



SEP-225289

Dasotraline

Clinical Study Protocol SEP360-321

**A 12-week, Randomized, Double-blind, Parallel-group,
Placebo-controlled, Fixed-dosed, Multicenter Study to Evaluate the
Efficacy, Safety, and Tolerability of Dasotraline in Adults with
Moderate to Severe Binge Eating Disorder**

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EMERGENCY CONTACTS**Table 1: Emergency Contact Information**

Role in Study	Name	Contact Information
Responsible Physician		
Medical Monitor		
SAE/Pregnancy Reporting		

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.
Name of Investigational Product: Dasotraline
Title of Study: A 12-week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dosed, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Dasotraline in Adults with Moderate to Severe Binge Eating Disorder
Proposed Indication: Binge Eating Disorder (BED)
Study Centers: approximately 50 clinical sites in the United States
Planned Study Period: approximately 15 months from first subject screened to last subject last visit
<p>Study Objective:</p> <p>Primary: Evaluate the efficacy of 2 doses of dasotraline (4 and 6 mg/day) compared with placebo in adults with moderate to severe BED as measured by the number of binge days per week</p> <p>Key Secondary: Evaluate the efficacy of 2 doses of dasotraline (4 and 6 mg/day) compared with placebo in adults with moderate to severe BED as measured by:</p> <ul style="list-style-type: none"> • Binge-eating Clinical Global Impression-Severity (BE-CGI-S) • 4-Week cessation from binge eating defined as a 100% reduction for at least 28 consecutive days in the number of binge eating episodes • Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) <p>Other Secondary:</p> <ul style="list-style-type: none"> • Evaluate the efficacy of 2 doses of dasotraline (4 and 6 mg/day) compared with placebo in adults with moderate to severe BED as measured by: <ul style="list-style-type: none"> ○ Number of binge episodes per week ○ Proportion of binge eating responders at Week 12 who show $\geq 75\%$ reduction in the number of binge eating episodes ○ Sheehan Disability Scale (SDS) ○ Montgomery-Asberg Depression Rating Scale (MADRS) ○ Hamilton Anxiety Rating Scale (HAM-A) ○ Eating Disorder Examination Questionnaire (EDE-Q) modified • Evaluate the safety and tolerability of 2 doses of dasotraline (4 and 6 mg/day) using physical examinations, 12-lead electrocardiograms (ECG), vital signs, adverse event (AE) reports, clinical laboratory results, body weight, body mass index (BMI), and Columbia – Suicide Severity Rating Scale (C-SSRS) • Assess potential withdrawal effects upon abrupt discontinuation of dasotraline after 12 weeks of continuous daily treatment using the following assessments (administered during the withdrawal period):

<ul style="list-style-type: none"> ○ 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 ● Assess the abuse potential of dasotraline utilizing a comprehensive abuse potential monitoring plan (APMP) ● Assess the relationship between dasotraline plasma concentration and the primary efficacy and selected secondary efficacy and safety endpoints
<p>Study Design: This is a randomized, double-blind, parallel-group, multicenter, outpatient study evaluating the efficacy and safety of 2 doses of dasotraline (4 and 6 mg/day) versus placebo over a 12-week treatment period in adults with BED. Subjects will be randomized to 3 treatment groups in a 1:1:1 ratio (4 mg/day dasotraline, 6 mg/day dasotraline, and placebo).</p> <p>Subjects randomized to placebo will receive placebo for the duration of the treatment period.</p> <p>Subjects randomized to 4 mg/day dasotraline will receive 4 mg/day for the duration of the treatment period.</p> <p>Subjects randomized to 6 mg/day dasotraline will be dosed with 4 mg/day dasotraline for the first 2 weeks of the treatment period and will be increased to 6 mg/day at Week 2.</p> <p>If, in the judgment of the Investigator, the subject does not tolerate the assigned dose, he or she will be discontinued from the study.</p> <p>The study will consist of 3 periods: Screening (up to 3 weeks), 12-weeks of treatment, and a 3-week study drug withdrawal period. Subjects who complete the 12-week double-blind treatment period in this study may be eligible to enroll and continue treatment for an additional 12 months in an open-label extension study (Study SEP360-322; see Figure 1). Subjects who do not enter the extension study will complete the study drug withdrawal period in this study.</p> <p>Efficacy will be evaluated at each visit using the subject binge eating diary and a clinician interview to assess the frequency of binge episodes and the number of binge days, defined as days with at least one binge episode. Additional assessments will include BE-CGI-S, Y-BOCS-BE, MADRS, HAM-A, SDS, and EDE-Q modified. Safety and tolerability will be monitored throughout the study by collection of physical examination results, ECGs, vital signs, AEs, clinical laboratory parameters, C-SSRS, body weight, and BMI will be calculated. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the Investigator for follow-up evaluation. Assessment of potential withdrawal effects 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.</p> <p>Blood samples for pharmacokinetics (PK) and biomarkers associated with eating disorders (to be determined) will be collected. Blood samples collected for PK assessment will be analyzed for plasma concentrations of dasotraline. The relationship between dasotraline plasma concentration and the primary and selected secondary clinical outcome measures will be evaluated. The relationship between biomarkers associated with eating disorders in relationship to the severity of BED and response to dasotraline will be evaluated at a later date in the development program. Plasma samples collected for PK and biomarker concentration analysis may also be used for the additional characterization of and/or bioanalytical method development for dasotraline.</p> <p>A blood sample will be collected from subjects who provide separate informed consent for pharmacogenomics (PGx) analysis for potential evaluation of associations between genetic polymorphisms such as, but not limited to Taq1DRD2, OPRM1, and DRD4-7R, and the severity of</p>

BED, the clinical response to dasotraline, in addition to the safety, efficacy, and PK profiles of dasotraline to be conducted at a later date in the development program. Separate consent is required for collection of this specific blood sample and will be obtained at Screening for subjects who agree to provide this sample (note: this separate consent is not required for participation in the study, it is required only for subjects who will provide this sample).

A comprehensive Abuse Potential Monitoring Plan (APMP) 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) will review safety data at regular intervals.

Screening Period (Days -22 to -2): Informed consent will be obtained from each subject before any study procedures are performed for this study. Study eligibility criteria will be assessed during this period, and subjects will be required to have discontinued from any protocol prohibited medications within 3 months of screening. The subject's eligibility assessment will be reviewed by the contract research organization's (CRO) oversight quality team along with the sponsor based on protocol specified inclusion and exclusion criteria. The sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility and will be copied on all communications between the CRO and the site. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled. Subjects may be rescreened once for out of range clinical laboratory results including urine drug screen (UDS) or ECG results following authorization of the medical monitor. During the screening visit, subjects will be trained to complete the daily binge eating diary and then complete the diary at home for at least 14 consecutive days immediately prior to the Baseline visit and starting no sooner than the day after the screening visit.

Baseline Visit (Day -1): Subjects who meet eligibility criteria at Screening will return to the study site on Day -1 for confirmation of screening evaluations as well as completion of predose assessments and procedures including clinician review of the daily binge eating diary. Any lapse in diary completion during the 14 day period (eg, 1 or more days are skipped) will be discussed with the subject. If 1 or 2 days per week are incomplete or missing, the subject may complete the diary with the clinician. However, if the subject cannot recall enough information to complete the diary in full after clinician review, the subject will be ineligible. Subjects will also be ineligible for randomization if there are more than 2 missed diary days in 1 week. Eligible subjects (based on confirmation of study entry criteria) will be randomized and dispensed study drug at Day -1.

Treatment Period (Day 1 [Week 0] through Day 84 [Week 12]): Subjects will self-administer the study drug on an outpatient basis once a day with or without food beginning on Day 1, the day after the Baseline visit, and continue for 12 weeks. Subjects will be instructed to administer study drug at approximately the same time each morning including on days when clinic visits occur. During the treatment period subjects will continue to complete a daily binge eating diary, which will be reviewed at each visit. During the treatment period, subjects will have one clinic visit every week for the first month, then one clinic visit every 2 weeks thereafter. In order to facilitate scheduling of clinic visits, a window of ± 2 days will be allowed for each weekly clinic visit and a window of ± 3 days will be allowed for each biweekly clinic visit.

Subjects who complete the 12-week Treatment Period may be eligible for participation in the open label extension study (SEP360-322). For subjects enrolling in the open label extension study, Week 12 will be the last visit for this study.

Study Medication Withdrawal Period (Day 85 through Day 105 [Week 15]): Subjects who do not enroll in the extension study for whatever reason, eg, less than 12 weeks treatment in this study, lack of interest in the extension study, or failure to meet all eligibility criteria for the extension study will return to the clinic at Weeks 13, 14, and 15, to assess safety and potential study medication withdrawal effects during the study medication withdrawal period. Subjects who discontinue from study drug

before completion of the 12-week treatment period will be asked to return to the clinic and complete the End of Treatment (EOT) visit as soon as possible following discontinuation of study drug and complete the 3 week withdrawal period. In addition, subjects will continue to complete the binge eating diary during this period.

Assessment of potential withdrawal effects will be conducted via administration of the CSSA, DESS, HAM-A, and MADRS at Week 12 (End of Treatment), then again at Weeks 13, 14, and 15 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 (up to 3 times per day if the clinical site staff are unable to contact the subject on the first 2 attempts). 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.

A window of ± 1 day will be 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.

Number of Subjects (planned): approximately 480 subjects (160 per treatment group)

Diagnosis and Main Criteria for Subject Inclusion: Male or female subjects between 18-55 years of age, inclusive, who meet the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for a diagnosis of BED confirmed based on the eating-disorders module of the Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H), clinician review of subject diaries, and the Eating Disorder Examination Questionnaire (EDE-Q) are eligible for this study. Subjects must have a BED diagnosis or be diagnosed at screening, have a history of at least 2 binge eating days a week for at least 6 months prior to screening, have BED of at least moderate severity with reports of at least 3 binge eating days for each of the 2 weeks prior to baseline as documented in the subject's binge diary, and have a BE-CGI-S score ≥ 4 at screening and baseline.

Subjects with any of the following are not eligible for the study: BMI of 18 kg/m² or less, or greater than 45 kg/m²; lifetime history or current symptoms consistent with bulimia nervosa or anorexia nervosa; started psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) within 3 months prior to screening; participating in a formal weight loss program (eg, Weight Watchers®) within 3 months prior to screening; used a psychostimulant or mood stabilizer within the 3 months prior to screening, or used any medications for the treatment of binge eating, other eating disorders, obesity, or weight gain or any other medication that could result in weight gain or weight loss including over-the-counter and herbal products within the 3 months prior to screening; started a new physical training/exercise program for the purpose of managing his or her weight or binge eating within 3 months prior to screening; a lifetime history of psychotic disorder, bipolar disorder, hypomania, dementia, or attention deficit hyperactivity disorder (ADHD) as defined by the DSM-5 criteria; a history of moderate to severe depression based on Investigator's judgment within the 6 months prior to screening or is currently taking or has taken any medication for depression during the 3 months prior to screening or has a MADRS score ≥ 18 ; a history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) within the 12 months prior to screening, as defined by the DSM-5 criteria.

See [Section 8](#) of the full protocol for complete eligibility information.

Investigational Product, Dosage and Mode of Administration: Dasotraline 4 mg and 6 mg capsules for once a day oral administration will be supplied.

Subjects randomized to 4 mg/day dasotraline will receive 4 mg/day for the duration of the treatment period.

Subjects randomized to 6 mg/day dasotraline will be dosed with 4 mg/day dasotraline for the first 2 weeks of the treatment period and will be increased to 6 mg/day at Week 2.
Duration of Treatment: 12 weeks
Reference Therapy, Dosage and Mode of Administration: Matching placebo capsules for once a day oral administration will be supplied.
<p>Selected Concomitant Medications: Use of certain medications, including but not limited to the following, is prohibited throughout the study from screening through the last in-clinic visit:</p> <ul style="list-style-type: none"> • psychostimulants • any medications for the treatment of binge eating or other eating disorders, obesity, or weight gain • antidepressant medications (eg, bupropion, selective serotonin reuptake inhibitor (SSRI)/serotonin norepinephrine reuptake inhibitor (SNRI), monoamine oxidase (MAO) inhibitors, tricyclics) and St. John's Wort • medications that are CYP2B6 substrates or inhibitors or inducers of CYP2B6, eg, bupropion, cyclophosphamide, carbamazepine, etc. • medications for the treatment of ADHD such as but not limited to lisdexamfetamine, methylphenidate, atomoxetine, clonidine, guanfacine, modafinil, and armodafinil • corticosteroids and anabolic steroids (Note: Topical, intra-nasal, and inhaled corticosteroids are permitted. Other formulations of corticosteroids may be permitted following consultation with the Medical Monitor.) • antiepileptic medications • benzodiazepines except for sleep (see Section 10.3.3) • mood stabilizers (eg, lithium, anticonvulsants) • antipsychotic medications • suvorexant • any medication that can result in either weight gain or weight loss (eg, insulin, liraglutide, metformin, diphenhydramine except topical formulations, etc.) including over-the-counter and herbal products <p>Initiation of psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) is prohibited within 3 months prior to screening and throughout the study.</p> <p>Any participation in a formal weight loss program such as Weight Watchers® is prohibited within 3 months of screening and throughout the study.</p> <p>See Section 10.3 of the full protocol for further information.</p>

Study Endpoints:**Primary Efficacy Endpoint:**

Change from baseline in number of binge days (defined as days during which at least 1 binge episode occurs) per week at Week 12.

Key Secondary Efficacy Endpoints:

- Change from baseline in BE-CGI-S score at Week 12
- Percent of subjects with a 4-week cessation from binge eating (defined as a 100% reduction for at least 28 consecutive days in the number of binge eating episodes prior to Week 12/EOT)
- Change from baseline in Y-BOCS-BE total score at Week 12

Other Secondary Efficacy Endpoints:

- Change from baseline in number of binge days per week at Weeks 1, 2, 3, 4, 6, 8, and 10
- Change from baseline in number of binge episodes per week at Weeks 1, 2, 3, 4, 6, 8, 10, and 12
- Change from baseline in BE-CGI-S score at Weeks 2, 4, 6, 8, and 10
- Change from baseline in Y-BOCS-BE total score at Weeks 2, 4, 6, 8, and 10 and subscale scores (obsessions and compulsions) at Weeks 2, 4, 6, 8, 10, and 12
- Change from baseline in SDS total score and subscale scores (school/work disability, social life disability, and family life disability) at Weeks 6 and 12
- Change from baseline in MADRS total score at Week 12
- Change from baseline in HAM-A total score at Week 12
- Proportion of binge eating responders who have $\geq 75\%$ reduction in the number of binge eating episodes from Baseline at Week 12
- Change from baseline in EDE-Q modified including EDE-Q7 global score and 3 subscale scores (dietary restraint, shape/weight overvaluation, and body dissatisfaction) at Week 12

Safety Endpoints:

- 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)
- Frequency and severity of suicidal ideation and suicidal behavior as assessed by the C-SSRS
- Change and percent change from baseline in body weight at Weeks 1, 2, 3, 4, 6, 8, 10, and 12

- Change and percent change from baseline in BMI at Weeks 1, 2, 3, 4, 6, 8, 10, and 12
- Change from baseline in a fasting lipid panel (triglycerides, total cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol) at Weeks 6 and 12
- Change from baseline in hemoglobin A1c level at Weeks 6 and 12
- Change from baseline in fasting glucose level at Weeks 6 and 12
- Change from baseline in insulin and high-sensitivity C-reactive protein (hs-CRP)
- Occurrence of symptoms of withdrawal from dasotraline measured by change from Week 12/EOT in:
 - CSSA total score at Weeks 13, 14, and 15
 - DESS total score at Weeks 13, 14, and 15
 - HAM-A total score at Weeks 13, 14, and 15
 - MADRS total score at Weeks 13, 14, and 15

Pharmacokinetic Endpoint:

Relationship between dasotraline plasma concentration and the primary endpoint in addition to selected secondary efficacy and safety endpoints

Statistical Methods:
Primary Efficacy Endpoint Analyses

The primary efficacy analyses of the primary efficacy endpoint (the change from baseline in the number of binge days per week at Week 12) will be performed using a likelihood-based mixed model for repeated measures (MMRM) model on the Intent-to-Treat (ITT) population. The response (dependent) variable is the change from baseline in the number of binge days per week assessed at Weeks 1, 2, 3, 4, 6, 8, 10, and 12. Specifically, the MMRM model includes fixed effects terms for treatment, visit (as a categorical variable), pooled center, baseline binge days category (stratification factor; refer to [Section 7.2.1](#) for categories), the number of binge days per week at baseline, and treatment-by-visit interaction. Restricted maximum likelihood estimation method will be applied using an unstructured covariance model. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. In case of a failure of convergence with the unstructured covariance, the following structures will be assessed in a sequential order: heterogeneous Toeplitz, Toeplitz, spatial exponential covariance pattern model. Of the above 3 covariance structures, the first covariance structure yielding convergence in the MMRM model will be used for the MMRM analysis. The spatial exponential model is selected for the analysis of data with unequally spaced time points. The least squares (LS) mean treatment differences (each dasotraline group minus placebo) of change from baseline at Week 12, their 2-sided 95% confidence intervals (CIs), and the associated p-values will be calculated based on this model. The model assumptions underlying the primary analysis will be assessed.

The primary efficacy analysis will be repeated for the Per Protocol (PP) population to examine the impact of premature dropouts and/or protocol deviations.

The primary efficacy endpoint also will be analyzed using an analysis of covariance (ANCOVA) model and the last observation carried forward (LOCF) approach, as a supportive analysis. The model will include terms for treatment, pooled center, baseline binge days category (stratification factor), and

the number of binge days per week at baseline as covariates.

To address early dropouts under the assumption of missing not at random (MNAR), a pattern-mixture model using a placebo-based multiple imputation method and a pattern mixture model using multiple imputations with penalties (ie, deflating the individually estimated treatment effect size by known factors) will be performed as sensitivity analyses to explore the robustness of the MMRM results for the primary analysis. In case of a deviation from the assumptions required for the primary analysis, to confirm the robustness of the primary analysis result, 2 additional sensitivity analyses will be performed: (1) permutation test: fit a large number of datasets based on a same MMRM for the primary analysis with randomly assigning pseudo-treatment group designations; (2) generalized linear mixed model (GLMM) analysis: fit count data over time (ie, number of binge days among number of assessed days at each period) based on a binomial distribution.

