system organ class (SOC) and preferred term for each analysis group.

Psychiatric history information prior to DB phase of core studies will be summarized in a same way as for core studies by analysis group. See Section 7.1.2 of SEP360-221 and SEP360-321 SAP for details. It should be noted that at study level, study SEP360-321 was coded using MedDRA 19.0 while study SEP360-221 was coded using MedDRA 18.0. For table summary of study SEP360-322, medical history will be summarized based on MedDRA Version 19.0 (ie, corresponding data from study SEP360-221 will be re-coded at programming level and summary output will be generated accordingly).

7.1.7. Psychotherapy

A listing of CRF collected psychotherapy will be provided for all safety subjects.

7.1.8. Protocol Deviations

Protocol deviations will be collected during monitoring visits. Protocol deviations will be placed into the following categories: concomitant medications, dosing, enrollment criteria, laboratory, non-compliance, visit schedule, visit/procedure requirement, and other. Each instance of a protocol deviation will be reviewed and determined to be major or minor prior to the final database lock.

A summary of protocol deviations will be provided as the number (%) of subjects with at least one protocol major deviation and the number (%) of subjects with a major deviation in each category for the safety population. A listing will be provided containing all protocol deviations.

7.2. Effectiveness Analyses

7.2.1. Definition

The effectiveness endpoints of interest are:

- Change in BE-CGI-S score
- Change in EDE-Q modified global score and 3 subscale scores (dietary restraint, shape concern, weight concern)
- Change in values of items 4, 5, and 6 of EDE-Q modified (ie, number of times of unusually large amount of food, number of times of having lost control eating, number of days of overeating episodes)
- Change in SDS total score and subscale scores (school/work disability, social life disability, and family life disability)

The subject-reported health status endpoint for subjects continued from SEP360-221 only is:

- Change in SF-12 two component scores (physical component, mental health component)

7.2.2. Analysis Methods

No inferential statistics on effectiveness will be presented. For all continuous effectiveness assessments, descriptive summary statistics (N, mean, standard deviation, median, range, and a 95% confidence interval) will be presented by analysis group, at DB baseline, OL baseline, each of post-OL visit, and endpoint in the open-label treatment period. All analyses for the scheduled assessments will be based on observed cases (OC). In addition, for all effectiveness evaluations, changes from DB baseline and changes from OL baseline will be presented in a similar way using summary statistics as described above.

In addition, the number and percentage of subjects in the following categories for the number of days of overeating episodes per Item 6 of EDE-Q Modified will be summarized by analysis group and at DB Baseline (for subjects from SEP360-321 only) or DB Screening (for subjects from SEP360-221 only), OL Baseline, post-OL Baseline visit, and endpoint:

- 0 day
- 1 day
- >1 to ≤4 days
- >4 to ≤8 days
- >8 to ≤12 days
- >12 to ≤ 20 days
- >20 days

Frequency distribution of BE-CGI-S score over time will be summarized similarly. Plots of the mean actual value, mean change from DB Baseline as well as mean change from OL Baseline in all effectiveness assessments over time by analysis group will be presented for the safety population.

7.3. Pharmacokinetics (PK) Analysis

Not applicable.

7.4. Safety

7.4.1. Analysis Specifications

All safety analyses and summaries will be based on the safety analysis population.

Unless otherwise specified, safety data will be presented separately by analysis group for the open-label treatment period (for data collected up to the end of open-label treatment period) and withdrawal period (for data collected during the withdrawal period), as appropriate. The CSSA and DESS, which are used to assess physical dependence and withdrawal symptoms, are collected only at the Week 52/EOT and in the withdrawal period; all other safety data are to be

collected in both treatment period and withdrawal period and will be presented by analysis group for the open-label treatment period and withdrawal period, separately, as appropriate.

For continuous data collected in the OL treatment period, actual observed value and change form baseline will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, range, 95% confidence interval [CI] as needed). Where changes are reported, the reference will be to "DB Baseline". Where relevant, changes from "OL Baseline" will also be reported.

For continuous data collected in the withdrawal period, the actual value, changes from DB and OL baseline (when applicable), and change from withdrawal baseline will be summarized by analysis group at study visits (ie, DB Baseline, OL Baseline, Withdrawal Baseline, and other post-withdrawal baseline visits and withdrawal endpoint).

There will be no imputation of missing values for clinical laboratory test results, vital sign measurements, and ECG evaluations in the by-visit analyses. All analyses of safety data are descriptive. No inferential analyses of safety data are performed.

7.4.2. Adverse Events

All AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher.

Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events (TEAEs) are those reported adverse events with onset data on or after the first day of the open-label treatment period through 7 days after study drug discontinuation (14 days for serious adverse events and deaths). The start of the open-label treatment period is defined as Day 1 for subjects previously randomized to placebo group and the OL Baseline visit date for subjects previously randomized to dasotraline groups.

AEs with a start date prior to the first day of the OL treatment period which are reported to have an increase in intensity, or which are reported to have a attribution in relationship to study medication (ie, attribution to possible related, probably related, related) after the first day of the OL treatment period are considered as TEAEs.

Discontinuation-emergent adverse events (DEAEs) are defined as AEs which have an onset after the last dose date of study drug through the Week 55 visit (ie, the last study visit in the withdrawal period).

Table summary of AEs will be limited to TEAEs and DEAEs. All AE data will be displayed in data listings. For the sake of simplicity, hereafter TEAE is referred to as AE.

The overall incidence (ie, number and percent of subjects with one or more AE in each category) of AEs, serious AEs, deaths, AEs leading to discontinuation, study drug-related AEs, study drug-related AEs leading to discontinuation, serious AEs leading to discontinuation, and serious

study drug-related AEs, and serious study drug-related AEs leading to discontinuation will be summarized by analysis group.

The AEs also will be summarized by system organ class (SOC) and preferred term (PT) by presenting the number and percentage of subjects with each AE category. The incidence of AEs (by preferred term, grouped by SOC, and presented by analysis group) will also be summarized by severity, by the relationship to study medication, by the action taken regarding the study medication, as well as by the outcome. If a subject has the same AE on multiple occasions, the highest severity (severe, moderate, mild) recorded for the event and the highest drug relationship (unrelated, unlikely to be related, possibly related, probably related, and definitely related) will be presented, respectively. The relationship to study medication will be presented by 2 categories: related (which includes possibly related, probably related, and related, as determined by investigators), and not related (which includes unrelated and unlikely to be related, as determined by investigators). Furthermore, for AE summary by SOC and PT or by PT only, the following combined preferred terms will be summarized as well:

- Insomnia: Insomnia, Initial insomnia, Middle insomnia, Terminal insomnia
- Hallucination: Hallucination; Hallucination, auditory; Hallucination, gustatory; Hallucination, olfactory; Hallucination, synaesthetic; Hallucination, tactile; Hallucination, visual; Hallucinations, mixed; Hypnagogic hallucination; Hypnopompic hallucination; Somatic hallucination.

A Kaplan-Meier plot of the time to the first onset of treatment emergent insomnia (combined term) during the extension study will be presented by analysis group. Time to the first onset (in days) is defined as the earliest onset date of insomnia – start date of OL treatment period + 1. Subjects who do not experience any insomnia on or before the last dose date will be censored on the day of last dose.

Prevalence rate of insomnia (combined term) at a study day in the open-label treatment period is defined as number of subjects experiencing insomnia on the day divided by number of subjects remaining on open-label study treatment period at that time point. It is notable that subjects may experience multiple insomnia episodes during the study. Prevalence rate over time will be summarized and presented graphically by analysis group.

AE maximum relationship

Each AE will be classified as ‘related’, ‘not related’, and ‘not specified’. TEAEs with a missing AE relationship will be classified as ‘not specified’. AE summary by the relationship to the study medication will be based on the highest relationship within an SOC and PT. Response values will be ranked in order from minimum to maximum as ‘not specified’ < ‘not related’ < ‘related’.

AE maximum severity

AEs with a missing severity will be classified as 'not specified'. AE summary by the severity will be based on the maximum severity within an SOC and PT. Response severity values will be ranked in order from minimum to maximum as 'not specified' < 'mild' < 'moderate' < 'severe'.

AE maximum action taken

AEs with a missing action taken will be classified as 'unknown'. AE summary by the action taken will be based on the maximum action taken within an SOC and PT. Response action values will be ranked in order from minimum to maximum as 'not applicable'< 'unknown' < 'dose increased' < 'unchanged'< 'dose reduced' < 'drug interrupted'< 'drug withdrawn'.