Key Secondary Efficacy Endpoint Analyses

Continuous key secondary variables (ie, change in BE-CGI-S score and Y-BOCS-BE total score) will be analyzed with an MMRM model similar to the primary efficacy analysis (adjusted with the corresponding baseline). The LS mean treatment differences (each dasotraline group minus placebo) of change from baseline at Week 12, their 2-sided 95% CIs, and the associated p-values will be calculated based on the model. Categorical key secondary efficacy endpoints (ie, percent of subjects with a 4-week cessation from binge eating) will be analyzed using a logistic regression model with treatment, baseline binge days category (stratification factor), and baseline number of binge days per week as covariates using a LOCF approach based on the ITT population. The odds ratios, their 2-sided 95% CIs, and the associated p-values for each dasotraline group over the placebo group will be derived from the model. Additional supportive and sensitivity analyses may be conducted as needed for the key secondary endpoints to address early dropouts or potential deviations from the model assumption(s).

Multiplicity Adjustment

To control the overall type I error rate strongly at 5% for the primary and key secondary endpoints, for the hypotheses to be tested (see [Section 15.2](#)), a sequential testing strategy will be used. Following the fixed sequence closed testing procedure provided in [Figure 2](#), testing will only proceed conditional on the statistical significance of the test(s) of prior level(s) at a 2-sided 5% significance level.

Safety Analyses:

Safety data will be analyzed by treatment group based on the Double-blind (DB) Safety population (for data up to the end of treatment period) and Withdrawal safety population (for data collected during the withdrawal period), separately, as appropriate.

Overall AEs (or SAEs) and AEs (or SAEs) leading to discontinuation will be summarized by system organ class, preferred term, and treatment group by presenting the number and percentage of subjects with each AE.

Descriptive statistics will be provided by visit and treatment group for observed values or changes from baseline of the safety variables. The change from baseline value at endpoint for selected laboratory parameters (eg, hemoglobin A1c, fasting glucose, fasting total cholesterol, fasting triglycerides, fasting HDL cholesterol, and fasting LDL cholesterol) will be evaluated using an ANCOVA model with terms for treatment and baseline binge days group, and corresponding baseline as covariate or nonparametric rank ANCOVA, as appropriate. A similar MMRM model as for the primary efficacy variable (with the corresponding baseline) will be applied to compare dasotraline with placebo for the following safety variables: change and percent change from baseline in body weight (kg); and change and percent change from baseline in BMI. Frequency and severity of suicidality using the C-SSRS will be summarized by treatment for the post-baseline treatment period and for the withdrawal period, separately.

CSSA total score, DESS total score, MADRS total score, and HAM-A total score will be summarized by presenting descriptive statistics of actual values and change from Week 12/EOT by treatment and

visit for the withdrawal period.

All PK data will be summarized descriptively by visit and treatment group.

Sample Size: The sample size for this study was estimated based on 2 hypotheses associated with the primary efficacy endpoint (change from baseline in number of binge days per week at Week 12). A fixed sequence closed testing procedure was used to adjust for 2 comparisons of dasotraline doses vs placebo (ie, with dasotraline 6 mg vs placebo tested first and dasotraline 4 mg vs placebo tested after if the previous one is significant at the 0.05 level) for the sample size justification. Based on the Study SEP360-221 results, assuming a common standard deviation (SD) of 1.75 and a mean improvement of 0.9 (effect size 0.517) and 0.8 (effect size 0.457) over placebo for change from baseline in number of binge days per week at Week 12 for dasotraline 6 mg/day and 4 mg/day doses respectively, a sample size of 96 subjects per treatment group will provide at least 85% conjunctive power to reject both null hypotheses. An upward adjustment of approximately 40% is assumed to compensate for subjects who are randomized but discontinue from the study, thus, a total sample of 480 subjects (160 subjects per group) will be randomized with a ratio of 1:1:1 for placebo, and dasotraline 4 mg/day and 6 mg/day. The sample size calculation was based on Monte Carlo simulation from EAST 6.4.

Table 2: Schedule of Assessments

Procedures	Screening	Baseline	Treatment Period								Withdrawal Period ^{a,b}		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 ^c	V11	V12	V13
			Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12/EOT ^a	Week 13	Week 14	Week 15
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 42 (± 3)	Day 56 (± 3)	Day 70 (± 3)	Day 84 (± 1)	Day 91 (± 1)	Day 98 (± 1)	Day 105 (± 1)
Informed Consent	X												
Informed Consent for PGx (optional)	X												
Inclusion/Exclusion Criteria	X	X											
Duplicate Enrollment Check	X												
CST Review ^e	X												
Randomization		X											
Dispense Study Drug ^f		X	X	X	X	X	X	X	X				
Study Drug Accountability			X	X	X	X	X	X	X	X			
Demographics	X												
Medical History	X												
Psychiatric History ^d	X												
Physical Examination	X	X								X			X
Neurological Examination	X	X								X			X
Prior and/or Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Assessments (Continued)

Procedures	Screening	Baseline	Treatment Period								Withdrawal Period ^{a,b}		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 ^c	V11	V12	V13
			Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12/EOT ^a	Week 13	Week 14	Week 15
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 42 (± 3)	Day 56 (± 3)	Day 70 (± 3)	Day 84 (± 1)	Day 91 (± 1)	Day 98 (± 1)	Day 105 (± 1)
Mini International Neuropsychiatric Interview (MINI)	X												
Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H)	X												
Eating Disorder Examination Questionnaire (EDE-Q)	X												
Eating Disorder Examination Questionnaire (EDE-Q) modified		X								X			
Binge eating diary training ^g	X	X	X		X								
Binge eating diary ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Binge-eating Clinical Global Impression-Severity (BE-CGI-S)	X	X		X		X	X	X	X	X			X

Table 2: Schedule of Assessments (Continued)

Procedures	Screening	Baseline	Treatment Period								Withdrawal Period ^{a,b}		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 ^c	V11	V12	V13
			Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12/EOT ^a	Week 13	Week 14	Week 15
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 42 (± 3)	Day 56 (± 3)	Day 70 (± 3)	Day 84 (± 1)	Day 91 (± 1)	Day 98 (± 1)	Day 105 (± 1)
Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE)		X		X		X	X	X	X	X			X
Montgomery-Asberg Depression Rating Scale (MADRS) ⁱ	X	X								X	X	X	X
Sheehan Disability Scale (SDS)		X					X			X			X
Hamilton Anxiety Rating Scale (HAM-A) ^j		X								X	X	X	X
Cocaine Selective Severity Assessment (CSSA)										X ^k	X	X	X
Cocaine Selective Severity Assessment (CSSA) – Telephone contact										In order to collect this assessment, clinical site staff will call the subject every other day (± 1 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. ^l			

Table 2: Schedule of Assessments (Continued)

Procedures	Screening	Baseline	Treatment Period								Withdrawal Period ^{a,b}		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 ^c	V11	V12	V13
			Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12/EOT ^a	Week 13	Week 14	Week 15
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 42 (± 3)	Day 56 (± 3)	Day 70 (± 3)	Day 84 (± 1)	Day 91 (± 1)	Day 98 (± 1)	Day 105 (± 1)
Discontinuation-Emergent Signs and Symptoms (DESS) Scale										X ^k	X	X	X
Discontinuation-Emergent Signs and Symptoms (DESS) Scale – Telephone contact										In order to collect this assessment, clinical site staff will call the subject every other day (± 1 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. ^l			
Vital Sign Measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight and body mass index (BMI) ^m	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X	X				X		X		X	X	X	X
Columbia – Suicide Severity Rating Scale (C-SSRS) ⁿ	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events ^o			X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X					X			X			X
Lipid panel ^p	X	X					X			X			X

Table 2: Schedule of Assessments (Continued)

Procedures	Screening	Baseline	Treatment Period								Withdrawal Period ^{a,b}		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 ^c	V11	V12	V13
			Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12/EOT ^a	Week 13	Week 14	Week 15
	Day -22 to -2	Day -1	Day 7 (± 2)	Day 14 (± 2)	Day 21 (± 2)	Day 28 (± 2)	Day 42 (± 3)	Day 56 (± 3)	Day 70 (± 3)	Day 84 (± 1)	Day 91 (± 1)	Day 98 (± 1)	Day 105 (± 1)
Hemoglobin A1c	X	X					X			X			X
Insulin ^p		X								X			
hs-CRP		X								X			
Hematology	X	X					X			X			X
Urinalysis	X	X					X			X			X
Serum Pregnancy Test (in females of child-bearing potential)	X												X
Urine Pregnancy Test (in females of child-bearing potential)		X				X		X		X			
Urine Drug Screen	X	X					X			X	X	X	X
Breath alcohol test	X	X					X			X	X	X	X
Blood sampling for plasma PK levels ^q				X			X			X			
Blood sampling for potential biomarkers		X								X			
Blood sampling genotyping		X											

Footnotes are on the next page.

Abbreviations: CST = Clinical Surveillance Team; EOT = End of Treatment; hs-CRP = high-sensitivity C-reactive protein; PK = pharmacokinetic; V = visit

- ^a Subjects who discontinue from study drug before completion of the 12-week treatment period will be asked to return to the clinic and complete the End of Treatment visit as soon as possible following discontinuation of study drug and complete the 3-week withdrawal period.
- ^b Subjects who complete the 12-week treatment period and do not enter the extension study (Study SEP360-322) will complete the 3-week withdrawal period.
- ^c For subjects who complete the 12-week double-blind treatment period and enter the extension study (Study SEP360-322), Visit 10 will be the last visit in this study.
- ^d Includes family history of psychiatric disorders.
- ^e For the prebaseline review, sites will be required to submit specific screening information for clinician and sponsor review, prior to proceeding to baseline. Details are provided in the Clinical Surveillance Team (CST) site manual.
- ^f All study drug will be administered by the subject, beginning on Day 1, the day after the Baseline visit, once a day at approximately the same time each morning including on the days when clinic visits occur.
- ^g Missing data, if any, will be reviewed by the clinical site staff with the subject and additional training on diary completion will be provided at other visits as needed.
- ^h Subjects complete a daily binge eating diary to record the date, duration (total hours of bingeing), type of binge episode (meal or non-meal), amount and type of food, and number of binges beginning 14 days prior to the Baseline visit and continue through the final clinic visit. At each in-clinic visit, the Investigator will review the diary with the subject. In addition, diaries will be sent to Bracket for central review.
- ⁱ The Structured Interview Guide for the MADRS (SIGMA) will be used for the administration of the MADRS.
- ^j The Structured Interview Guide for the HAM-A (SIGH-A) will be used for the administration of the HAM-A.
- ^k Only for subjects not entering the extension study.
- ^l Clinical site staff will call the subject every other day (± 1 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, in order to collect the Cocaine Selective Severity Assessment (CSSA) and Discontinuation-Emergent Signs and Symptoms (DESS). Clinical site staff may call 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 CSSA and DESS from the missed day(s) and the current day.
- ^m Body mass index (BMI) at screening will be calculated by the clinical site using BMI table or the BMI formula provided ([Section 27](#), Appendix VIII). BMI on all other visits will be derived within the Electronic Data Capture (EDC) system.
- ⁿ Subjects who answer “yes” to “suicidal ideation” item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Screening (in the past month) must be referred to the Investigator for follow up evaluation.
- ^o Untoward medical occurrences that occur prior to the first dose of study drug will be collected as pre-treatment events.
- ^p Subjects must be fasting for at least 8 hours (may have water and study drug) prior to the indicated laboratory tests. Visits should be scheduled in the morning.
- ^q The date and time of the last 3 doses of study drug prior to PK blood sample collection are to be recorded in the source documents and the CRF.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and [Table 4](#).

Table 3: List of Abbreviations

Abbreviation	Full Form
ADHD	Attention deficit hyperactivity disorder
ADHD-RS-IV	ADHD Rating Scale Version IV with adult prompts
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APMP	Abuse Potential Monitoring Plan
AST	Aspartate aminotransferase
BE-CGI-S	Binge-eating Clinical Global Impression-Severity
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Controlled release
CRF	Case report form
CRO	Clinical research organization
C-SSRS	Columbia-suicide severity rating scale
CSSA	Cocaine Selective Severity Assessment
CST	Clinical Surveillance Team
CTM	Clinical trial material
DA	Dopamine
DAT	Dopamine transporter
DB	Double blind
DBL	Database lock
DEAE	Discontinuation-emergent adverse event
DESS	Discontinuation-Emergent Signs and Symptoms

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
DHPG	3,4-dihydroxyphenylglycol
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DNRI	Dopamine and norepinephrine reuptake inhibitor
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revised
DSMB	Data and Safety Monitoring
ECG	Electrocardiogram
EDC	Electronic data capture
EDE-Q	Eating Disorder Examination Questionnaire
EOT	End of treatment
ESAM	Event subject to additional monitoring
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
GLMM	Generalized linear mixed model
5-HT	5-hydroxytryptamine (serotonin)
HAM-A	Hamilton Anxiety Rating Scale
HDL	High-density lipoprotein (cholesterol)
HIV	Human immunodeficiency virus
HR	Heart rate
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPW	Inverse probability weighting
IRB	Institutional Review Board
ITT	Intention-to-Treat
IUD	Intrauterine device
IXRS	Interactive Response System

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
LDL	Low-density lipoprotein (cholesterol)
LOCF	Last Observation Carried Forward
LS	Least squares
MADRS	Montgomery-Asberg Depression Rating Scale
MAO	Monoamine oxidase
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication Handling Irregularity
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effects Models Repeated Measures
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NE	Norepinephrine
NET	Norepinephrine transporter
OTC	Over-the-counter (medications)
PCOS	Polycystic ovarian syndrome
PET	Positron emission tomography
PGx	Pharmacogenomics
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per-Protocol
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

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
SCID-I Module H	Structured Clinical Interview for DSM-IV Axis I Disorders, Module H
SD	Standard deviation
SDS	Sheehan Disability Scale
SERT	Serotonin transporter
SIGH-A	Structured Interview Guide for the HAM-A
SIGMA	Structured Interview Guide for the MADRS
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SOC	System organ class
SOP	Standard operating procedure
t_{\max}	Time to maximum concentration
UDS	Urine drug screen
ULN	Upper limit of normal
USP	United States Pharmacopeia
VAS	Visual analog scale
WBC	White blood cells
WHO-DD	World Health Organization drug dictionary
Y-BOCS-BE	Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and/or active control.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and is assigned a randomization number.
End of Treatment	The day that the subject receives protocol-defined last dose of the study drug.

4. INTRODUCTION

4.1. Background

Binge eating disorder (BED) is a neuropsychiatric disorder characterized by recurrent episodes (on average at least once per week for 3 months) of excessive food consumption during a limited time period, accompanied by feelings of loss of control and distress in the absence of regular compensatory behaviors characteristic of bulimia nervosa (BN) ([Diagnostic and Statistical Manual of Mental Disorders, 5th Edition](#) [DSM-5]). BED is the most common eating disorder in the United States and Western Europe, with an estimated lifetime prevalence of 2.5% in adults (~3.5% in adult women, 2.0% in adult men, and 1.6% in adolescents) and a mean age of onset of 25.4 ± 1.2 years ([McElroy-2012](#), [Kessler-2013](#), [Hudson-2007](#)). Binge eating disorder is defined in DSM-5 as:

- Recurrent episodes of binge eating characterized by both:
 - Eating an amount of food larger than what most people would eat, in a discrete period of time (eg, 2 hours)
 - Sense of lack of control over eating episode
- Binge eating episode associated with ≥ 3 :
 - Eating much more rapidly than normal
 - Eating until uncomfortably full
 - Eating large amounts when not feeling hungry
 - Eating alone because of embarrassment
 - Feeling disgusted with oneself, guilty afterward
- Marked distress regarding binge eating is present
- Binge eating occurs, on average, at least once a week for 3 months
- Not associated with recurrent use of compensatory behavior (eg, bulimia nervosa).

Patients with BED show significantly higher prevalence or risk for a range of comorbid psychiatric and medical disorders when compared to healthy individuals. The majority of patients fulfill Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for one or more psychiatric disorders, including depression, anxiety, and phobias. BED patients also have a 2-3 fold greater risk for physical ailments, including obesity, hypertension, diabetes mellitus, and chronic pain. Taken together, these findings signify that BED presents a major public health problem with significant social and economic consequences ([Kessler-2013](#)). Considering the severity of clinical symptomology, the negative impact on quality of life and physical measures of health, there is a significant need for safe and efficacious treatments for adults with BED.

4.1.1. Neurobiology of Binge Eating Disorder

Non-clinical and clinical studies have implicated dopamine, opioid, and norepinephrine systems within the brain reward circuit in the pathogenesis of eating and addictive disorders, including binge eating disorder (Murray-2014, Gold-2013, Smith-2013, Hoebel-1989). In particular, disturbances in dopamine and the dopamine D_{2/3} receptor play a key role in binge eating, suggesting that drugs targeting disturbances in dopaminergic transmission may be effective in treating the disorder.

Non-clinical studies show that rats continue to self-administer substances that act like dopamine, or stimulate dopamine release, in response to a dysregulated reward circuit (Murray-2014, Ikemoto-1997, Carlezon-1995). Rats continuously fed a cafeteria diet or a high-fat, high sugar meal show reduced levels of dopamine and dopamine D_{2/3} receptors in the dorsal striatum and nucleus that form part of the reward circuit (van de Giessen-2012, van de Giessen-2013). Knockout of striatal dopamine D₂ receptors induces compulsive-type behavior in response to highly palatable food (Johnson-2010). High-fat diets are associated with reduced dopamine transporter (DAT) expression and dopamine efflux (Speed-2011). In non-clinical studies of drug abuse, reduced availability of dopamine D₂ receptors in the striatum lead to increased and habitual drug intake, further supporting the importance of this transmitter system in addictive behaviors, and suggesting that BED and other impulse control disorders, such as substance abuse, share overlapping neural mechanisms (Trifilieff-2014, Smith-2013).

Clinical, genetic, and neuroimaging studies of eating behaviors in humans have shown parallel disturbances in the brain reward circuit and dopamine transmission in patients with BED, including reduced availability of dopamine D₂ receptors in the striatum (Murray-2014, Smith-2013). Down regulation of dopamine D₂ receptors in response to overeating leads to a hyper-responsive reward system that is sensitized to food, perpetuating patterns of recurrent food craving and overconsumption that result in BED in susceptible individuals. Further evidence for a hyper-responsive reward circuit in BED patients comes from neuroimaging studies using positron emission tomography (PET). Administration of methylphenidate, an inhibitor of the dopamine reuptake transporter, results in greater increases in dopamine levels in the caudate nucleus in response to food in BED patients when compared to individuals without BED. These increases are significantly correlated with binge eating scores (Wang-2011). Further in vivo support for the role of the dopaminergic system in regulating reward behaviors has come from PET studies in methamphetamine addicted individuals and healthy volunteers, which have shown negative correlations between impulsivity, a core personality trait in BED patients, and availability of dopamine D_{2/3} receptors in the striatum and midbrain (Lee-2009, Buckholtz-2010).

Similar to findings from the PET studies, functional magnetic resonance imaging (MRI) studies show a dysregulated and hyper-responsive reward circuit in response to food in BED patients. Exposure to high-calorie or highly palatable food stimuli elicits greater activation in reward areas, such as the nucleus accumbens and orbital frontal cortex in BED patients compared to controls, which directly correlates with the severity of binge eating symptoms (Schienle-2009, Filbey-2012). Together results from these studies show that dysregulation of the dopaminergic driven reward circuit is associated with BED and suggest that therapies targeting this system may offer effective interventions for the disorder.

4.1.2. Pharmacological Management of Binge Eating Disorder

Although cognitive, behavioral and interpersonal psychotherapies improve binge eating symptoms, many patients do not respond ([McElroy-2012](#)). Recent studies suggest that pharmacotherapies that target one or more of the neurotransmitter systems implicated in BED may play a critical role in its management ([McElroy-2012](#)).

Several classes of pharmacological agents have been evaluated for the treatment of BED in randomized, double-blind, placebo-controlled or open-label studies, including selective serotonin reuptake inhibitors (SSRIs), antiobesity agents, anticonvulsants, and stimulants ([Hudson-1998](#), [McElroy-2000](#), [Arnold-2002](#), [McElroy-2003A](#), [Stunkard-1996](#), [Appolinario-2003](#), [Grilo-2005](#), [McElroy-2003B](#), [McElroy-2006](#), [McElroy-2007](#), [Leombruni-2006](#), [NCT01718483](#), [NCT01718509](#)).

Lisdexamfetamine dimesylate is a central nervous stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD). In two 12-week, randomized, placebo-controlled registration studies, lisdexamfetamine dimesylate showed significant reductions in binge eating frequency ([NCT01718483](#), [NCT01718509](#)) and these results supported FDA approval of Vyvanse® as a treatment for adults with BED ([Shire-2015](#)).

4.2. Study Conduct Rationale

Dasotraline (also known as SEP-225289), a new chemical entity currently in clinical trials for BED and ADHD, blocks the pre-synaptic dopamine transporter (DAT) and the norepinephrine transporter (NET). Unlike psychostimulants such as amphetamine, which facilitate the direct release of dopamine and norepinephrine ([Hutson-2014](#), [Minzenberg-2012](#)), dasotraline is a dual reuptake inhibitor (dopamine/norepinephrine reuptake inhibitor; DNRI). Dasotraline has a long time to maximum concentration (t_{max} ; approximately 10 to 12 hours after dosing) and mean apparent half-life (47.1 to 77.0 hours).

A non-clinical study was conducted to compare the acute effects of dasotraline in a rat model of BED with lisdexamfetamine dimesylate, and its pharmacologically active metabolite, *d*-amphetamine. Rats that were allowed irregular and limited access to chocolate developed robust and intermittent hyperphagia that mirrored BED without any associated obesity. Binge eating of chocolate was markedly reduced by a single oral dose of dasotraline. The reduction in chocolate consumption was dose dependent and comparable to the effects observed with both lisdexamfetamine dimesylate and *d*-amphetamine in this rat BED model.

Previous clinical studies support dasotraline as a potentially safe and efficacious treatment option for adults with ADHD. In one study, adults taking dasotraline 8 mg/day experienced a significant improvement in ADHD symptoms compared to placebo, as measured by the Attention Deficit Hyperactivity Disorder Rating Scale Version IV (ADHD-RS-IV) with adult prompts total score ($P = .010$, effect size 0.41). A trend was seen for efficacy of the dasotraline 4 mg/day dose compared to placebo on the ADHD-RS-IV at Week 4 study endpoint ($P = .076$). Statistically significant improvement compared to placebo was observed in Clinical Global Impression-Severity scale (CGI-S) scores at Week 4 for both the 4 and 8 mg/day doses. In a second study, the dasotraline 6 mg/day group showed numerically greater improvement relative to placebo in ADHD symptoms at Week 8 study endpoint, as measured by the ADHD-RS-IV with adult prompts, that was not statistically significant after adjustment for multiple comparisons (least

squares [LS] mean change from baseline: -16.51 vs -13.9; $P = .074$). Notably, the dasotraline 6 mg/day group was statistically superior to placebo on the ADHD-RS-IV at the Week 4 ($P = .027$), Week 6 ($P = .019$), and Week 8 ($P = .037$) timepoints (non-adjusted p-values). Statistically significant improvement on the CGI-S was also observed for the 6 mg/day group at Weeks 4 and 6, as well as at the Week 8 study endpoint ($P = .011$). The dasotraline 4 mg/day group did not show improvement relative to placebo on the ADHD-RS-IV and CGI-S assessments at the Week 8 study endpoint.

Consistent with DNRI pharmacology, the most frequent adverse events (AEs) reported in these ADHD studies were insomnia, decreased appetite, and dry mouth. In addition, significant dose dependent decreases were observed in appetite and weight. Increases in mean supine and standing heart rate (HR) observed during treatment and follow-up were generally dose dependent.

A recently completed 12-week, randomized, double-blind, placebo-controlled, flexibly-dosed, study (SEP360-221) of dasotraline (4, 6, or 8 mg/day) in adults with BED showed significant reduction in the number of binge eating days/week compared to placebo at Week 12 ($P < .0001$) with an effect size of 0.74. Significant separation from placebo was observed at all weeks starting at Week 1 ($P < .0001$). In addition, dasotraline achieved significant results compared to placebo in the key secondary endpoints including improvement in the BE-CGI-S ($P < .0001$, effect size = 0.95); reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (YBOCS-BE) score ($P < .0001$, effect size = 0.96); and a greater number of subjects achieving 4-week cessation from binge eating ($P < .0001$; effect size = 0.66). The highest incidence of AEs for subjects receiving dasotraline ($\geq 5\%$) in descending order were insomnia, dry mouth, decreased appetite, anxiety, nausea, decreased weight, headache, dizziness, irritability, dyspepsia, constipation, thirst, and diarrhoea. There were no deaths in this study and 1 serious adverse event (SAE) was reported (suicidal ideation). There were no clinically important changes in vital signs or electrocardiograms (ECG) observed except for a mild increase in pulse rate and orthostatic pulse rate, consistent with the known pharmacology of dasotraline.

The current study is being conducted to replicate the efficacy results from Study SEP360-221, to explore the dose response, and to further assess the safety and tolerability of dasotraline in the treatment of BED.

4.3. Risk-Benefit Assessment

Overall, in previous clinical studies dasotraline was generally safe and well tolerated. An overview of safety results from the recently completed study in adult subjects with BED is presented in [Section 4.2](#). To date, over 2700 subjects have received one or more doses of dasotraline during the clinical development programs in ADHD, BED, and major depressive disorder (MDD) in the range of 0.5 to 32 mg/day. A total of > 400 subjects have been exposed to dasotraline for a minimum of 6 months.

Risks associated with dasotraline treatment have been well characterized and are as expected given the DAT/NET pharmacology. The most common AEs in the BED study were similar to findings in studies of adult subjects with ADHD.

In an effort to maximize tolerability, an initial dose of 4 mg/day for 2 weeks will be used for the dasotraline 6 mg/day treatment arm in this study.

Dasotraline was evaluated in a dedicated human abuse liability study and compared with methylphenidate and placebo. Unlike methylphenidate, dasotraline did not differentiate from placebo on the primary end-point of Drug Liking and was disliked at the highest dose studied (36 mg). Standardized queries, as well as a comprehensive Abuse Potential Monitoring Plan (APMP), have not detected signals of drug abuse, dependence or withdrawal across clinical studies with dasotraline.

The current study will be conducted in accordance with relevant regulatory guidance and law with regards to handling, distribution, storage, dispensation, accountability, and destruction of study drug. In addition the APMP will be implemented for this study ([Section 26](#), Appendix VII). Additionally, a Data and Safety Monitoring Board (DSMB) will be established for this study to review safety data at regular intervals.

An overview of efficacy results from the recently completed study in adult subjects with BED is presented in [Section 4.2](#). Dasotraline was statistically superior to placebo in change from baseline in the number of binge eating days/week at Week 12 with highly statistically significant separation from placebo observed at each week starting at Week 1. The study also met all 3 key secondary endpoints.

The current study is designed to optimize the balance of efficacy and tolerability of dasotraline in the treatment of adult subjects with BED.

4.4. Hypotheses

4.4.1. Primary Hypotheses

In adults with moderate to severe BED, after 12 weeks of treatment,

- Dasotraline 6 mg/day reduces change from baseline in the number of binge days per week relative to placebo
- Dasotraline 4 mg/day reduces change from baseline in the number of binge days per week relative to placebo

4.4.2. Secondary Hypotheses

In adults with moderate to severe BED, after 12 weeks of treatment, 6 mg/day dasotraline or both doses of dasotraline:

- Reduce change from baseline in BE-CGI-S score relative to placebo
- Provide a greater proportion of subjects with a 4-week cessation from binge eating at Week 12 relative to placebo
- Reduce change from baseline in Y-BOCS-BE total score relative to placebo

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of 2 doses of dasotraline (4 and 6 mg/day) compared with placebo in adults with moderate to severe BED as measured by the number of binge days per week.

5.2. Key Secondary Objectives

To evaluate the efficacy of 2 doses of dasotraline (4 and 6 mg/day) compared with placebo in adults with moderate to severe BED as measured by:

- Binge-eating Clinical Global Impression-Severity (BE-CGI-S)
- 4-Week cessation from binge eating defined as a 100% reduction for at least 28 consecutive days in the number of binge eating episodes
- Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE)

5.3. Other Secondary Objectives

The other secondary objectives of the study are:

- To evaluate the efficacy of 2 doses of dasotraline (4 and 6 mg/day) compared with placebo in adults with moderate to severe BED as measured by:
 - Number of binge episodes per week
 - Proportion of binge eating responders at Week 12 who show $\geq 75\%$ reduction in the number of binge eating episodes
 - Sheehan Disability Scale (SDS)
 - Montgomery-Asberg Depression Rating Scale (MADRS)
 - Hamilton Anxiety Rating Scale (HAM-A)
 - Eating Disorder Examination Questionnaire (EDE-Q) modified
- To evaluate the safety and tolerability of 2 doses of dasotraline (4 and 6 mg/day) using physical examinations, 12-lead electrocardiograms (ECG), vital signs, AE reports, clinical laboratory results, body weight, body mass index (BMI), and Columbia – Suicide Severity Rating Scale (C-SSRS)

- To assess potential withdrawal effects upon abrupt discontinuation of dasotraline after 12 weeks of continuous daily treatment 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 HAM-A
 - Symptoms of depression utilizing the MADRS
- To assess the abuse potential of dasotraline utilizing a comprehensive abuse potential monitoring plan (APMP)
- To assess the relationship between dasotraline plasma concentration and the primary efficacy and selected secondary efficacy and safety endpoints

6. STUDY ENDPOINTS

6.1. Primary Efficacy Endpoint

Change from baseline in number of binge days (defined as days during which at least 1 binge episode occurs) per week at Week 12.

6.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Change from baseline in BE-CGI-S score at Week 12
- Percent of subjects with a 4-week cessation from binge eating (defined as a 100% reduction for at least 28 consecutive days in the number of binge eating episodes prior to Week 12/end of treatment [EOT])
- Change from baseline in Y-BOCS-BE total score at Week 12

6.3. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- Change from baseline in number of binge days per week at Weeks 1, 2, 3, 4, 6, 8, and 10
- Change from baseline in number of binge episodes per week at Weeks 1, 2, 3, 4, 6, 8, 10, and 12
- Change from baseline in BE-CGI-S score at Weeks 2, 4, 6, 8, and 10
- Change from baseline in Y-BOCS-BE total score at Weeks 2, 4, 6, 8, and 10 and subscale scores (obsessions and compulsions) at Weeks 2, 4, 6, 8, 10, and 12
- Change from baseline in SDS total score and subscale scores (school/work disability, social life disability, and family life disability) at Weeks 6 and 12
- Change from baseline in MADRS total score at Week 12
- Change from baseline in HAM-A total score at Week 12
- Proportion of binge eating responders who have $\geq 75\%$ reduction in the number of binge eating episodes from Baseline at Week 12
- Change from baseline in EDE-Q modified including EDE-Q7 global score and 3 subscale scores (dietary restraint, shape/weight overvaluation, and body dissatisfaction) at Week 12

6.4. Safety Endpoints

The safety endpoints are:

- 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)
- Frequency and severity of suicidal ideation and suicidal behavior as assessed by the C-SSRS
- Change and percent change from baseline in body weight at Weeks 1, 2, 3, 4, 6, 8, 10, and 12
- Change and percent change from baseline in BMI at Weeks 1, 2, 3, 4, 6, 8, 10, and 12
- Change from baseline in a fasting lipid panel (triglycerides, total cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol) at Weeks 6 and 12
- Change from baseline in hemoglobin A1c level at Weeks 6 and 12
- Change from baseline in fasting glucose level at Weeks 6 and 12
- Change from baseline in insulin and high-sensitivity C-reactive protein (hs-CRP)
- Occurrence of symptoms of withdrawal from dasotraline measured by change from Week 12/EOT in:
 - CSSA total score at Weeks 13, 14, and 15
 - DESS total score at Weeks 13, 14, and 15
 - HAM-A total score at Weeks 13, 14, and 15
 - MADRS total score at Weeks 13, 14, and 15

6.5. Pharmacokinetic Endpoint

Relationship between dasotraline plasma concentration and the primary endpoint in addition to selected secondary efficacy and safety endpoints

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, parallel-group, multicenter, outpatient study evaluating the efficacy and safety of 2 doses of dasotraline (4 and 6 mg/day) versus placebo over a 12-week treatment period in adults with BED. This study is projected to randomize approximately 480 subjects to 3 treatment groups in a 1:1:1 ratio (4 mg/day dasotraline, 6 mg/day dasotraline, and placebo).

Subjects randomized to placebo will receive placebo for the duration of the treatment period.

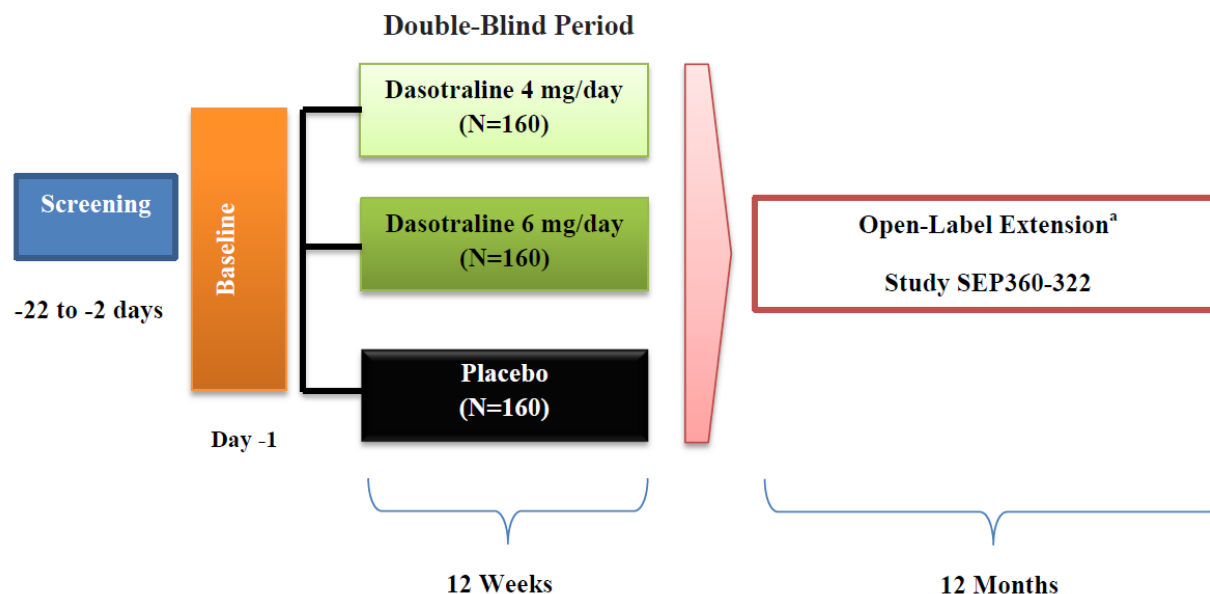
Subjects randomized to 4 mg/day dasotraline will receive 4 mg/day for the duration of the treatment period.

Subjects randomized to 6 mg/day dasotraline will be dosed with 4 mg/day dasotraline for the first 2 weeks of the treatment period and will be increased to 6 mg/day at Week 2.

If, in the judgment of the Investigator, the subject does not tolerate the assigned dose, he or she will be discontinued from the study.

The study will consist of 3 periods: Screening (up to 3 weeks), 12-weeks of treatment, and a 3-week study drug withdrawal period. Subjects who complete the 12-week double-blind treatment period in this study may be eligible to enroll and continue treatment for an additional 12 months in an open-label extension study (Study SEP360-322). Subjects who do not enter the extension study will complete the study drug withdrawal period in this study. A study schematic is presented in Figure 1.

Figure 1: Study Schematic



Note: Subjects randomized to placebo will receive placebo for the duration of the treatment period. Subjects randomized to 4 mg/day dasotraline will receive 4 mg/day for the duration of the treatment period. Subjects randomized to 6 mg/day dasotraline will be dosed with 4 mg/day dasotraline for the first 2 weeks of the treatment period and will be increased to 6 mg/day at Week 2.

^a Subjects who do not enter the extension study will return to the clinic for withdrawal (Cocaine Selective Severity Assessment [CSSA], Discontinuation-Emergent Signs and Symptoms [DESS], Hamilton Anxiety Rating Scale [HAM-A], and Montgomery-Asberg Depression Rating Scale [MADRS]) and safety assessments at Weeks 13, 14, and 15 during the study medication withdrawal period.

Efficacy will be evaluated at each visit using the subject binge eating diary and a clinician interview to assess the frequency of binge episodes and the number of binge days, defined as days with at least one binge episode. Additional assessments will include BE-CGI-S, Y-BOCS-BE, MADRS, HAM-A, SDS, and EDE-Q modified. Safety and tolerability will be monitored throughout the study by collection of physical examination results, ECGs, vital signs, AEs, clinical laboratory parameters, C-SSRS, body weight, and BMI will be calculated. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the Investigator for follow-up evaluation. Assessment of potential withdrawal effects 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.