AE maximum outcome

AEs with a missing outcome will be classified as 'unknown''. AE summary by the outcome will be based on the maximum outcome within an SOC and PT. Response outcome_values will be ranked in order from minimum to maximum as 'unknown' < 'recovered/resolved' < 'recovered/resolved with sequelae' < 'recovering/resolving' < 'not recovered/not resolved'< 'fatal'.

AEs of Special Interest (AESI)

A list of preferred terms that are to be combined for assessment of each of pre-specified adverse events category as below are provided in Attachment 9.3.

- cardiovascular-related AEs
  - Cardiac arrhythmias
  - Vital signs-related
- metabolic-related AEs
  - Weight-related
  - Metabolic-Related (excluding weight)
- Neuropsychiatric-related AEs,
  - Neuropsychiatric AEs
  - Psychosis or Mania
  - Psychosis
  - Mania
- Combined insomnia
- Suicide and self-injury related AEs
- Spontaneous abortion /miscarriage (for female subjects only).
- Drug abuse and dependence (for AEs onset on/prior to the last study dose)
- Potential drug abuse (for AEs onset on/prior to the last study dose)
- Drug withdrawal related AEs (for AEs onset after the last study dose)

Definition of above AESI categories were initially provided in the integrated statistical analysis plan (ISAP) of the Integrated Summary of Safety (ISS) of Dasotraline BED NDA (NDA number: 213025). For final analysis of study SEP360-322, definitions of AESIs, including cardiac

arrhythmias, combined insomnia, psychosis, mania, suicide and self-injury**,** spontaneous abortion /miscarriage, drug abuse and dependence**,** drug withdrawal, and potential drug abuse, are exactly same as what were defined in the ISAP, since their definitions are either directly based on standard SMQs or from other standard terms.

For other AESI categories, including vital signs-related AEs, weight-related AEs, metabolic-related (excluding weight) related AEs, and neuropsychiatric AEs, their AE preferred terms are determined and verified by medical review of coded AE terms during data review and finalized prior to the final database lock. Definitions of these AESIs were obtained per medical review from the accumulative database of dasotraline clinical program. Since more data are obtained from study SEP360-322 after the BED NDA submission, additional AE preferred terms might be identified and added to preferred lists of definition. AE preferred terms that had been already identified in ISS ISAP of BED NDA will be kept as they are.

Except of category of drug withdrawal related AEs, the incidence of TEAEs with special interest by AESI category and PT will be summarized by analysis group, by severity, by the action taken regarding the study medication, as well as by the outcome based on the safety population. For "Spontaneous abortion /miscarriage" related AEs, the incidence will calculated based on the number of female subjects in each analysis group as denominator.

Listings will also be generated for deaths, SAEs, AESI, and discontinuations due to AEs. All adverse events regardless of treatment emergent status will be provided in the AE data listing.

AEs by Exposure

The TEAEs will be summarized by exposure to study drug using time intervals beginning with the earliest concurrent exposure to study drug for following AE summary as needed. Denominators for exposure intervals will be based on the number of subjects who were exposed as of the first day of the interval; for cases where events meet the treatment-emergent definition but start after the last dose, the exposure interval for the event will be considered the interval of the last day of exposure to study medication.

- AEs by SOC and PT, Serious AEs by SOC and PT, and AEs leading to discontinuation by SOC and PT (sorted alphabetically by SOC and PT within SOC).
- AEs by PT, AEs with special interest by PT (sorted by descending order per frequency count)

Exposure categories to be summarized are given below:

- Exposure categories : 1-13 days, 14-27 days, 28-83 days, 84-167 days, ≥168 days.

AEs by Subgroup

The TEAEs will be summarized by SOC, PT for subgroups (see Section 6.1.12) below:

- Age group at OL Baseline (years): < 40 years, ≥ 40 years
- Gender: Male, Female
- Race: White, Non-white
- BMI at OL Baseline: Non-obese , Obese class I/II, Obese class III

Discontinuation-Emergent Adverse Event (DEAE) (ie, AEs Onset After Last Study Dose)

All summary of DEAEs will be based on a 'modified' withdrawal population (see Section 6.1.8), which includes all subjects in the withdrawal population plus the subjects who do not enter withdrawal period, but their last study dose dates are at least 2 days earlier than their last study visit (ie, Week 52/EOT visit). The rationale of defining 'modified' withdrawal population is that the AE information after the last study dose is expected to be continuously collected till the last study visit

The overall incidence of DEAEs and serious DEAEs will be summarized by analysis group. The DEAEs also will be summarized by SOC and PT, and by PT of each analysis group.