Blood samples for pharmacokinetics (PK) and biomarkers associated with eating disorders (to be determined) will be collected. Blood samples collected for PK assessment will be analyzed for plasma concentrations of dasotraline. The relationship between dasotraline plasma concentration and the primary and selected secondary clinical outcome measures will be evaluated. The relationship between biomarkers associated with eating disorders in relationship to the severity of BED and response to dasotraline will be evaluated at a later date in the development program. Plasma samples collected for PK and biomarker concentration analysis may also be used for the additional characterization of and/or bioanalytical method development for dasotraline.

A blood sample will be collected from subjects who provide separate informed consent for pharmacogenomics (PGx) analysis for potential evaluation of associations between genetic polymorphisms such as, but not limited to Taq1DRD2, OPRM1, and DRD4-7R, and the severity of BED, the clinical response to dasotraline, in addition to the safety, efficacy, and PK profiles of dasotraline to be conducted at a later date in the development program. Separate consent is required for collection of this specific blood sample and will be obtained at Screening for subjects who agree to provide this sample (note: this separate consent is not required for participation in the study, it is required only for subjects who will provide this sample).

A comprehensive APMP 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 (see [Section 26](#), Appendix VII for details).

An independent Data and Safety Monitoring Board (DSMB) will review safety data at regular intervals.

Screening Period (Days -22 to -2): Informed consent will be obtained from each subject before any study procedures are performed for this study. Study eligibility criteria will be assessed during this period, and subjects will be required to have discontinued from any protocol prohibited medications within 3 months of screening. The subject's eligibility assessment will be reviewed by the contract research organization's (CRO) oversight quality team along with the sponsor based on protocol specified inclusion and exclusion criteria. The sponsor will participate

in the eligibility review process with the CRO to ascertain the subject's eligibility and will be copied on all communications between the CRO and the site. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled. Subjects may be rescreened once for out of range clinical laboratory results including urine drug screen (UDS) or ECG results following authorization of the medical monitor. During the screening visit, subjects will be trained to complete the daily binge eating diary and then complete the diary at home for at least 14 consecutive days immediately prior to the Baseline visit and starting no sooner than the day after the screening visit.

Baseline Visit (Day -1): Subjects who meet eligibility criteria at Screening will return to the study site on Day -1 for confirmation of screening evaluations as well as completion of predose assessments and procedures including clinician review of the daily binge eating diary. Any lapse in diary completion during the 14 day period (eg, 1 or more days are skipped) will be discussed with the subject. If 1 or 2 days per week are incomplete or missing, the subject may complete the diary with the clinician. However, if the subject cannot recall enough information to complete the diary in full after clinician review, the subject will be ineligible. Subjects will also be ineligible for randomization if there are more than 2 missed diary days in 1 week. Eligible subjects (based on confirmation of study entry criteria) will be randomized and dispensed study drug at Day -1.

Treatment Period (Day 1 [Week 0] through Day 84 [Week 12]): Subjects will self-administer the study drug on an outpatient basis once a day with or without food beginning on Day 1, the day after the Baseline visit, and continue for 12 weeks. Subjects will be instructed to administer study drug at approximately the same time each morning including on days when clinic visits occur. During the treatment period subjects will continue to complete a daily binge eating diary, which will be reviewed at each visit. During the treatment period, subjects will have one clinic visit every week for the first month, then one clinic visit every 2 weeks thereafter. In order to facilitate scheduling of clinic visits, a window of ± 2 days will be allowed for each weekly clinic visit and a window of ± 3 days will be allowed for each biweekly clinic visit, and a window of ± 1 day for the end of treatment (EOT) visit and each clinic visit of the withdrawal period.

Subjects who complete the 12-week Treatment Period may be eligible for participation in the open label extension study (SEP360-322). For subjects enrolling in the open label extension study, Week 12 will be the last visit for this study.

Study Medication Withdrawal Period (Day 85 through Day 105 [Week 15]): Subjects who do not enroll in the extension study for whatever reason, eg, less than 12 weeks treatment in this study, lack of interest in the extension study, or failure to meet all eligibility criteria for the extension study will return to the clinic at Weeks 13, 14, and 15, to assess safety and potential study medication withdrawal effects during the study medication withdrawal period. Subjects who discontinue from study drug before completion of the 12-week treatment period will be asked to return to the clinic and complete the End of Treatment visit as soon as possible following discontinuation of study drug and complete the 3 week withdrawal period. In addition, subjects will continue to complete the binge eating diary during this period.

Assessment of potential withdrawal effects will be conducted via administration of the CSSA, DESS, HAM-A, and MADRS at Week 12 (End of Treatment), then again at Weeks 13, 14, and 15 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 (up to 3 times per day if the clinical site staff are unable to contact the subject on the first 2 attempts). 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 will be 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.

7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

After successfully meeting study entry criteria, subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment arms:

- Dasotraline 4 mg/day
- Dasotraline 6 mg/day
- Placebo

To avoid potential imbalanced treatment allocation among subjects with different baseline levels of BED, the randomization will be balanced using permuted blocks with baseline number of binge eating days per week, which is defined as number of binge days/week determined from the 2 weeks before the Baseline visit (3 – 4 binge eating days per week, > 4 binge eating days per week). The stratification process will be handled by an IXRS, an integrated web-based subject and drug-management system.

An IXRS will be used to manage randomization at Day -1 and, if necessary, for emergency unblinding (see [Section 7.2.3](#)) of treatment assignment during the study.

Study medication will be assigned by an IXRS at Day -1 based on the randomization schedule. The IXRS will generate instructions on which medication number to assign to a subject. Each randomized subject will be dispensed one 10-day blister pack per scheduled visit up to and including Visit 5 and two 10-day blister packs per scheduled visit thereafter through Visit 9.

7.2.2. Blinding

This is a double-blind study.

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories will remain blind to the identity of the treatment from the time of randomization until database lock (DBL) and unblinding, using the following methods: (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: external bioanalytical personnel involved in the analysis of PK samples, DSMB members involved in regular review of safety data, external statistician and programmer who prepare materials for DSMB review, and Clinical Trial Materials Management personnel and

(2) the identity of the treatments will be concealed by the use of study medication that are all identical in packaging, labeling, schedule of administration, and appearance.

During the study and prior to database lock, the treatment assignments for all subjects will be provided to the Bioanalytical Contract Research Organization (CRO) to facilitate plasma PK sample handling and analysis. No PK samples will be analyzed for placebo subjects.

7.2.3. Emergency Unblinding Procedures

The IXRS will be used, if necessary, for emergency unblinding of treatment assignment during the study. The blinded dose information is to be broken only in an emergency when knowledge of such treatment may have an impact on further treatment decisions or aid in the emergency treatment of the subject. Every effort must be made to contact the CRO Medical Monitor ([Table 1](#)) before any unblinding of the study drug. The circumstances that lead to unblinding are to be promptly communicated via telephone and in writing to the CRO Medical Monitor. Any subject for whom the blind is broken is to be discontinued from receiving any additional study medication and should undergo final evaluation procedures, in accordance with the EOT Visit as described in [Section 11.8.9](#).

7.3. Rationale

7.3.1. Rationale for the Study Design

This study is being conducted in order to replicate the efficacy results from SEP360-221 and to evaluate dose response to dasotraline in adult subjects with BED.

Similar to Study SEP360-221, the current study is a randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the efficacy and safety of dasotraline over a 12-week outpatient treatment period.

In order to evaluate dose response to dasotraline, this study is a fixed-dose design of 2 doses of dasotraline compared with placebo.

7.3.2. Rationale for the Dosages

The dasotraline doses to be utilized in this study (4 mg/day and 6 mg/day) were selected based on the effects of dasotraline in the initial BED study in adults, Study SEP360-221.

In the current study, dasotraline will be administered once daily based on its pharmacokinetic profile. One dasotraline treatment arm will receive 4 mg/day for the duration of the treatment period, and the other arm randomized to 6 mg/day will receive 4 mg/day for the first 2 weeks of treatment.

The 4 mg/day dose was chosen because efficacy analyses in Study SEP360-221 at Week 2, where all dasotraline treated subjects were on 4 mg/day, showed a significant change from baseline in the number of binge days per week with an effect size 0.5. The 6 mg/day dasotraline dose was chosen because the results in Study SEP360-221 showed its use resulted in an acceptable balance of safety and efficacy, further evidenced by the fact that it was the modal dose in that study, whereas subjects on 8 mg/day were those who failed to respond to the lower doses. One-half of these subjects, however, did not respond to 8 mg/day. Together these results

suggest that 6 mg/day is the optimal dose with regards to benefit and risk and 4 mg/day is the minimum effective dose in the treatment of BED. SEP360-321 will test these 2 hypotheses.

7.3.3. Rationale for the Study Population

The patient population for this study will range from 18 to 55 years of age, inclusive, and have symptoms consistent with a diagnosis of moderate to severe BED. Subjects must meet the DSM-5 criteria for a diagnosis of BED established using the eating-disorders module of the Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H), clinician review of subject diaries, and the EDE-Q. These instruments have been extensively used in previous trials and show excellent reliability (McElroy-2007, Hudson-1998, Grilo-2005). To optimize signal detection for the primary endpoint, enrolled subjects must have moderate to severe BED, as demonstrated by at least 3 binge eating days for each of the 2 weeks prior to the Baseline visit, and have a diagnosis of BED or is diagnosed at screening and has had a history of at least 2 binge eating days a week for at least 6 months prior to screening.

Treatment effects observed in the proposed population will be generalizable to BED patients diagnosed based on DSM-5 criteria as studies have shown that patients with mild BED are behaviorally comparable to those who binge more frequently (Wilson-2009). To reduce the potential confounding effects of comorbid disorders and certain concomitant medications on the efficacy and safety measures, subjects will be excluded who have significant or unstable comorbid medical disorders (eg, cardiovascular disease, diabetes mellitus); psychiatric disorders (eg, psychosis, bipolar disorder); and/or are taking medications used for the treatment of BED (eg, lisdexamfetamine dimesylate, topiramate, SSRIs); or medications associated with weight gain or weight loss (eg, insulin, liraglutide, metformin, stimulants).

7.3.4. Rationale for the Endpoints

The efficacy assessments and their timing are considered appropriate to assess the efficacy of dasotraline in adults with BED and are consistent with those used in previous trials (McElroy-2007, NCT01718483, and NCT01718509). The symptom and functional assessments were selected to address the potential effectiveness of dasotraline on these parameters. The standard safety assessments and their timing are appropriate to assess the safety of dasotraline in adults with BED.

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study before study completion, the following study design and conduct elements are implemented: (i) clinic visits every week for the first month, every 2 weeks for the remainder of double-blind treatment, and every week during the study drug withdrawal period, (ii) during the treatment period a window of ± 2 days for each weekly clinic visit, a window of ± 3 days for each biweekly clinic visit, and a window of ± 1 day for the EOT visit (iii) training the sites on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial, (iv) the clinical sites will train subjects on appropriate binge eating diary completion at Visits 1, 2, 3, and 5 and retraining will be provided throughout the study as needed, and (v) monitoring of data collection for adherence during the study.

8. SELECTION OF SUBJECTS

Approximately 480 total subjects will be randomized (160 subjects per treatment group) at approximately 50 clinical sites in the United States.

The subject's eligibility assessment will be reviewed by the CRO's Clinical Surveillance Team (CST) along with the sponsor based on protocol specified inclusion and exclusion criteria to promote appropriate subject enrollment and data quality. For the prebaseline review, sites will be required to submit specific screening information for clinician and sponsor review, prior to proceeding to baseline. The sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility and will be copied on all communications between the CRO and the site. In the event the CRO/sponsor and site do not agree on a subject's eligibility, then the subject will not be enrolled. Decisions regarding inclusion of subjects and assessment of subject safety throughout the trial primarily remain at the discretion of the Investigator; however, the Medical Monitor or Sponsor may request exclusion or discontinuation of a subject based on entry criteria or subject safety.

Subjects must meet all inclusion criteria and no exclusion criteria at both the Screening and Baseline visits unless otherwise noted under the Inclusion or Exclusion Criteria. Eligibility criteria involving clinical laboratory values will be based on results from samples obtained at Screening.

Subjects may be rescreened once for out of range clinical laboratory results including UDS or ECG results following authorization of the medical monitor. Each time a subject is rescreened a new subject number will be assigned. Screening numbers cannot be reassigned to another subject.

Subjects whose study participation is prematurely terminated will not be replaced.

8.1. Subject Inclusion Criteria

Subjects must meet all of the inclusion criteria in order to be eligible for the study.

1. Male or female subject between 18-55 years of age, inclusive, at time of informed consent.
2. Subject meets the following DSM-5 criteria for a diagnosis of BED. An episode of binge eating is characterized by both:
 - Eating an amount of food larger than what most people would eat, in a discrete period of time (eg, 2 hours)
 - Sense of lack of control over eating episodeBinge eating episodes are associated with ≥ 3 of the following:
 - Eating much more rapidly than normal
 - Eating until uncomfortably full
 - Eating large amounts when not feeling hungry
 - Eating alone because of embarrassment

- Feeling disgusted with oneself, guilty afterward

Binge eating episodes are also associated with marked distress regarding the episode and not associated with recurrent use of compensatory behavior (eg, bulimia nervosa). Note: A subject using compensatory behavior less than 1 time every 2 weeks over the 3 months prior to screening may be permitted to enroll in the study.

3. Diagnosis is confirmed based on the Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H), clinician review of subject diaries, and the EDE-Q.
4. Subject has a BED diagnosis or is diagnosed at screening and has a history of at least 2 binge eating days a week for at least 6 months prior to screening.
5. Subject's BED is of at least moderate severity with subject reporting at least 3 binge eating days for each of the 2 weeks prior to baseline as documented in the subject's binge diary. A binge eating day is defined as having at least one binge eating episode.
6. Subject has a BE-CGI-S score ≥ 4 at screening and baseline.
7. Subject has a negative breath alcohol test and a negative UDS for any illicit drug.
8. Female subject must have a negative serum pregnancy test at screening; females who are post-menopausal (defined as at least 12 months of spontaneous amenorrhea) and those who have undergone hysterectomy or bilateral oophorectomy will be exempted from the pregnancy test.
9. Female subject of childbearing potential and male subject with female partner of childbearing potential must agree to use an effective and medically acceptable form of birth control (see [Section 10.4](#) throughout the study period. Note: Continued use of an effective and medically acceptable form of birth control is recommended for 30 days after study completion.
10. Subject must be able to comply with study drug administration and adhere to protocol requirements including all study assessments.
11. Subject can read well enough to understand the informed consent form and other subject materials.

8.2. Subject Exclusion Criteria

Subjects meeting any of the exclusion criteria are not eligible for the study:

1. Subject has BMI of 18 kg/m² or less, or greater than 45 kg/m² (see [Section 27](#), Appendix VIII).
2. Subject has a lifetime history or current symptoms consistent with bulimia nervosa or anorexia nervosa.
3. Subject has started psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) within 3 months prior to screening. Note: Subjects receiving stable ongoing psychotherapy for longer than 3 months are permitted to enroll.

4. Subject has participated in a formal weight loss program (eg, Weight Watchers®) within 3 months prior to screening.
5. Subject has used a psychostimulant or mood stabilizer within the 3 months prior to screening.
6. Subject has used any medications for the treatment of binge eating, other eating disorders, obesity, or weight gain or any other medication that could result in weight gain or weight loss including over-the-counter and herbal products within the 3 months prior to screening.
7. Subject has received lisdexamfetamine dimesylate (Vyvanse®) for any reason, including but not limited to participation in any Phase 2 or 3 trial.
8. Subject has a lifetime history of psychotic disorder, bipolar disorder, hypomania, dementia, or ADHD as defined by the DSM-5 criteria.
9. Subject has a history of moderate to severe depression based on Investigator's judgment within the 6 months prior to screening or is currently taking or has taken any medication for depression during the 3 months prior to screening.
10. Subject has MADRS score ≥ 18 at screening and Baseline visit.
11. Subject has a history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) within the 12 months prior to screening, as defined by the DSM-5 criteria.
12. Subject is considered a suicide risk in the investigator's opinion or has any previous history of suicide attempt within the past 12 months.
13. Subject answers "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at screening (in the past month). Subjects who answer "yes" to this question must be referred to the Investigator for follow-up evaluation.
14. Subject has type I diabetes mellitus or insulin-dependent diabetes mellitus.
15. Subject with type II diabetes mellitus, has hemoglobin A1c $\geq 6.5\%$ at screening, or has initiated treatment with or changed the dose of a glucose-lowering agent within 3 months prior to screening.
16. Subject has known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, documented heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems.
17. Subject has initiated treatment with or changed the dose of a lipid-lowering medication within the 3 months prior to screening.
18. Subject has a history of moderate or severe hypertension that in the Investigator's opinion has not been medically stable or has required a change in dosage and/or medication during the 3 months prior to screening.

19. Subject has a history of focal or diffuse brain disorder including but not limited to epilepsy, seizures (except childhood febrile seizures), stroke, benign or malignant tumors, or head trauma with loss of consciousness lasting more than 5 minutes; unexplained syncope or other unexplained blackouts (except single incident); or a history of clinically significant repeated head-traumas without loss of consciousness.
20. Subject has had polycystic ovarian syndrome (PCOS) in the previous 12 months, even if no treatment was provided.
21. Subject is female and pregnant or nursing.
22. Subject has had major bariatric surgery, eg, gastric jejunal bypass, Roux-en-Y gastric bypass, sleeve gastrectomy, duodenal switch with biliopancreatic diversion for weight loss at any time.
23. Minor bariatric surgery (eg, lap bands) within 3 years of screening. Note: Surgeries for cosmetic reasons are not exclusionary but should be discussed with the medical monitor.
24. Subject has a history of positive test for either Hepatitis B surface antigen or Hepatitis C antibody, and has liver function test results at screening above the upper limit of normal (ULN) for the reference laboratory.
25. Subject without a history of positive test for Hepatitis B surface antigen or Hepatitis C antibody has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value ≥ 2 times the ULN at screening.
26. Subject has a blood urea nitrogen (BUN) value ≥ 1.5 times the ULN for the reference range, serum creatinine > 1.5 times the ULN for the reference range, fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L), or hemoglobin A1c $\geq 6.5\%$ at screening.
27. Subject is known to have tested positive for human immunodeficiency virus (HIV).
28. Subject has a clinically significant abnormality on screening evaluation including physical examination, vital signs, ECG, or laboratory tests that the Investigator considers to be inappropriate to allow participation in the study.
29. The subject's screening ECG shows a corrected QT interval using Fridericia's formula (QTcF) of ≥ 450 msec for male subjects or ≥ 470 msec for female subjects. Eligibility will be based on the core laboratory ECG interpretation report.
30. Subject has any life-time history of abuse or diversion of stimulants.
31. Subject has a history of allergic reaction or has a known or suspected sensitivity to any substance that is contained in the study drug formulation.
32. Subject who in the opinion of the Sponsor and Investigator has any other psychiatric or medical condition or disorder or any other psychosocial or work-related issue not previously listed that could interfere with the diagnosis of BED at screening or subsequent evaluations during the course of the study.
33. Subject who may experience or who is currently experiencing significant psychosocial or environmental stressors (eg, loss of employment, loss of housing, financial hardship, divorce) that could impede their ability to adhere to protocol requirements, as judged by the Investigator.