In addition, incidence of DEAEs by SOC and PT will be also summarized using time intervals beginning with the earliest AE concurrent withdrawal duration in the withdrawal period, where denominators in percentage calculation for withdrawal duration intervals (in days) will be based on the number of subjects whose withdrawal duration are no less than the first day of the interval. Withdrawal duration (in days) will be derived as the last withdrawal visit date minus the last dose date +1 and withdrawal duration categories to be assessed are 1-7 days, 8-14 days, and ≥ 15 days.

7.4.3. Laboratory Measurements

Laboratory data will be summarized for each laboratory test listed in Attachment 9.4.1.

7.4.3.1. Treatment Period

Descriptive statistics (N, mean, standard deviation, median, and range) will be reported for each continuous laboratory analyte at DB baseline, OL baseline, each post-OL baseline time point, and endpoint for observed actual value as well as change from DB baseline and OL baseline, respectively. Categorical results (eg, urinalysis tests) will be summarized at DB baseline, OL baseline, each post-OL baseline visit, and endpoint by analysis group using frequency and percentage. All lab values will be presented in the data listings.

Results for glucose and lipid tests (HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides) will be presented separately by fasting status, which includes fasting only and overall (fasting, non-fasting, or unknown).

The normal reference ranges for laboratory tests will be used to determine whether the laboratory test value is below, within, or above the normal range. Shifts from DB baseline and shift from

OL baseline over time will be produced by analysis group to show the percentage of subjects with laboratory test values below, within, and above the normal range. Criteria for Markedly Abnormal Laboratory Values (MALV) per International System of Units (SI) unit of selected laboratory parameters can be found in Table 6. Equivalent MALV criteria for conventional unit are provided in Attachment 9.4.2. The criterion of MALV is satisfied if a value falls into the markedly abnormal range at an assessed visit or if subjects have experienced at least once MALV in the open-label treatment period. The number and percentage of subjects with a particular MALV at each OL visit, endpoint, and during the open-label treatment period (treatment emergent, up to and including endpoint), will be presented by analysis group.

Table 6: – Criteria for Markedly Abnormal Laboratory Values (MALV) (SI Unit)

	Criteria for Markedly Abnormal Status	
Laboratory Test	Low	High
Hematology		
Hematocrit	Male: ≤ 0.37 Female: ≤ 0.32	Male: ≥ 0.60 Female: ≥ 0.54
Hemoglobin	Male: ≤ 115 g/L Female: ≤ 95 g/L	Male: ≥ 190 g/L Female: ≥ 175 g/L
RBC	≤ 3.5 $x10^{12}$/L	≥ 6.4 x 10^{12}/L
Total WBC Count	≤ 2.8 $x10^{9}$/L	≥ 16 $x10^{9}$/L
Basophils	N/A	≥ 10 % ≥ 1.6 $x10^{9}$/L
Eosinophils	N/A	≥ 10 % ≥ 1.6 $x10^{9}$/L
Lymphocytes	N/A	≥ 75 % ≥ 12.0 $x10^{9}$/L
Monocytes	N/A	≥ 15 % ≥ 2.4 $x10^{9}$/L
Neutrophils	≤ 15 % ≤ 0.42 $x10^{9}$/L	≥ 85 % ≥ 13.6 $x10^{9}$/L
Platelet Count	≤ 75 $x10^{9}$/L	≥ 700 $x10^{9}$/L
Chemistry		
Albumin	≤ 25 g/L	N/A
ALP	N/A	≥ 3 x ULN
AST	N/A	≥ 3 x ULN
ALT	N/A	≥ 3 x ULN
Bicarbonate	≤ 16 mmol/L	≥ 35 mmol/L
Calcium	≤ 2.05 mmol/L	≥ 2.99 mmol/L
Chloride	≤ 90 mmol/L	≥ 118 mmol/L
Creatinine	N/A	≥ 176.8 µmol/L
Glucose (fasting)	≤ 2.22 mmol/L	≥ 9.71 mmol/L
Inorganic Phosphorus	≤ 0.5 mmol/L	≥ 1.7 mmol/L
Magnesium	≤ 0.6 mmol/L	≥ 1.15 mmol/L
Potassium	≤ 3 mmol/L	≥ 6 mmol/L