34. Subject is currently participating in or has participated in any clinical trial within the last 90 days or has participated in more than 2 clinical trials within the past year. This includes studies using marketed compounds or devices.
35. Subject has previously been enrolled in a clinical trial of dasotraline (SEP-225289).
36. Subject is an investigational site staff member or the relative of an investigational site staff member.
37. Subject has started a new physical training/exercise program for the purpose of managing his or her weight or binge eating within 3 months prior to screening. Note. Subjects participating in a stable physical training/exercise program for longer than 3 months are permitted to enroll.
38. Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. History of a pituitary tumor, whether benign or malignant, is exclusionary.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

The study medication is described in Table 5.

Table 5: Investigational Product

Attribute	Study Medication		
Product name	Dasotraline 4.0 mg	Dasotraline 6.0 mg	Matching Placebo
Dosage form	capsules	capsules	capsules
Unit dose	capsule	capsule	capsule
Route of administration	oral	oral	oral
Physical description	Swedish orange, size #4	Swedish orange, size #4	Swedish orange, size #4

In addition to dasotraline, the active ingredient, each capsule contains: mannitol, sodium starch glycolate, talc, and magnesium stearate.

Matching placebo capsules contain all ingredients except active dasotraline.

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in 1-week blister cards containing 10 capsules of dasotraline 4 mg or 6 mg capsules or placebo capsules (7 days + 3 extra days).

9.2.2. Labeling Description

All packaging for the study medications will be labeled with:

- Protocol number
- Sponsor's name and address
- Content (eg number of tablets)
- Investigational New Drug statement
- Instructions for use and storage
- Blank space for subject identifiers
- Batch number
- Blank space to record visit number identifier
- Unique medication number

9.3. Study Drug Storage

All study medication should be stored at United States Pharmacopeia (USP) Controlled Room Temperature: 20°C to 25°C (68°F - 77°F); excursions are permitted to 15°C to 30°C (59°F - 86°F) but must still be reported to CRO (please see Clinical Trial Material Manual for instructions). The subject will be instructed to store the study medication at room temperature.

9.4. Dispensing of Study Drug

An IXRS will be used to manage subject screening and enrollment. The IXRS is an integrated web-based subject and drug management system.

Study drug blister cards will be assigned by the IXRS based on the treatment schedule and dose adjustment criteria. The IXRS will generate instructions with regard to which medication number to assign to a subject. Each subject will be dispensed one or two 10-day blister cards per scheduled visit depending on the timing of the next scheduled visit (see [Section 7.2.1](#)).

Subjects will self-administer the study drug on an outpatient basis. Subjects will take one capsule of study drug per day at approximately the same time each morning including on the days when clinic visits occur.

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that include the dates, quantity, and use by subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/ CRO.

Upon receipt of clinical trial material (CTM), the Investigator or designee will inventory the supplies and verify receipt of supplies. The site will send an Acknowledgement of Receipt to Sunovion Pharmaceuticals, or designee, confirming date of receipt, inventory, and condition of CTM received.

The Investigator on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned study medication for use as the primary source for study drug accountability.

9.6. Study Drug Handling and Disposal

On an ongoing basis, the Investigator or designee must maintain a study medication inventory record of supplied, received, dispensed, and returned medication.

The study medication will not be dispensed to any person who is not a study subject under this protocol.

The Investigator or designee is required to return all used and unused study medication to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of medication shipping receipts, study medication accountability records, and records of return of the study medication.

10. TREATMENT OF SUBJECTS

10.1. Study Medication

Dasotraline 4 mg and 6 mg capsules and placebo capsules for oral administration will be supplied for the study as described in [Section 9](#).

Subjects will self-administer the study drug on an outpatient basis once a day beginning on Day 1, the day after the Baseline visit, and continue for 12 weeks. Subjects will be instructed to administer study drug at approximately the same time each morning including on days when clinic visits occur. If an individual subject requires a change to time of dosing (eg, evening shift worker), this must be approved by the Medical Monitor, and the subject should take the study drug at the same time of day throughout the study. All doses of study drug will consist of 1 capsule taken orally.

Subjects may take study medication with or without food.

Study medication capsules should not be opened or tampered with in any way; the active ingredient is an ocular irritant.

10.1.1. Dose or Dosage for Study Drug

Subjects randomized to placebo will receive placebo for the duration of the treatment period.

Subjects randomized to 4 mg/day dasotraline will receive 4 mg/day for the duration of the treatment period.

Subjects randomized to 6 mg/day dasotraline will be dosed with 4 mg/day dasotraline for the first 2 weeks of the treatment period and will be increased to 6 mg/day at Week 2.

No other changes in dose are allowed during the study. Subjects who cannot tolerate the assigned dose at any time in the study will be discontinued.

10.2. Treatment Compliance

Compliance with study medication will be monitored closely and determined at each visit during treatment. Subjects will be instructed to bring all unused study medication with them to each visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant. Evidence of noncompliance must be immediately reported to the Medical Monitor. Potential noncompliance will be discussed with subjects, and at the Investigator's discretion may result in termination of the subject from the study. All subjects will be reminded of the importance of strict compliance with taking study medication for the accurate evaluation of the safety, tolerability, and effectiveness of the study drug.

10.3. Concomitant Medications and Therapies

The following information on all medication administered between Screening and Week 15 (Day 105) or at study discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

Information on the format and version of the coding dictionary is provided in the Data Management Plan (DMP). All medications will be coded using World Health Organization drug dictionary (WHO-DD).

Directions regarding prior medications are provided in [Section 11.1](#).

10.3.1. Prohibited Medications

Any discontinuation of medications at any time prior to study participation is at the discretion of the potential subject in conjunction with the prescribing physician.

Use of certain medications, including but not limited to the following, is prohibited throughout the study from screening through the last in-clinic visit:

- psychostimulants
- any medications for the treatment of binge eating or other eating disorders, obesity, or weight gain
- antidepressant medications (eg, bupropion, SSRI/ serotonin norepinephrine reuptake inhibitor (SNRI), monoamine oxidase (MAO) inhibitors, tricyclics) and St. John's Wort
- medications that are CYP2B6 substrates or inhibitors or inducers of CYP2B6, eg, bupropion, cyclophosphamide, carbamazepine, etc. (see [Section 25](#), Appendix VI)
- medications for the treatment of ADHD such as but not limited to lisdexamfetamine, methylphenidate, atomoxetine, clonidine, guanfacine, modafinil, and armodafinil
- corticosteroids and anabolic steroids (Note: Topical, intra-nasal, and inhaled corticosteroids are permitted. Other formulations of corticosteroids may be permitted following consultation with the Medical Monitor.)
- antiepileptic medications
- benzodiazepines except for sleep (see [Section 10.3.3](#))
- mood stabilizers (eg, lithium, anticonvulsants)
- antipsychotic medications
- suvorexant
- any medication that can result in either weight gain or weight loss (eg, insulin, liraglutide, metformin, diphenhydramine except topical formulations, etc.) including over-the-counter and herbal products. Periodic use of diphenhydramine or diphenhydramine containing products for sleep or allergies is permitted with authorization from the Medical Monitor.

10.3.2. Prohibited Therapies

Initiation of psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) is prohibited within 3 months prior to screening and throughout the study.

Any participation in a formal weight loss program such as Weight Watchers® is prohibited within 3 months of screening and throughout the study.

For permitted therapies, see [Section 10.3.4](#).

10.3.3. Permitted Medications

The following medications are permitted during the study, with the restrictions noted:

- Sleep aids should be administered no more than once nightly and should not be used in combination. Concomitant use of lorazepam, temazepam, eszopiclone, zaleplon, zolpidem, zolpidem controlled release (CR), and melatonin is permitted at the discretion of the Investigator with the following restrictions:
 - Lorazepam (or equivalent benzodiazepine) is a permitted hypnotic up to a maximum daily dose of 2 mg/day
 - Temazepam (≤ 30 mg/day), eszopiclone (≤ 3 mg/day), zaleplon (≤ 20 mg/day), zolpidem (≤ 10 mg/day for males; ≤ 5 mg/day for females), zolpidem CR (≤ 12.5 mg/day for males; ≤ 6.25 mg/day for females), and melatonin (≤ 5 mg/day) may be administered at bedtime for insomnia, as needed
 - Use of any other sleep aids should be approved by the Medical Monitor
- Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor
- Contraceptives

The date and time of the last dose taken prior to scheduled efficacy assessments of any sleep aid listed above must be recorded at each visit.

10.3.4. Permitted Therapies

Subjects receiving a stable course of psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) ongoing for more than 3 months prior to screening are eligible to enroll in the study and to continue that therapy during the study.

New programs of psychotherapy are not permitted to be started during the study from screening through the last clinic visit.

10.4. Contraception Requirements

Female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to use an effective and medically acceptable form of birth control throughout the study period. Medically acceptable and effective contraceptives for females include one or more of the following: abstinence, prescription hormonal contraceptives (oral, patch, vaginal ring, implant, or injection), diaphragm with spermicide, intrauterine device (IUD), condom with spermicide, surgical sterilization, or vasectomy of male partner. For male subjects

adequate contraception is defined as abstinence or continuous use of 2 barrier methods of contraception (eg, male condom in addition to a diaphragm or a contraceptive sponge).

It is recommended that female subjects of childbearing potential and male subjects with female partners of childbearing potential continue to use an effective and medically acceptable form of birth control for 30 days after study completion.

10.5. Guidance for Overdose

There is no overdose experience with dasotraline in humans. Signs and symptoms of overdose in non-clinical studies were consistent with exaggerated pharmacology and included hyperactivity, stereotypy, aggressiveness, and reduced food intake and body weight loss.

Activated charcoal may be of value if administered very soon after a dasotraline overdose (ie, during the absorption process).

10.6. Cautions

Dasotraline is an ocular irritant. Therefore appropriate precautions should be taken to avoid ocular exposure to the contents of the dasotraline capsules.

11. STUDY ASSESSMENTS

A study schematic is presented in [Figure 1](#). A summary of assessments to be conducted at each visit is presented in [Table 2](#).

Training, as appropriate, will be provided for study site staff administering each of the effectiveness and safety assessments. In an effort to improve the consistency of subject assessment across sites, an independent rater qualification service will provide training on the Mini International Neuropsychiatric Interview (MINI), SCID-I Module H, EDE-Q, EDE-Q modified, Y-BOCS-BE, BE-CGI-S, MADRS, SDS, HAM-A, CSSA, and DESS rating scales. In an effort to improve rater consistency and precision, an independent rater qualification service, in collaboration with the sponsor, will develop a credential and experience survey to identify raters with appropriate experience. The sponsor has final discretion regarding allowing raters to participate in the study.

Table 6 outlines the clinical assessments that will be conducted by site raters or self-report by subject. It is recommended that the assessments are conducted in the sequence noted in Table 6.

Table 6: Recommended Schedule for Clinical Assessments

Screening Visit (Visit 1)	Baseline Visit (Visit 2)	Visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 (as applicable, see Table 2 , schedule of assessments above and Section 11.8)
SCID-I Module H	Review binge diary	Review binge diary
MINI	Y-BOCS-BE	Y-BOCS-BE
EDE-Q (by subject)	EDE-Q modified (by subject)	EDE-Q modified (by subject)
MADRS	SDS (by subject)	SDS (by subject)
C-SSRS	MADRS	MADRS
BE-CGI-S	C-SSRS	C-SSRS
Binge-diary training	BE-CGI-S	BE-CGI-S
	HAM-A	HAM-A
		CSSA
		DESS

11.1. Demographics and Baseline Characteristics

Subject self-report will be acceptable for listing all prior and concomitant medication use, demographics, medical history, psychiatric history including family history of psychiatric disorders, and evaluation for inclusion/exclusion except where specific protocol procedures are mandated to ensure appropriate enrollment (eg, certain baseline laboratory values). All medications taken within the 90 days before screening will be recorded as prior medications; data collected will be the same as for concomitant medications (see [Section 10.3](#)).

Demographics collected at screening will include sex, race, ethnicity, date of birth, weight, and height. BMI will be calculated from weight and height.

For medical history, only relevant/significant medical history and recurrence of any condition will be collected.

At screening, subjects will be checked for multiple study enrollments by clinical site staff using an available registry(s) of subjects participating in clinical trials. Clinical site staff will be provided training

11.2. Diagnostic Scales to Determine Study Eligibility

11.2.1. Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H)

The Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H) is a primary diagnostic measure developed to establish the presence of binge eating disorder in adults. The SCID is often used to characterize a study population in terms of current and past psychiatric diagnoses ([Spitzer-1992](#), [First-2007](#)).

11.2.2. Eating Disorder Examination Questionnaire (EDE-Q)

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. The EDE-Q yields scores on the same subscales (dietary restraint, eating concern, weight concern, and shape concern), global score, and binge eating frequency variables as the EDE interview. Research with clinical samples of patients with BED has reported acceptable agreement between the EDE-Q and EDE interview ([Grilo-2001A](#); [Grilo-2001B](#)).

11.2.3. Mini International Neuropsychiatric Interview (MINI)

The MINI is a short structured diagnostic interview, developed for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revised (DSM-IV-TR) and DSM-5 psychiatric disorders ([Sheehan-1989](#)). With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology. The MINI 7 will be used for this study.

11.3. Efficacy Assessments and Scales

11.3.1. Binge Eating Diary

All binge episodes will be captured daily by the subject in a binge eating diary using paper format provided by the CRO to record the date, duration (total hours of binging), type of binge episode (meal or non-meal), amount and type of food, and number of binges. At each visit, the Investigator will review the completed diary with the subject and assess the number of binges for each day. The Investigator assessment of number of binges for each day will be recorded in the diary and recorded in the CRF. Missing data, if any, will be reviewed by the clinical site staff with the subject and additional training on diary completion will be provided as needed.

11.3.2. Sheehan Disability Scale (SDS)

The SDS was developed to assess functional impairment in 3 domains: work/school, social, and family life. The subject rates the extent to which work/school, social life, and home life have been impaired by his/her symptoms on an 11-point visual analog scale. The 3 items can be summed into a single global measure of impairment that ranges from 0 (unimpaired) to 30 (highly impaired). This anchored visual analog scale uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability across 3 domains: work; social life, and family life. There are verbal descriptors for the points on the scale as well as numerical scores that provide more precise levels of the verbal descriptors. The SDS takes approximately 10 minutes to complete.

11.3.3. Montgomery-Asberg Depression Rating Scale (MADRS)

The Montgomery-Asberg Depression Rating Scale (MADRS) is a widely used clinician-rated assessment of the subject's level of depression. The measure 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 points, with higher scores indicating increased depressive symptoms.

The Structured Interview Guide for the MADRS (SIGMA) will be used for the administration of the MADRS.

11.3.4. Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a widely used and well-validated tool for measuring the severity of a patient's anxiety. It should be administered by an experienced clinician. The HAM-A consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a 5-point scale, ranging from 0 = not present to 4 = severe.

The Structured Interview Guide for the HAM-A (SIGH-A) will be used for the administration of the HAM-A.

11.3.5. Binge-eating Clinical Global Impressions–Severity of Illness (BE-CGI-S)

The BE-CGI-S (based on [Guy-1976](#)) asks the clinician one question: *“Considering your total clinical experience with this population, how mentally ill is the subject at this time?”* The clinician's answer is rated on the following 7-point scale: 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.

This rating is based upon observed and reported BED symptoms, behavior, and function in the past 7 days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the 7 days.

11.3.6. Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE)

The Yale Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) is a clinician-rated scale that measures the obsession of binge eating, thoughts and compulsiveness of

binge eating behaviors. The 10-item scale, is rated from 0 (no symptoms) to 4 (extreme symptoms). Total scores range from 0 to 40. A score of 0-7 is sub-clinical; 8-15 is mild; 16-23 is moderate; 24-31 is severe; and 32-40 is extreme ([Goodman-1989](#)). The Y-BOCS-BE can be divided into 2 subscales: obsessions and compulsions.

11.3.7. Eating Disorder Examination Questionnaire (EDE-Q) Modified

Convergent findings from confirmatory factor analyses of item data from the EDE-Q obtained from patients with BED ([Grilo-2010](#)) and patients with overweight/obesity ([Grilo-2012](#); [Grilo-2013](#); [Hrabosky-2008](#)) as well as non-clinical groups ([Grilo-2015](#)) support an alternative, brief version of the EDE-Q and EDE comprising 7 items to generate a global score and 3 subscales (dietary restraint, shape/weight overvaluation, and body dissatisfaction) referred to as the EDE-Q7 ([Grilo-2015](#)). In the present study, the EDE-Q7 along with 3 items to assess binge eating, including the number of binge eating days will be used and referred to as the EDE-Q modified.

11.4. Safety Assessments and Scales

11.4.1. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct.

11.4.1.1. Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, “Has there been any change in your health status since your last visit?”). See [Section 12](#) , Safety Reporting.

AEs and SAEs will be monitored throughout the study at all visits following the first dose of study drug.

Untoward medical occurrences that occur prior to the first dose of study drug will be collected as pre-treatment events.

11.4.1.2. Clinical Laboratory Tests

Clinical laboratory tests will include routine serum chemistry, hematology, urinalysis, lipid panel, hemoglobin A1c, insulin, and hs-CRP. The specific clinical laboratory tests required by protocol are listed in [Section 21](#), Appendix II.

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed centrally to ensure consistency. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. All clinical laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

If a subject has an unscheduled visit, clinical laboratory tests may be repeated (as necessary).

Blood samples for clinical laboratory tests should be collected after scheduled 12-lead ECG and vital signs assessments.