Laboratory Test	Criteria for Markedly Abnormal Status	
	Low	High
Sodium	≤ 126 mmol/L	≥ 156 mmol/L
Total Bilirubin	N/A	≥ 34.2 µmol/L
Total Protein	≤ 45 g/L	≥ 100 g/L
Uric Acid	Male: N/A Female: N/A	Male: ≥ 625 µmol/L Female: ≥ 506 µmol/L
Urea (BUN)	N/A	≥ 11 mmol/L
Lipids panel		
Total Cholesterol (fasting)	N/A	≥7.77 mmol/L
LDL Cholesterol (fasting)	N/A	≥5.18 mmol/L
HDL (fasting)	≤ 1.036 mmol/L	N/A
Triglycerides (fasting)	N/A	≥ 3.39 mmol/L
HbA1c	N/A	≥ 7.5%
Urinalysis		
Urine Blood	N/A	≥ 1+
Urine Glucose	N/A	≥ 3+
Urine Ketones	N/A	≥ 2+
Urine Protein	N/A	≥ 2+

Note: ULN = Upper Limit of Normal; N/A = Not Applicable

A listing of subject data for those who have experienced at least once MALV during the open-label treatment period will be generated. Urine drug screen results will be presented for each parameter by DB baseline, OL baseline, post-OL baseline visit, and endpoint. Number and percentage of positive and negative results will be displayed. Summary statistics of laboratory outputs will be generated per conventional unit and SI unit, separately.

7.4.3.2. Withdrawal Period

Laboratory data will be summarized by presenting descriptive statistics of actual values, change from DB baseline and OL baseline, and changes from withdrawal baseline by visit and analysis group.

7.4.4. ECG Evaluations

As a part of each ECG, heart rate (HR), axis, and the following intervals will be measured: RR, PR, QRS, and QT. Corrected QT intervals (QT_cB and QT_cF) values are based on the following formula:

- Bazett: QT_cB (msec) = QT (msec) / $(RR/1000)^{1/2}$
- Fridericia: QT_cF (msec) = QT (msec) / $(RR/1000)^{1/3}$

where RR will be reported in milliseconds (msec).

7.4.4.1. Treatment Period

Descriptive statistics (eg, mean, SD, median, range, 95% CI) for observed actual value at the DB baseline, OL baseline, each post-OL baseline visit, and endpoint and changes from DB baseline and OL baseline, respectively will be displayed for continuous variables (ie, HR, QRS, QTcF, etc) by analysis group.

The overall ECG assessment is conducted by central reading and a determination is made whether the reading is normal (or absent if applicable) or abnormal). Shifts from OL baseline and Shifts from DB baseline over time will be produced by analysis group.

Bazett and Fridericia corrected QT_c values will be classified as having QT_c prolongation according to Table 7.

Table 7: – QTc Prolongation

QTc Prolongation
> 450 msec for males > 470 msec for females
> 480 msec
> 500 msec
Increase from OL baseline QTc ≥ 30 msec Increase from DB baseline QTc ≥ 30 msec Increase from OL baseline QTc ≥ 60 msec Increase from DB baseline QTc ≥ 60 msec

The number and percentage of subjects having a QT_c prolongation using Fridericia correction method for DB baseline, OL baseline, post-OL baseline visit, endpoint, and any open-label treatment period (treatment emergent, the worst case), will be summarized by analysis group. A listing of ECG data for subjects with at least one prolonged QT_c will also be produced.

For other ECG parameters, subjects are classified as normal or abnormal using the limits specified in Table 8. For abnormal ECG parameter reporting, counts and percentages of subjects will be presented for DB baseline, OL baseline, each post-OL baseline visit, endpoint, and any open-label treatment period (treatment emergent) by analysis group.

Table 8: – Definition of Abnormal ECG Values by Parameter

ECG parameter (unit)	Abnormally Low	Abnormally High
HR (bpm)	≤50	≥100
PR interval (msec)	N/A	≥210
QRS interval (msec)	N/A	≥120
QT interval (msec)	N/A	> 500

Note: N/A = Not Applicable

7.4.4.2. Withdrawal Period

ECG data will be summarized by presenting descriptive statistics of observed values, change from DB baseline and OL baseline, and changes from withdrawal baseline by visit and analysis group.

7.4.5. Vital Signs, Weight, and BMI

7.4.5.1. Treatment Period

Descriptive statistics (mean, SD etc.) will be provided for observed at the DB baseline, OL baseline, post-OL baseline visit, and endpoint, and change from DB baseline and OL baseline values, respectively of each vital sign parameters, weight, and BMI listed below:

- Systolic blood pressure (SBP) in supine and standing positions
- Diastolic blood pressure (DBP) in supine and standing positions
- pulse rate in supine and standing positions
- Orthostatic change in SBP
- Orthostatic change in DBP
- Orthostatic change in pulse rate
- Respiratory rate
- Temperature
- Body weight and BMI,

Percent change from DB baseline and OL baseline values in weight and BMI will be summarized in a similar way.

The number and percentage of subjects with Markedly Abnormal Vital Signs (MAVS), defined in Table 9.1, will be presented by analysis group at DB baseline and OL baseline, post-OL baseline visits, endpoint, and any open-label treatment period (treatment-emergent, the worst case).

A listing of subject data for those who satisfy MAVS during the open-label treatment period will be presented.

Table 9.1: – Criteria for Markedly Abnormal Vital Signs and Weight

Parameter (unit)	Markedly Low	Markedly High
SBP (supine, standing) (mmHg)	<90	≥180
	Value ≤ 90 and ≥ 20 decrease from baseline	Value ≥ 180 and ≥ 20 increase from baseline
DBP (supine, standing) (mmHg)	<50	≥105
	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 105 and ≥ 15 increase from baseline
Pulse rate (supine, standing) (bpm)	<50	≥120
	Value ≤ 50 and ≥ 15 decrease from baseline	≥120 and increased >15 from baseline
Weight (kg)	≥ 7% decrease from baseline	≥ 7% increase from baseline
Temperature (˚C)	N/A	Value ≥ 38.3°C and ≥0.8°C

		increase from baseline
Orthostatic Criteria		
SBP orthostatic criteria (mmHg)	≥ 20 mmHg reduction from supine to standing position	N/A
DBP orthostatic criteria (mmHg)	≥ 10 mmHg reduction from supine to standing position	N/A
Orthostatic tachycardia (bpm)	N/A	≥ 20 bpm increase from supine to standing position in pulse rate.

BMI measurements will be used to classify a subject's weight status as underweight, normal, overweight or obese using Table 9.2 and as underweight/normal, overweight, obesity class I, obesity class II, and obesity class III using Table 9.3.

Shifts from OL baseline and shifts from DB baseline to endpoint for weight status categories (Tables 9.3) will be summarized by analysis group to show the number and percentage of subjects that fall into each category.

In addition, the number and percentage of subjects with 3%, 5%, 7%, and 10% reduction in body weight will be presented by visit and analysis group.

Table 9.2: – BMI Weight Status Category 1

BMI (kg/m^2)	**Weight Status**
< 18.5	Underweight
18.5 ≤ BMI < 25.0	Normal
25.0 ≤ BMI < 30	Overweight
≥ 30.0	Obese

Table 9.3: – BMI Weight Status Category 2

BMI (kg/m^2)	**Weight Status**
BMI < 25	Underweight/ Normal
25 ≤ BMI < 30	Overweight
30 ≤ BMI < 35	Obesity Class I
35 ≤ BMI < 40	Obesity Class II
40 ≤ BMI	Obesity Class III

7.4.5.2. Withdrawal Period

Vital sign data will be summarized by presenting descriptive statistics of observed values, change from DB baseline and OL baseline, and changes from withdrawal baseline by visit and analysis group.

7.4.6. Assessments of Withdrawal Effects (CSSA, DESS, HAM-A, and MADRS)

7.4.6.1. Treatment Period

MADRS total score, HAM-A total score, and the individual scores collected in the OL treatment period will be summarized by presenting descriptive statistics (N, mean, median, and range) of observed values and change from DB baseline and OL baseline over time by analysis group for safety population.