11.4.1.3. Physical and Neurological Examinations

Clinically significant physical and neurological examination findings, as judged by the Investigator, at screening will be recorded as medical history and after screening will be recorded as AEs.

The physical examination will consist of an assessment of body systems including but not limited to head, ears, eyes, nose and throat (HEENT), cardiovascular (heart and vascular system), respiratory (lungs and chest), gastrointestinal (abdomen), and skin.

Neurological examinations will include a brief assessment of mental status, cranial nerves, motor strength and coordination, sensory function in addition to deep tendon reflexes.

11.4.1.4. Vital Signs

Following 5 minutes of rest, respiration rate, oral temperature, and supine systolic and diastolic blood pressures and pulse rate will be measured. Systolic and diastolic blood pressures and pulse rate will be taken again with the subject standing after the subject has been standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG, whenever possible.

11.4.1.5. Electrocardiograms

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 10 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained before drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core laboratory according to established quality additional information assurance procedures for inter/intra reader variability. Refer to [Section 20](#), Appendix I for additional information.

Standard 12-lead ECG will record heart rate (HR), PR interval, RR interval, QT interval, QTc intervals (QTcB and QTcF), and QRS duration.

11.4.2. Safety Scales

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

The C-SSRS ([Posner-2007](#)) is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study. 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 scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

This study will utilize 2 versions of the C-SSRS. At the screening visit, the “Baseline/Screening” version will be completed; for all subsequent visits, the “Since Last Visit” version of the C-SSRS will be administered.

Subjects who answer “yes” to “suicidal ideation” item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Screening (in the past month) must be referred to the Investigator for follow-up evaluation.

11.4.2.2. Cocaine Selective Severity Assessment (CSSA)

The CSSA ([Kampman-1998](#)) is a clinician-administered scale designed to evaluate withdrawal signs and symptoms related to stimulants over the past 24 hours. It takes approximately 10 minutes to administer the 18-item scale.

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 is scored as follows: cocaine craving scores are obtained by having subjects record the highest intensity and frequency of cocaine craving experienced during the preceding 24 hours using visual analog scales. All items except item 14, are scored 0 to 7 according to instructions on the CSSA 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. Heart rate is determined by radial pulse measurement.

On non-clinic days, the CSSA will be completed by site staff during a call to the subject.

In order to complete the visual analog scale (VAS) portion of the CSSA on days when there are no scheduled clinic visits, subjects will be provided with copies of the VAS in advance, and will record their response at the time of scale administration.

In order to complete the radial pulse portion of the CSSA on days when there are no scheduled clinic visits, subjects will measure their own radial pulse and provide the measurement to the site staff over the phone.

For consistency of radial pulse measurements, subjects also will take their own radial pulse for the CSSA completed during in-clinic visits.

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

The DESS Scale ([Rosenbaum-1998](#)) is a clinician-rated instrument of 43 items used to evaluate signs and symptoms associated with discontinuation or interruption of monoamine reuptake inhibitor treatment.

On non-clinic days, the DESS Scale will be completed by site staff during a call to the subject.

11.4.2.4. Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A will be used to evaluate changes in severity of anxiety during the study medication withdrawal period. See [Section 11.3.4](#).

11.4.2.5. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS will be used to evaluate changes in severity of anxiety during the study medication withdrawal period. See [Section 11.3.3](#).

11.5. Pharmacokinetic Assessments

The plasma concentrations for dasotraline will be determined using a validated bioanalytical method. PK samples collected from placebo subjects will not be analyzed. The relationship between dasotraline plasma concentration and the primary and selected secondary efficacy and safety endpoints will be evaluated.

Plasma samples collected from the study could be utilized for relevant exploratory research work such as further method development and metabolic profiling and identification.

Blood samples for PK assessments should be collected at the same time as other blood samples, whenever possible.

The dates and times of the previous 3 doses of study drug prior to PK blood sample collection are to be recorded in the CRF.

11.6. Collection of Blood Samples for Biomarker Analysis

A blood sample will be collected to evaluate biomarkers associated with eating disorders to be determined in relationship to the severity of BED and response to dasotraline at a later date in the development program.

Plasma/serum samples collected for biomarker concentration analysis may also be used for the additional characterization of and/or bioanalytical method development for dasotraline.

11.7. Collection of Specimens for Genetic Analysis

A blood sample will be collected from subjects who provide a separate informed consent for pharmacogenomics (PGx) analysis for potential evaluation of associations between genetic polymorphisms such as, but not limited to Taq1DRD2, OPRM1, and DRD4-7R, and the severity of BED, the clinical response to dasotraline, in addition to the safety, efficacy, and PK profiles of dasotraline to be conducted at a later date in the development program.

Pharmacogenetic sampling and sample handling guidelines are provided in [Section 24](#), Appendix V. Pharmacogenetic blood samples will be shipped in anonymized fashion to a qualified central laboratory for processing. Processing will include extraction of deoxyribonucleic acid (DNA) genetic material. The DNA material will be stored for no more than 15 years, unless a written request for destruction of the sample is provided by a subject to the site at which the subject participated in the Sunovion-sponsored dasotraline clinical trial.

Subjects must provide a written request requesting destruction of their genetic sample to the study site at which they participated in a Sunovion-sponsored clinical trial. The request will be sent to the Sponsor for processing using the study subject number identifier. The Sponsor will identify the sample using the study subject number and instruct the central laboratory to destroy the stored anonymized sample corresponding to the study subject number. Upon destruction of the sample, the Sponsor will provide written documentation to the site that the sample has been destroyed. Genetic information obtained from individual subjects (including genotype information) will be stored in anonymized fashion in the Sponsor's pharmacogenetic database. When reported, the data will not include any subject-level identifying information and will reflect anonymized information regarding subject characteristics.

The DNA samples collected in this study will be maintained exclusively by Sunovion or designee. Processing, analysis, or storage of these samples by third parties will be conducted only by qualified third parties. The scope of genetic analysis performed by third parties using DNA extracted from samples provided by subjects in a Sunovion-sponsored trial will be determined by the Sponsor.

The timing of the analysis will be following completion of this study and as such may be reported separately.

11.8. Study Visits and Assessments

11.8.1. Screening: Visit 1 (Day -22 to -2)

Subjects will be evaluated at the Screening Visit to determine their eligibility to enroll in the study. The screening visit should be scheduled in the morning. Subjects must be fasting for at least 8 hours (may have water only) prior to the indicated laboratory tests.

The following study related procedures will be performed at Screening:

- Obtain informed consent and optional informed consent for PGx
- Review inclusion/exclusion criteria
- Collect demographics
- Collect medical history, and psychiatric history including family history of psychiatric disorders
- Record prior and concomitant medications
- Perform physical and neurological examinations
- Measure height and weight, calculate BMI
- Collect vital signs
- Perform ECG
- Administer scales:
 - SCID-I Module H
 - MINI
 - EDE-Q
 - MADRS (with SIGMA)
 - C-SSRS
 - BE-CGI-S
- Collect samples for hematology, serum chemistry, fasting lipid panel, hemoglobin A1c level, urinalysis, UDS, serum pregnancy test for females of child-bearing potential
- Perform breath alcohol test

- Binge eating diary training
- Remind subject to fast for at least 8 hours (may have water only) prior to the Baseline visit (Day -1)

Subjects will be checked for multiple study enrollments by site staff.

Subjects will complete the daily binge eating diary each day for 14 consecutive days immediately prior to the Baseline visit and starting no sooner than the day after the screening visit.

Subjects may be rescreened once for out of range clinical laboratory results including UDS or ECG results following authorization of the medial monitor. If the retest for out of range laboratory or ECG results can be conducted within the allotted screening period then a complete rescreen is not required.

For the prebaseline review, sites will be required to submit specific screening information for clinician and sponsor review, prior to proceeding to baseline. Details are provided in the Clinical Surveillance Team (CST) site manual.

11.8.1.1. Baseline: Visit 2 (Day -1)

The Baseline visit should be scheduled in the morning. Subjects must be fasting for at least 8 hours (may have water only) prior to the indicated laboratory tests. The following study related procedures will be performed:

- Review inclusion/exclusion criteria
- Record concomitant medications
- Perform physical and neurological examinations
- Collect vital signs and weight
- Perform ECG
- Clinician review of binge eating diary
- Administer scales:
 - Y-BOCS-BE
 - EDE-Q modified
 - SDS
 - MADRS (with SIGMA)
 - C-SSRS
 - BE-CGI-S
 - HAM-A (with SIGH-A)
- Collect samples for hematology, serum chemistry, fasting lipid panel, hemoglobin A1c level, insulin, hs-CRP, urinalysis, UDS, urine pregnancy test for females of child-bearing potential

- Collect blood samples for biomarkers and genotyping
- Perform breath alcohol test
- Randomization
- Dispense study medication
- Binge eating diary training

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.2. Week 1 (Day 7 [\pm 2 days]): Visit 3

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Record AEs
- Clinician review of binge eating diary and retraining
- Administer scales:
 - C-SSRS
- Perform study medication accountability
- Dispense study medication

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.3. Week 2 (Day 14 [\pm 2 days]): Visit 4

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Record AEs
- Clinician review of binge eating diary
- Administer scales:
 - Y-BOCS-BE
 - C-SSRS
 - BE-CGI-S
- Collect blood sample for plasma PK levels
- Perform study medication accountability
- Dispense study medication

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.4. Week 3 (Day 21 [± 2 days]): Visit 5

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Record AEs
- Clinician review of binge eating diary and retraining
- Administer scales:
 - C-SSRS
- Perform study medication accountability
- Dispense study medication

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.5. Week 4 (Day 28 [± 2 days]): Visit 6

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - Y-BOCS-BE
 - C-SSRS
 - BE-CGI-S
- Collect sample for urine pregnancy test for females of child-bearing potential
- Perform study medication accountability
- Dispense study medication
- Remind subject to fast for at least 8 hours (water and study drug only) prior to the Visit 7 Week 6 (Day 42) visit.

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.6. Week 6 (Day 42 [± 3 days]): Visit 7

The Week 6 visit should be scheduled in the morning. Subjects must be fasting for at least 8 hours (may have water and study drug only) prior to the indicated laboratory tests. The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - SDS
 - Y-BOCS-BE
 - C-SSRS
 - BE-CGI-S
- Collect sample for UDS
- Perform breath alcohol test
- Collect samples for hematology, serum chemistry, fasting lipid panel, hemoglobin A1c level, urinalysis
- Collect blood sample for plasma PK levels
- Perform study medication accountability
- Dispense study medication

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.7. Week 8 (Day 56 [\pm 3 days]): Visit 8

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - Y-BOCS-BE
 - C-SSRS
 - BE-CGI-S
- Collect samples for urine pregnancy test for females of child-bearing potential
- Perform study medication accountability
- Dispense study medication

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.8. Week 10 (Day 70 [\pm 3 days]): Visit 9

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - Y-BOCS-BE
 - C-SSRS
 - BE-CGI-S
- Perform study medication accountability
- Dispense study medication

Remind subject to fast for at least 8 hours (water and study drug only) prior to the Visit 10 Week 12 (Day 84) visit.

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.9. Week 12 (Day 84 [\pm 1 day]) End of Treatment (EOT): Visit 10

The EOT should be scheduled in the morning. Subjects must be fasting for at least 8 hours (may have water and study drug only) prior to the indicated laboratory tests. The following study related procedures will be performed:

- Record concomitant medications
- Perform physical and neurological examinations
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - Y-BOCS-BE
 - MADRS (with SIGMA)
 - EDE-Q modified
 - SDS
 - C-SSRS

- BE-CGI-S
- HAM-A (with SIGH-A)
- CSSA (only for subjects not entering the extension study)
- DESS (only for subjects not entering the extension study)
- Collect samples for hematology, serum chemistry, fasting lipid panel, hemoglobin A1c level, insulin, hs-CRP, urinalysis, UDS, urine pregnancy test for females of child-bearing potential
- Collect blood samples for plasma PK levels and biomarkers
- Perform breath alcohol test
- Perform study medication accountability

Subjects will complete the daily binge eating diary each day until the next clinic visit.

At this visit, subjects who have completed treatment will have the option to enroll and continue treatment for an additional 12 months in an extension study, Study SEP360-322. For subjects entering the extension study, Week 12 in this study will be baseline for the extension study and subjects will not need to return for further visits for this study.

Subjects who do not enter the extension study, for any reason, will complete the study medication withdrawal period assessments and visits.

11.8.10. Three-week Study Medication Withdrawal Period

In addition to during in-clinic visits, the CSSA and DESS will 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 (up to 3 times per day if the clinical site staff are unable to contact the subject on the first 2 attempts). Clinical site staff will record the responses to the CSSA and DESS in the subject's source information and in the CRF with the contact date and time. During these calls, clinical site staff will also assess and record AE(s) and concomitant medications.

A window of ± 1 day will be 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.

11.8.10.1. Week 13 (Day 91 [± 1 day]¹): Visit 11

The following study related procedures will be performed:

¹ For early terminating subjects 7 days post last dose ± 1 day

- Record concomitant medications
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - MADRS (with SIGMA)
 - C-SSRS
 - HAM-A (with SIGH-A)
 - CSSA
 - DESS
- Collect sample for UDS
- Perform breath alcohol test

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.10.2. Week 14 (Day 98 [\pm 1 day]²): Visit 12

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Clinician review of binge eating diary and retraining, as necessary
- Administer scales:
 - MADRS (with SIGMA)
 - C-SSRS
 - HAM-A (with SIGH-A)
 - CSSA
 - DESS

² For early terminating subjects 14 days post last dose \pm 1 day

- Collect sample for UDS
- Perform breath alcohol test
- Remind subject to fast for at least 8 hours (water only) prior to Visit 13.

Subjects will complete the daily binge eating diary each day until the next clinic visit.

11.8.10.3. Week 15 (Day 105 [\pm 1 day]³) Visit 13

The Week 15 visit should be scheduled in the morning. Subjects must be fasting for at least 8 hours (may have water) prior to the indicated laboratory tests. The following study related procedures will be performed:

- Record concomitant medications
- Perform physical and neurological examinations
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Clinician review of binge eating diary
- Administer scales:
 - Y-BOCS-BE
 - MADRS (with SIGMA)
 - C-SSRS
 - SDS
 - BE-CGI-S
 - HAM-A (with SIGH-A)
 - CSSA
 - DESS
- Collect sample for UDS
- Perform breath alcohol test
- Collect samples for hematology, serum chemistry, fasting lipid panel, hemoglobin A1c level, urinalysis, serum pregnancy test for females of child-bearing potential

³ For early terminating subjects 21 days post last dose \pm 1 day

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the informed consent form (ICF) and first drug administration are pre-treatment events. Those that occur after first administration of study drug are considered AEs.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from after first administration of study drug to the last study visit.

Lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way.

New signs and symptoms of underlying disease, or signs and symptoms of emerging disease must be recorded as AEs.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above.
Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term “severe” is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see [Section 12.3](#)); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as

“serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the case report form (CRF).

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. Laboratory reports will be initialed and dated on all pages by the Investigator.

- **Clinical Laboratory Tests Outside the Normal Range:** Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during Screening is indicated as clinically significant and is not covered by the inclusion or exclusion criteria in [Section 8](#), the subject will **not** be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or during the withdrawal period this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalised or stabilised.

All on-site ECG tracings and ECG over-read reports will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

12.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All pre-treatment events and AEs/all AEs must be recorded on the CRF.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** – Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** – Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** – Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.
- **Dose Not Changed**
- **Not Applicable**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**
 - **Not related** – Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
 - **Unlikely** – occurred within a reasonable time frame after administration/discontinuation of the study medication, but there is a likely association of an intercurrent/underlying medical condition or other drugs.
- **Related**
 - **Possible** – occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
 - **Probable** – occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
 - **Definite** – occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in [Table 1](#) of this protocol.

12.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after first administration of study drug through 30 days following the last dose of the study medication, this must be reported within 24 hours to PPD-PVG, the medical monitor, and Sunovion responsible physician whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs “spontaneously” to the PPD-PVG if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see [Table 1](#)) to PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) by the Investigator or the appropriate person at the study center if required per IRB guidelines.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 30 days following the last dose of the study medication will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to immediately stop taking the study medication. Further, the subject will be instructed to return promptly/within 48 hours of the first notification of pregnancy to the research site and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the subject will no longer receive any additional study medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

If a pregnancy is reported for the study subject's partner, the study subject must agree to complete abstinence for the duration of the study or until resolution of the pregnancy, whichever comes first, or discontinue study drug and withdraw from the study. If the subject chooses to withdraw from the study, continued abstinence is recommended for 30 days after the last dose of study medication.

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

If the subject received blinded study medication, unblinding of the study medication will be offered to the subject when knowledge of such treatment may have an impact on further treatment decisions. Otherwise, information regarding to what treatment the subject was assigned may be provided when the study has ended.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

12.5. Data Monitoring Committee/Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will monitor safety throughout the study (and may review blinded, partially blinded, or unblinded data). The DSMB will be independent of the Sponsor, CRO, and the Investigators and will be empowered to recommend stopping the study due to safety concerns but not for efficacy or futility. The membership of the DSMB and its mandate will be described in a separate DSMB charter.

13. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

13.1. Criteria for Study Drug Discontinuation

Subjects may be discontinued from the study drug at any time during the treatment period. The possible reasons for discontinuation of study drug are as follows:

- Adverse event
- Lack of efficacy (specify)
- Lost to follow-up (specify)
- Non-compliance with study drug (specify)
- Protocol violation (specify)
- Pregnancy
- Withdrawal by subject (specify)
- Other (specify)

If, at any time during the course of the treatment period, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study drug.

The primary reason and information for study drug discontinuation will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

13.2. Criteria for Subject Termination from the Withdrawal Period

Subjects may terminate during the withdrawal period for any reason.

The possible reasons for termination during the withdrawal period are as follows:

- Adverse event
- Lost to follow-up (specify)
- Pregnancy
- Withdrawal by subject (specify)
- Protocol deviation (specify)
- Other (specify)

The reason for termination during the withdrawal period will be recorded on the appropriate CRF.

Subjects who prematurely terminate study participation will not be replaced.

13.3. Clinical Assessments After Study Drug Discontinuation

Subjects who discontinue study medication before completion will be asked to return to the site and complete the EOT visit assessments ([Section 11.8.9](#)), as soon as possible following discontinuation of study drug, and complete the study medication withdrawal assessments and visits ([Section 11.8.10](#)).

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center or at multiple centers for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study medications pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study at his or her site after consultation with the Sponsor.

In the event of study or site termination, subjects will be asked to return to the site and complete the EOT visit assessments ([Section 11.8.9](#)) as soon as possible after discontinuation of study drug.