7.4.6.2. Withdrawal Period

MADRS total score, HAM-A total score, and each of the individual item scores in the withdrawal period will be summarized by presenting descriptive statistics (N, mean, median, and range) of observed values and change from DB baseline, OL baseline, and withdrawal baseline by analysis group and visit; a similar analysis will be performed by gender as well.

CSSA total score, DESS total score, and the individual scores will be summarized by presenting descriptive statistics (N, mean, median, and range) of observed values and change from withdrawal baseline by analysis group and visits based on the withdrawal population; the visits will be displayed in an order defined as follow: withdrawal Baseline, day 1-2, day 3-4, day 5-6, day 7-8, withdrawal Week 1, day 9-10, day 11-12, day 13-14, withdrawal Week 2, day 15-16, day 17-18, day 19-20, day 21-22, withdrawal Week 3. See Section 6.1.2.2 for details about how to define these analysis visits per both clinic and non-clinic visits. A similar analysis will be performed by gender as well. Number and percentage of subjects with a new symptom or worsen old symptom for each DESS individual score (ie, each individual score of DESS with value of 1) by study visit and the worst case during the withdrawal period will be summarized based on the withdrawal population as well.

The number and percentage of subjects in each of the following breakdown will be summarized by study visit during the withdrawal period.

- CSSA total score: 0-7, 8-15, 16-30, 31-45, 46-60, >60;
- DESS total score category 1: 0-2, 3-5, 6-10, 11-15,16-20;
- DESS total score category 2: 0-10, 11-20, 21-30, 31-43.

In addition, the number and percentage of subjects with change in DESS total score from withdrawal baseline by withdrawal visit and during any time point of the withdrawal period (per the worst case value) will be summarized in each of the following categories: ≤0, +1, +2, +3, ≥+4.

7.4.7. Columbia Suicide Severity Rating Scale (C-SSRS)

According to FDA draft guidance for suicidal ideation and behavior ([2]), the following C-SSRS outcomes, which have binary responses (yes/no), will be re-ordered and numbered to facilitate the further definitions of the composite endpoint and comparative endpoint of C-SSRS as below.

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt
Category 10 – Completed Suicide
Category 11– Self-injurious behavior without suicidal intent

Unless otherwise specified, C-SSRS table outputs will be presented by analysis group for one analysis time point 'Any extension (treatment emergent)', whose definition is given in Table 10.

The analysis time point is applied to suicidal ideation score and ideation intensity total score.

Table 10: Definition of Analysis Timepoint

Analysis Timepoint	eCRF Visit(s) to be Involved	C-SSRS Version /Assessment Period	Derivation Rule
Any extension visit (treatment emergent)[(a)]	all visits in the open-label treatment period (up to EOT)	Since last visit	Most severe value
Any withdrawal visit	all visits after the last study dose	Since last visit	Most severe value
[(a)]: including all visits in open-label treatment period (see Section 6.1.1.1).			

At each analysis time point, the following binary variables will be derived.

- Any Suicidal Ideation (Categories 1-5)
- Any Suicidal Behavior (Categories 6-10)
- Any Suicidality (Categories 1-10)
- Individual Item for Category 6-11, respectively.

Comparative endpoints for 'Emergence' (outcomes that include events that first emerge) and 'Worsen' (outcomes that include events that worsen) will be derived as below. See Table 11.

Table 11: Comparative Endpoint of C-SSRS Relative to DB Baseline

Comparative Endpoints	**Analysis Time Points Involved**	**Derivation Rule**
Emergence of Suicidal Ideation	DB Baseline[(a)] Any extension visit (treatment emergent) [(b)]	No suicidal ideation at DB Baseline, and any type of suicidal ideation in 'any extension visit (treatment emergent)'
Emergence of Serious Suicidal Ideation		No suicidal ideation at DB Baseline, and any serious suicidal ideation [ideation score of 4 or 5] in 'any extension visit (treatment emergent)'
Emergence of Suicidal Behavior		No suicidal behavior at DB Baseline, and any type of suicidal behavior in 'any extension visit (treatment emergent)'
Emergence of Suicidality		No suicidality at DB Baseline, and any suicidality in 'any extension visit (treatment emergent)'
Worsening of Suicidal Ideation		Most severe suicidal ideation in 'any extension visit (treatment emergent)' is more severe than the most severe value at DB Baseline
[(a)]: Definition of DB Baseline: see Table 12 in SEP360-221 SAP and Table 12 in SEP360-321 SAP; [(b)]: see Table 10.		