15. STATISTICS

The Statistical Analysis Plan (SAP) will provide details on the statistical methods planned for this study and will be finalized before data base lock.

15.1. Sample Size

The sample size for this study was estimated based on 2 hypotheses associated with the primary efficacy endpoint (change from baseline in number of binge days per week at Week 12). A fixed sequence closed testing procedure was used to adjust for 2 comparisons of dasotraline doses vs placebo (ie, with dasotraline 6 mg vs placebo tested first and dasotraline 4 mg vs placebo tested after if the previous one is significant at the 0.05 level) for the sample size justification. Based on the Study SEP360-221 results, assuming a common standard deviation (SD) of 1.75 and a mean improvement of 0.9 (effect size 0.517) and 0.8 (effect size 0.457) over placebo for change from baseline in number of binge days per week at Week 12 for dasotraline 6 mg/day and 4 mg/day doses, respectively, a sample size of 96 subjects per treatment group will provide at least 85% conjunctive power to reject both null hypotheses. An upward adjustment of approximately 40% is assumed to compensate for subjects who are randomized but discontinue from the study, thus, a total sample of 480 subjects (160 subjects per group) will be randomized with a ratio of 1:1:1 for placebo, and dasotraline 4 mg/day and 6 mg/day, respectively. The sample size calculation was based on Monte Carlo simulation from EAST 6.4.

15.2. Statistical Hypotheses

The hypotheses associated with the primary endpoint and key secondary endpoints will be tested using a testing procedure in [Section 15.4.1.4](#).

Primary Hypotheses

In adults with moderate to severe BED, after 12 weeks of treatment,

- Dasotraline 6 mg/day reduces change from baseline in the number of binge days per week relative to placebo
- Dasotraline 4 mg/day reduces change from baseline in the number of binge days per week relative to placebo

Key Secondary Hypotheses

In adults with moderate to severe BED, after 12 weeks of treatment, 6 mg/day dasotraline or both doses of dasotraline:

- Reduce change from baseline in BE-CGI-S score relative to placebo
- Provide a greater proportion of subjects with a 4-week cessation from binge eating at Week 12 relative to placebo
- Reduce change from baseline in Y-BOCS-BE total score relative to placebo

15.3. Analysis Populations

Intent-to-Treat (ITT) Population: All randomized subjects who receive at least one dose of study medication and have at least 1 post-baseline result in any efficacy evaluation. The ITT population is the primary population for efficacy analyses, ie, unless otherwise specified, all efficacy analyses will be based on ITT population.

Per-Protocol (PP) Population: All ITT subjects who have no major protocol violations that may affect the interpretation of the primary efficacy endpoint.

The PP population will be used to assess robustness of the primary efficacy analysis. Major protocol violations and the PP population will be determined through a blinded data review meeting and identified prior to the database lock.

Subjects in the ITT and PP populations will be analyzed based on the treatment to which they are randomized.

Double-blind (DB) Safety Population: All randomized subjects who receive at least one dose of study medication.

The DB Safety population mainly will be used for the data analyses of the safety data collected through Week 12 or during the treatment period. Subjects will be analyzed based on the predominant treatment received, in the event that a subject receives a treatment other than the one to which he or she is randomized. The predominant treatment is defined as the treatment (ie, placebo, dasotraline 4 mg/day, or dasotraline 6 mg/day) to which the subject is exposed for the greatest duration during the treatment period. The predominant treatment will generally be the same as the randomized treatment group, unless the subject takes incorrect study medication during the entire study.

Withdrawal Safety Population: The Withdrawal safety population includes all randomized subjects who receive at least one dose of study medication, and either discontinue the study drug during the treatment period before the Week 12 visit or complete the 12-week treatment period but do not enter the extension study (Study SEP360-322), and have at least one assessment after the last dose of study medication for any safety or efficacy evaluation. The Withdrawal safety population mainly will be used to summarize the assessments collected in the withdrawal period.

15.4. Data Analysis

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 treatment group and visit as appropriate. All subject data will be presented in data listings by subject.

15.4.1. Efficacy Analyses

15.4.1.1. Assessments from Binge Eating Diary

The number of binge days per week at each assessment timepoint will be derived based on clinician review of the binge eating diary collected in the time intervals as follows:

- Baseline: binge eating diary completed for 14 consecutive days immediately prior to the Baseline visit and starting no sooner than the day after the screening visit;

- Weeks 1, 2, 3, and 4 (ie, Visits 3, 4, 5, and 6): binge eating diary collected at each visit, which will span from the previous visit to the current visit and therefore cover Weeks 1, 2, 3, and 4, respectively;
- Weeks 6, 8, 10 and 12 (ie, Visits 7, 8, 9, and 10): binge eating diary collected at each visit, which will span from the previous visit to the current visit and therefore cover Weeks 5/6, 7/8, 9/10, and 11/12, respectively.

Specifically, the number of binge eating days per week at baseline is calculated as the number of binge eating days in the 14 days immediately prior to the Baseline visit multiplied by 7 and divided by the number of days in the Baseline period (ie, 14 days); the number of binge days per week in a visit that spans between 2 scheduled visits is calculated as (total number of binge days) x 7 / (total number of assessed days in the visit span). If missing diary entries exist during an assessed period for a subject, the available non-missing diaries from the subject will be used to derive the number of binge days per week adjusted by the number of non-missing diary days accordingly.

15.4.1.2. Primary Efficacy Endpoint Analyses

The primary efficacy endpoint is the change from baseline in the number of binge days per week at Week 12.

15.4.1.2.1. Primary Efficacy Analyses

The primary efficacy analyses of the primary efficacy endpoint (the change from baseline in the number of binge days per week at Week 12) will be performed using a likelihood-based mixed model for repeated measures (MMRM). The response (dependent) variable is the change from baseline in the number of binge days per week assessed at Weeks 1, 2, 3, 4, 6, 8, 10, and 12. Specifically, the MMRM model includes fixed effects terms for treatment, visit (as a categorical variable), pooled center, baseline binge days category (stratification factor; refer to [Section 7.2.1](#) for categories), the number of binge days per week at baseline, and treatment-by-visit interaction. Restricted maximum likelihood estimation method will be applied using an unstructured covariance model. The Kenward Roger approximation will be used to estimate denominator degrees of freedom. In case of a failure of convergence with the unstructured covariance, the following structures may be assessed in a sequential order: heterogeneous Toeplitz, Toeplitz, and spatial exponential covariance pattern model. Of the above 3 covariance structures, the first covariance structure yielding convergence in the MMRM model will be used for the MMRM analysis. The spatial exponential model is selected for the analysis of data with unequally spaced time points. The LS mean treatment differences (each dasotraline group minus placebo group) of change from baseline at Week 12, their 2-sided 95% CIs, and the associated p-values will be calculated based on this model.

The normality assumption underlying the primary MMRM model will be assessed graphically. Conditional studentized and scaled residuals will be plotted against the predicted values, respectively, and Q-Q (quantile-quantile) plots of these residuals versus the expected quantiles of the standard normal distribution will be presented to provide a graphical view of similarity and difference in the two distributions. Cumulative distribution function (CDF) of the primary endpoint will be also provided by treatment group.

The primary efficacy analysis will be repeated for the PP population to examine the impact of premature dropouts and/or protocol deviations.

15.4.1.2.2. Supportive Analyses

The primary efficacy endpoint also will be analyzed using an analysis of covariance (ANCOVA) model and the last observation carried forward (LOCF) approach, as a supportive analysis. The model will include terms for treatment, pooled center, baseline binge days category (stratification factor), and the number of binge days per week at baseline as covariates.

15.4.1.2.3. Sensitivity Analyses

To address early dropouts under the assumption of missing not at random (MNAR), a pattern-mixture model using a placebo-based multiple imputation method and a pattern mixture model using multiple imputations with penalties (ie, deflating the individually estimated treatment effect size by known factors) will be performed as sensitivity analyses to explore the robustness of the MMRM results for the primary analysis. In case of a deviation from the assumptions required for the primary analysis, to confirm the robustness of the primary analysis result, 2 additional sensitivity analyses will be performed: (1) permutation test: fit a large number of datasets based on a same MMRM for the primary analysis with randomly assigning pseudo-treatment group designations; (2) generalized linear mixed model (GLMM) analysis: fit count data over time (ie, number of binge days among number of assessed days at each period) based on a binomial distribution. The details of these sensitivity analyses will be outlined in the SAP.

15.4.1.3. Key Secondary Efficacy Endpoints Analyses

The key secondary efficacy endpoints involved in the hypothesis testing of each dasotraline dose (4 mg/day and 6 mg/day) versus placebo include change from baseline at Week 12 in BE-CGI-S score and Y-BOCS-BE total score, and percent of subjects with a 4-week cessation from binge eating. If a subject is early terminated in the double-blind treatment period prior to collection of 28 days of diary data or the subject has missing diary data in the last 28 days prior to Week 12/EOT the subject will be counted as having no cessation.

Continuous key secondary variables (ie, change in BE-CGI-S score and Y-BOCS-BE total score) will be analyzed with an MMRM model similar to the primary efficacy analysis ([Section 15.4.1.2.1](#)) adjusted with the corresponding baseline. The LS mean treatment differences (each dasotraline group minus placebo) of change from baseline at Week 12, their 2-sided 95% CIs, and the associated p-values will be calculated based on the model.

Categorical secondary efficacy endpoints (ie, percent of subjects with a 4-week cessation from binge eating) will be analyzed using a logistic regression model with treatment, baseline binge days category (stratification factor; refer to [Section 7.2.1](#) for categories), and baseline number of binge days per week as covariate using a LOCF approach based on the ITT population. The odds ratios, their 2-sided 95% CIs, and the associated p-values for each dasotraline group over the placebo group will be derived from the model.

Additional supportive and sensitivity analyses may be conducted as needed for the key secondary endpoints to address early dropouts or potential deviation from the model assumption(s). To address early dropouts or potential deviation from the model assumption(s), supportive and sensitivity analyses similar to those described in [Section 15.4.1.2.3](#) may be

conducted as needed for the continuous key secondary endpoints. For the categorical key secondary endpoint, supportive and sensitivity analyses, such as a GLMM analysis with random effect(s) and a pattern-mixture model using placebo-based multiple imputations, may be conducted as appropriate. The details will be provided in the SAP.

15.4.1.4. Multiplicity Adjustment

To control the overall type I error rate strongly at 5% for the primary and key secondary endpoints, for the hypotheses to be tested (see [Section 15.2](#)), a sequential testing strategy will be used. Following the fixed sequence closed testing procedure in [Figure 2](#), testing will only proceed conditional on the statistical significance of the test(s) of prior level(s) at a 2-sided 5% significance level. See [Section 15.2](#) for details about the definition of statistical hypotheses.

Figure 2: Fixed Sequence of Hypothesis Testing for Primary and Key Secondary Efficacy Endpoints

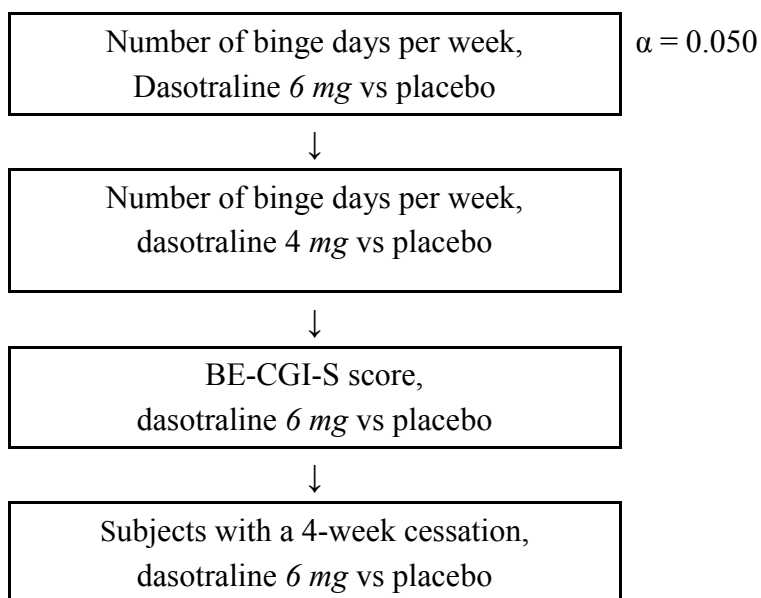
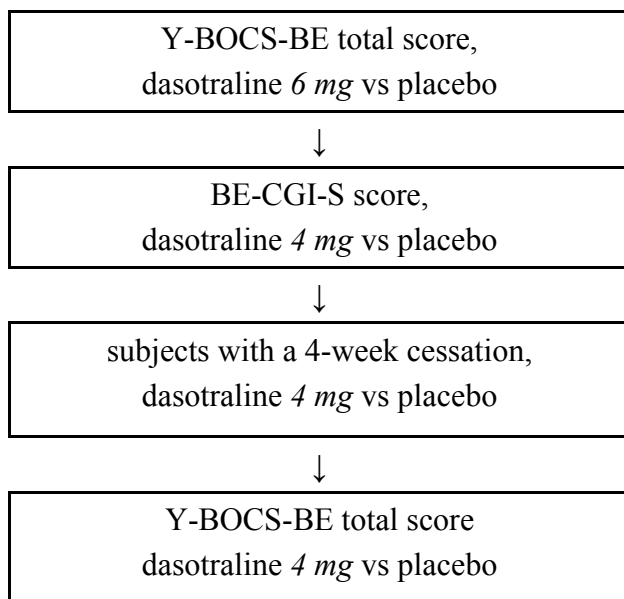


Figure 2: Fixed Sequence of Hypothesis Testing for Primary and Key Secondary Efficacy Endpoints (Continued)



15.4.1.5. Other Secondary Efficacy Endpoints Analyses

The other secondary endpoints are:

- Change from baseline in number of binge days per week at Weeks 1, 2, 3, 4, 6, 8, and 10
- Change from baseline in number of binge episodes per week at Weeks 1, 2, 3, 4, 6, 8, 10, and 12
- Change from baseline in BE-CGI-S score at Weeks 2, 4, 6, 8, and 10
- Change from baseline in Y-BOCS-BE total score at Weeks 2, 4, 6, 8, and 10 and subscale scores (obsessions and compulsions) at Weeks 2, 4, 6, 8, 10, and 12
- Change from baseline in MADRS total score at Week 12
- Change from baseline in HAM-A total score at Week 12
- Change from baseline in SDS total score and subscale scores (school/work disability, social life disability, and family life disability) at Weeks 6 and 12
- Proportion of binge eating responders (ie, $\geq 75\%$ reduction in the number of binge eating episodes) at Week 12
- Change from baseline in EDE-Q modified including EDE-Q7 global score and 3 subscale scores (dietary restraint, shape/weight overvaluation, and body dissatisfaction) at Week 12

Continuous variables (ie, change in number of binge days per week, number of binge episodes per week, BE-CGI-S, Y-BOCS-BE total score, and SDS total score and subscale scores) will be analyzed using an MMRM model similar to the primary efficacy analysis ([Section 15.4.1.2.1](#)) adjusting for the corresponding baseline. Other continuous variables (eg, change in EDE-Q7 global score and subscale scores) will be analyzed using an ANCOVA model similar to the supportive analysis for the primary efficacy endpoint ([Section 15.4.1.2.2](#)), adjusting for the corresponding baseline as a covariate.

The proportion of binge eating responders at Week 12 will be analyzed using a logistic regression model and LOCF approach with factors of treatment, pooled center, baseline binge days category (stratification factor), and baseline number of binge episodes per week as covariate. For subjects who are discontinued, binge eating responders at Week 12 LOCF is defined per the last post-baseline time period during the treatment period that binge diary is assessed. To ensure that the logistic regression model is feasible, pooled center may be removed from the analysis model if some pooled center has no responder either because of a small number of subjects in the pooled center or subjects experiencing little change. As a supportive analysis, the proportion of binge eating responders over time will be analyzed by an inverse probability weighting (IPW) Generalized Estimating Equations (GEE) model. The details will be provided in the SAP.

In addition, the number and percentage of subjects in the following categories for reduction in the number of binge eating episodes from baseline will be summarized over time by treatment:

- cessation (defined as 100% reduction)
- 99% to 75% reduction
- 74% to 50% reduction
- other

15.4.1.6. Subgroup Analyses

The primary efficacy variable (the change from baseline in the number of binge days per week at Week 12) and a key secondary variable (ie, change from baseline in BE-CGI-S at Week 12) will be examined to explore the consistency of the treatment effect across certain subgroups at Week 12. Subgroups, including but not limited to gender, race and age group, will be detailed in the SAP. For each subgroup, subgroup analysis will be conducted based on a similar MMRM model to the corresponding primary efficacy analysis with 3 additional terms: subgroup, treatment-by-subgroup interaction, and 3-way interaction of treatment*subgroup*visit. Summary statistics with 95% CIs will be provided by treatment group within each subgroup, as well.

15.4.2. Safety Analyses

Safety data including AEs, laboratory values, ECG, vital signs, weight, C-SSRS, and other assessments will be analyzed by treatment group based on the DB Safety population (for data up to the end of treatment period) and Withdrawal safety population (for data collected during the withdrawal period), separately, as appropriate.

The data (including CSSA, DESS, MADRS, and HAM-A), which are used to assess physical dependence and withdrawal symptoms, will be analyzed by treatment for data collected in the withdrawal period based on the Withdrawal safety population.

Unless otherwise specified, for continuous data collected in the withdrawal period, the actual value and change from Week 12/EOT (last value during the treatment period) will be summarized by treatment and visit.

15.4.2.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or higher.

The terms used in the CRFs by Investigators to identify adverse events.

An adverse event (AE) is defined as having a start date on or after the date of first dose through 7 days after study drug discontinuation (14 days for serious adverse events and deaths) for subjects who complete or discontinue this study but do not enter into the extension study), or through the last study day of the double-blind treatment period for subjects continuing into the extension study.

A discontinuation-emergent adverse event (DEAE) is defined as an AE with a start date after the date of last dose of study drug through the last study visit in the withdrawal period for subjects who either complete the 12-week treatment period but do not enter into the extension study, or for subjects who are terminated early in the treatment period.

The summary of overall AEs (and SAEs) will be limited to AEs and DEAEs.

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, serious study drug-related AEs, study drug-related AEs leading to discontinuation, and serious AEs leading to discontinuation, serious study drug-related AEs, will be summarized by treatment 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 PT, grouped by SOC, and presented by treatment group) also will be summarized by severity, by the relationship to study medication, by the action taken regarding the study medication, as well as by the outcome.