7.4.7.1. Treatment Period

The number and percentage of subjects with following categories will be summarized by analysis group for any extension visit (treatment emergent).

- each type of suicidal ideation,
- any suicidal ideation,
- each type of suicidal behavior,
- any suicidal behavior,
- any having self-injurious behavior without suicidal intent,
- any suicidality

In addition, for any extension visit (treatment emergent), the number and percentage of subjects with following categories will be also summarized by analysis group.

- emergence of suicidal ideation,
- emergence of serious suicidal ideation,
- worsening of suicidal ideation,
- emergence of suicidal behavior,
- emergence of suicidality

Shifts from DB baseline and OL baseline to any post-OL baseline visit (ie, the worst case) in suicidal ideation score will be presented by analysis group, to show the percentage of subjects with values 0 ('No ideation present') to 5 ('Active ideation with plan and intent'). Descriptive statistics (N, mean, standard deviation, median, and range) will be reported for Ideation intensity total score at DB baseline, OL baseline, each post-OL baseline visit, and endpoint for observed value as well as change from DB and OL baseline. Data collected on actual suicide attempts (lethality of actual attempts and potential lethality of attempts) will be presented in a data listing.

All summaries pertaining to the C-SSRS will be based on subjects in the Safety population.

7.4.7.2. Withdrawal Period

The number and percentage of subjects with following categories will be summarized by analysis group for any withdrawal visit for withdrawal population.

- each type of suicidal ideation,
- any suicidal ideation,
- each type of suicidal behavior,
- any suicidal behavior,
- any having self-injurious behavior without suicidal intent,
- any suicidality

7.4.8. Other Safety Assessments

7.4.8.1. Breath Alcohol Test

The number and percentage of subjects at each assessment (negative/positive) will be summarized at each visit by analysis group.

7.4.8.2. Neurological Examination

Frequency distribution of each category of assessment (ie, Cranial Nerves, Motor System, sensory System, Reflexes, Coordination, Gait and Rhomberg's test) will be summarized by analysis group at each visit. A shift table of each assessment for DB and OL baseline to endpoint and the worst case during open-label treatment period will also be presented by analysis group.

7.4.8.3. Abuse Potential Monitoring Plan (APMP)

The Abuse Potential Monitoring Plan (APMP) for dasotraline has been designed to detect potential abuse of the compound and to more closely monitor AEs consistent with the pharmacology. The plan detects irregularities in the handling of dasotraline in clinical trials and

identifies the misuse of dasotraline or other psychoactive substances. Moreover, the APMP provides a process by which events subject to additional monitoring are identified, processed, and reviewed. Events subject to additional monitoring are identified based on the pharmacology of dasotraline, as well as adverse event profiles of compounds with similar mechanisms of action.

APMP results will be provided by sites before DBL and provided in a listing.

7.4.8.3.1. Medication Handling Irregularities

Medication handling irregularities will be summarized using the following categories:

- Drug accounting errors, not involving suspected abuse or diversion by subject
- Non-compliance with study procedures, not involving suspected abuse or diversion by subject
- Other cases not involving suspected abuse or diversion by subject
- Suspected or known abuse or diversion of study drug
- Suspected abuse (nonmedical use) of alcohol, illicit substances, OTC drugs or prescription drugs obtained outside the study protocol

Instances that meet the threshold criteria for a medication handling irregularity will be summarized descriptively. Both the number of instances and the number (%) of subjects experiencing medical drug irregularities will be provided for each category and by analysis group. Instances of medication handling irregularity will be listed for all enrolled subjects.

7.4.8.3.2. Events Subject to Additional Monitoring (ESAMs)

In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse potential, will receive special attention. The adverse experiences or related signs and symptoms that will require additional monitoring (ESAMs) are listed in Attachment 9.5. AEs identified as ESAMs will be summarized by ESAM type and PT by analysis group for safety population (OL treatment period) and withdrawal population (withdrawal period), respectively. ESAMs will also be listed for all enrolled subjects.