The overall incidence of DEAEs and serious DEAEs will be summarized by treatment group. The DEAEs also will be summarized by SOC and PT by presenting the number and percentage of subjects with each AE category.

The incidence of AEs of special interest, including but not limited to neuropsychiatric-related and cardiovascular-related AEs, will be summarized by treatment group.

15.4.2.2. Clinical Laboratory Assessments

Treatment Period

Laboratory data will be summarized by presenting descriptive statistics of actual values and changes from baseline and shift tables. The number and percentage of subjects with markedly

abnormal post-baseline values for selected parameters will be presented. Individual subject listings of laboratory data also will be provided.

The change from baseline value at endpoint for selected laboratory parameters (eg, hemoglobin A1c, fasting glucose, fasting total cholesterol, fasting triglycerides, fasting HDL cholesterol, fasting LDL cholesterol, fasting insulin, and hs-CRP) will be evaluated using an ANCOVA model with terms for treatment and baseline binge days group, and corresponding baseline as covariate or nonparametric rank ANCOVA, when appropriate.

Withdrawal Period

Laboratory data will be summarized by presenting descriptive statistics of actual values, change from baseline, and changes from Week 12/EOT by treatment.

15.4.2.3. Centrally-read ECG

Treatment Period

Standard 12-lead ECG parameters HR, PR interval, RR interval, QT interval, Bazett's corrected QT (QTcB) and Fridericia's corrected QT (QTcF) intervals, and QRS duration will be assessed. Results of each ECG parameter and their changes from baseline will be summarized by visit using descriptive statistics.

The number and percentage of subjects with markedly abnormal post-baseline ECG results will be summarized for the overall treatment period.

Withdrawal Period

Results for each ECG parameter, changes from baseline, and changes from Week 12/EOT will be summarized by treatment and visit using descriptive statistics.

15.4.2.4. Vital Signs, Weight, and BMI

Treatment Period

Vital signs parameters will be summarized by presenting descriptive statistics of actual values and change from baseline values. The number and percentage of subjects with markedly abnormal post-baseline values for selected parameters will be presented.

Descriptive statistics of actual value, and change and percent change from baseline value will be presented by treatment and study visit for weight and BMI. A similar MMRM model as for the primary efficacy variable (with the corresponding baseline) will be applied to compare dasotraline with placebo for the following safety variables:

- Change and percent change from baseline in body weight (kg) at Weeks 1, 2, 3, 4, 6, 8, 10, and 12.
- Change and percent change from baseline in BMI at Weeks 1, 2, 3, 4, 6, 8, 10, and 12.

Withdrawal Period

Vital signs parameters, weight, and BMI will be summarized by presenting descriptive statistics of actual values, change from baseline values, and change from Week 12/EOT by treatment and visit.

15.4.2.5. Neurological Examination

The number and percentage of neurological abnormalities will be summarized by visit and treatment. Shift from baseline to endpoint in neurological examinations will be presented by treatment.

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

The number and percentage of subjects with suicidal ideation, suicidal behavior, emergence or worsening of suicidal ideation or suicidal behavior will be summarized by treatment for overall post-baseline treatment period and for the withdrawal period, separately. Shift from baseline to any post-baseline in the treatment period (worst case) in suicidal ideation score will be presented by treatment.

15.4.2.7. Endpoints to Assess Physical Dependence and Withdrawal Symptoms during Withdrawal Period

CSSA total score, DESS total score, MADRS total score, and HAM-A total score will be summarized by presenting descriptive statistics of actual values and change from Week 12/EOT by treatment and visit for the withdrawal period.

15.4.2.8. Prior and Concomitant Medications

All medications will be coded using the World Health Organization drug dictionary (WHO-DD).

The prior medications will include medications taken before initiation and stopped prior to initiation of double-blind study medication. The concomitant medications will include medications taken after initiation of double-blind study medication that were either started prior to or after initiation of double-blind study medication.

The number and percentage of subjects taking prior and concomitant medication will be summarized by anatomical therapeutic chemical (ATC) classification and preferred name by treatment group.

15.4.3. Interim Analysis

No interim analysis is planned for this study.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL/DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results, electrocardiogram results, and IXRS data) will be recorded in the subject's electronic CRF. The study sites will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11, Medidata Rave[®]. The binge eating diary, SDS, MINI, SCID-I Module H, C-SSRS, EDE-Q, EDE-Q modified, MADRS, Y-BOCS-BE, BE-CGI-S, HAM-A, CSSA, and DESS will be completed on paper forms and then entered into the EDC system. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

16.2. Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 7: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Informed Consent	A
Informed Consent for PGx (optional)	A
Inclusion/Exclusion Criteria	A
Duplicate Enrollment Check	NA
CST Review	NA
Randomization	A, D
Dispense Study Drug	A, D
Study Drug Accountability	A
Demographics	A
Medical History	A
Psychiatric History	A
Physical Examination	A
Neurological Examination	A
Prior and/or Concomitant Medications	A
Mini International Neuropsychiatric Interview (MINI)	A

Table 7: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Structured Clinical Interview for DSM-IV Axis I Disorders, Module H (SCID-I Module H)	A
Eating Disorder Examination Questionnaire (EDE-Q)	A
Eating Disorder Examination Questionnaire (EDE-Q) modified	A
Binge eating diary training	NA
Binge eating diary	A
Binge-eating Clinical Global Impression-Improvement (BE-CGI-S)	A
Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE)	A
Montgomery-Asberg Depression Rating Scale (MADRS)	A
Sheehan Disability Scale (SDS)	A
Hamilton Anxiety Rating Scale (HAM-A)	A
Cocaine Selective Severity Assessment (CSSA)	A
Cocaine Selective Severity Assessment (CSSA) – Telephone contact	A
Discontinuation-Emergent Signs and Symptoms (DESS)	A
Discontinuation-Emergent Signs and Symptoms (DESS) – Telephone contact	A
Vital Sign Measurements	A
Height	A
Weight and body mass index (BMI)	A
12-lead electrocardiogram (ECG)	C
Columbia – Suicide Severity Rating Scale (C-SSRS)	A
Adverse Events	A
Serum chemistry	B
Lipid Panel	B
Hemoglobin A1c	B
Hematology	B
Urinalysis	B
Serum Pregnancy Test (in females of child-bearing potential)	B
Urine Pregnancy Test (in females of child-bearing potential)	A
Urine Drug Screen	A
Breath alcohol test	A
Blood sampling for plasma PK levels	B
Blood sampling for biomarkers	B

Table 7: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Blood sampling genotyping	B
Statistical analysis	SAS®, version 9.1.3 or higher

A = EDC (Medidata Rave®); B = LIMS; C = Core Lab Over-read; D = IXRS.

Abbreviations: CST = Clinical Surveillance Team; EDC = electronic data capture; IXRS = interactive response system; LIMS = laboratory information management system; NA = not applicable.

16.3. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with International Conference on Harmonization (ICH) Good Clinical Practice (GCP). On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.4. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of center facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center standard operating procedures (SOPs), protocol, ICH GCP, and local regulations. The principal investigator (PI) or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the IRB. Should the PI or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

16.5. Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft,

preliminary, and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.6. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis for most of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director's curricula vitae and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH GCP, ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the “Investigator Approval” page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license, current Drug Enforcement Agency [DEA] license, where applicable), and financial disclosure information. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on curriculum vitae.
- Appropriate diploma number stated on curriculum vitae.
- Copy of the diploma.

The Investigator must sign and return a completed Form FDA 1572 “Statement of Investigator” to Sponsor/CRO.

17.2. Institutional Review Board/Independent Ethics Committee

Documented approval for conducting the study from appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB/IEC chairman or designee identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB/IEC complies with the requirements in 21 CFR Part 56 for a study conducted under a US IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally

specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval. The Sponsor/CRO may submit informed consent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study medication, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject, and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent form must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm uphold the subjects confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

If any cases are identified where the subject's confidentiality has been breached, this must be rectified immediately. All subject identifiable information should be removed and the Sponsor notified.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately/within 5 business days of the occurrence, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before

the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

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19. INVESTIGATOR APPROVAL

I have read the protocol, SEP360-321, Version 3.00, “A 12-week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dosed, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Dasotraline in Adults with Moderate to Severe Binge Eating Disorder,” and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by the ECG vendor and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The site personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested for at least 10 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subject eligibility or continuance in the study.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the site for review and signature.
- The ECG tracing will be kept with subject's source documentation. The original ECG and the cardiologist's over-read will be retained at the site.

4. Data Standardization

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

21. APPENDIX II. CLINICAL LABORATORY TESTS

The following clinical laboratory tests are to be performed:

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)

Hemoglobin, Hematocrit, Platelet Count, red blood cell (RBC) Count, white blood cell (WBC) - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES:

Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

URINALYSIS:

Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

URINE DRUG SCREENING:

Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone, Tricyclic Antidepressants

LIPID PANEL:

Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, Triglycerides

OTHER TESTS:

Hemoglobin A1c, Insulin, hs-CRP, Breath Alcohol Test, Serum Pregnancy Test (β -hCG) (in female subjects of child-bearing potential only), Urine Pregnancy Test (in female subjects of child-bearing potential only).

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

22. APPENDIX III. PHARMACOKINETIC SAMPLING AND SAMPLE HANDLING GUIDELINE

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

All collection devices, labels, and requisitions will be provided by the central laboratory.

PK Plasma Samples

Collect the blood sample in a 4 mL Vacutainer® (or equivalent) tube for the preparation of plasma. The anticoagulant is lithium heparin for PK samples. Within 30 minutes of drawing blood, the blood sample will be centrifuged for 15 minutes at ca. $\times 2000$ g to isolate plasma at **ambient temperatures**. Transfer 2 aliquots of plasma into 2 prelabeled polypropylene tubes (PK-Set 1 and PK-Set 2). Store samples at -20°C freezer before shipping to the central laboratory (within 15 min of plasma transfer). Samples may be placed on dry ice prior to shipping, if the site does not have a -20°C freezer.

Blood (for PK plasma) samples will be collected from study subjects at the time points indicated in Table 8. Samples from subjects that receive placebo will not be analyzed.

Table 8: Schedule for Blood (for Plasma) for PK Analysis

Specimen	Week (Day)
Plasma (PK) (Anticoagulant: Lithium Heparin)	Week 2 (Day 14 \pm 2)
	Week 6 (Day 42 \pm 3)
	Week 12 (Day 84 \pm 1) or End of Treatment

Shipping:

PK-Set 1 and PK-Set 2 plasma samples will be shipped in 2 separate shipments to the appropriate Central Laboratory.

Refer to the LABORATORY Investigator Manual for additional collection instructions and detailed procedures.

23. APPENDIX IV. SAMPLING FOR POTENTIAL BIOMARKER ANALYSIS AND SAMPLE HANDLING GUIDELINES

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

BLOOD SAMPLES FOR POTENTIAL BIOMARKER ANALYSES

All collection devices, labels, and requisitions will be provided by the central laboratory.

Plasma Samples

Collect the blood sample in a 4-mL K₂EDTA Vacutainer[®] (or equivalent) tube for the preparation of plasma. The anticoagulant is ethylene diamine tetraacetic acid (EDTA) for plasma samples. Within **5 minutes** of drawing blood, the blood sample will be centrifuged for 15 minutes at ca. 1,000 – 1,200 g to isolate plasma at refrigerated conditions (recommended if available).

If the sample will not be centrifuged promptly, it must be kept on ice until it is centrifuged.

Transfer 2 aliquots of plasma into 2 prelabeled cryovials (PD-Plasma Set 1 and PD-Plasma Set 2) immediately after centrifugation.

Store samples at -70°C prior to shipping to the central laboratory (within 15 min of plasma transfer). If samples cannot be stored at -70°C, refer to the Laboratory Investigator Manual for appropriate storage and shipping instructions.

Serum Samples

Collect blood in a 4-mL serum separator tube and allow clotting for 30 to 60 minutes at room temperature before centrifugation. Within 1 hour of collection, centrifuge for 10 minutes at ca. 2,000 g. Transfer 2 aliquots of serum into 2 prelabeled cryovials (PD-Serum Set 1 and PD-Serum Set 2) immediately after centrifugation.

Store samples at -70°C prior to shipping to the central laboratory (within 15 min of serum transfer). If samples cannot be stored at -70°C, refer to the Laboratory Investigator Manual for appropriate storage and shipping instructions.

Blood (biomarker in plasma and serum) samples will be collected from study subjects at the time points indicated in Table 9.

Table 9: Schedule for Blood (Plasma and Serum) for Biomarker Analysis

Specimen	Week (Day)
Plasma (Anticoagulant: EDTA)	Baseline visit (Day -1)
Serum	Week 12 (Day 84 ±1) or End of Treatment

Shipping:

Shipment to the appropriate Central Laboratory of PD-Set 1 Plasma and Serum samples will be done separately from shipment of PD-Set 2 Plasma and Serum samples.

Refer to the LABORATORY Investigator Manual for additional collection instructions and detailed procedures.

24. APPENDIX V. PHARMACOGENETIC SAMPLING AND SAMPLE HANDLING GUIDELINES

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

BLOOD SAMPLES FOR PHARMACOGENETICS/PHARMACOGENOMICS

- A blood sample (approximately 4 mL) will be collected from each subject using a 4 mL Vacutainer® (or equivalent) collection tube containing EDTA as an anticoagulant.
- The tubes containing the blood sample will be labeled with a unique barcode (if possible), protocol number, subject number, and sample date of collection.
- The blood samples will be kept on wet ice during transfer and labeling.
- All blood samples will be stored in an upright position within 10 minutes of collection in a freezer set to maintain -70°C ($\pm 10^{\circ}\text{C}$) until shipment to the appropriate laboratory. If samples cannot be stored at -70°C , refer to the Laboratory Investigator Manual for appropriate storage and shipping instructions.
- Freeze samples for at least several hours before shipping to the appropriate laboratory.

25. APPENDIX VI. CLINICALLY RELEVANT CYP2B6 SUBSTRATES OR INDUCERS OR INHIBITORS (GENERIC NAMES)

The following drugs are prohibited during this study.

Substrate	Inhibitor	Inducer
artemisinin	clopidogrel	artemisinin
bupropion	thiotepa	carbamazepine
cyclophosphamide	ticlopidine	efavirenz
efavirenz	voriconazole	nevirapine
ifosfamide		phenobarbital
ketamine		phenytoin
meperidine		rifampin
methadone		
nevirapine		
propafol		
selegiline		
sorafenib		

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26. APPENDIX VII. ABUSE POTENTIAL MONITORING PLAN

Overview of Abuse Potential Monitoring Plan

Dasotraline is a new chemical entity being investigated for the treatment of Binge Eating Disorder (BED). Dasotraline is a diastereomer of the major metabolite of sertraline but is not a metabolite of sertraline, nor is it converted to the demethylated metabolite of sertraline in vivo. Dasotraline is a potent inhibitor of the reuptake of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) via the respective transporters SERT, NET, and DAT, with preferential inhibition of the dopamine transporter (DAT) and norepinephrine transporter (NET) relative to the serotonin transporter (SERT) without significant off-target activities. Clinical studies demonstrated central SERT occupancies in healthy subjects well below those attained at DAT, in addition decreases in 3,4-dihydroxyphenylglycol (DHPG) were observed, indicating central NET inhibition. This pharmacological profile warrants the implementation of an Abuse Potential Monitoring Plan, which surpasses the clinical monitoring, and adverse event (AE) reporting historically implemented in development programs for SSRIs.

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 will detect irregularities in the handling of dasotraline in clinical trials and identify 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 were identified based on the pharmacology of dasotraline, as well as adverse event profiles of compounds with similar mechanisms of action.

Procedure for Managing Medication Irregularities

Defining Threshold Criteria

The purpose of this procedure is to capture information about all medication-handling irregularities that meet the predefined threshold criteria. All instances meeting the medication irregularity threshold criteria will require a clinical risk assessment by the Investigator with classification of the nature of the irregularity. The Investigator will be required to complete Attachment A, the Medication Handling Irregularity (MHI) form in these situations.

For clinical trials utilizing dasotraline, we define the threshold criteria for medication irregularities as any one of the following:

- 10% or more of dispensed drug is either used in excess of prescribed dose or is unaccounted for; **and/or**
- Suspected abuse or diversion of dasotraline; **and/or**
- Suspected abuse of any other substance including alcohol, illicit substances, and over-the-counter (OTC) medications or prescription drugs.

Instances of Medication Irregularity

For all instances where the predefined threshold criteria are met covering medication irregularities, the Investigator must complete the Medication Handling Irregularity (MHI) form ([Attachment A](#)) and fax to the contact provided within 3 business days of its occurrence or discovery every time a threshold medication handling irregularity occurs. The contact will fax the completed MHI form to Sunovion within 1 business day of receipt and determine whether further action is warranted (ie, discontinuation of subject due to noncompliance with study protocol, education of the subject, etc.). [Attachment B](#) displays the process flow for handling medication irregularities. Any instance of medication irregularity may further be classified as an event subject to additional monitoring (ESAM).

The management of documented medication handling irregularities will be driven by the particular classification of the irregularity. As shown on Attachment A, items coded #1-3 describe situations of accounting errors and/or noncompliance with study procedures without evidence of study medication misuse or abuse of other substances. In these instances (code #1-3 on the MHI form), the Investigator will complete Attachment A and fax to the contact provided within 3 business days of knowledge of the irregularity.

Suspected or Known Abuse or Diversion of Study Medication

All cases of suspected or known abuse or diversion of study medication should be documented on the MHI form and coded #4. The Investigator will complete Attachment A and fax to the contact provided within 3 business days of knowledge of the irregularity. For all cases of medication irregularities coded as #4, the Investigator will attempt to obtain a urine drug screen from the subject, perform early termination procedures and discontinue the subject from the study.

Suspected or Known Abuse of Alcohol or Other Substances

The abuse of alcohol, illicit substances, OTC medication or prescription drugs while a subject is participating in a dasotraline clinical trial should be documented on the MHI form and coded #5. The Investigator will complete Attachment A and fax to the contact provided within 3 business days of knowledge of the irregularity. For all cases of medication irregularities coded as #5, the Investigator will attempt to obtain a urine drug screen from the subject, perform early termination procedures and discontinue the subject from the study.

Event Subject to Additional Monitoring (ESAM)

A key objective of the Abuse Potential Monitoring Plan is to monitor for instances of abuse or diversion of the study medication and other psychoactive substances. In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue, will also receive special attention. The following adverse experiences or related signs and symptoms may be associated with increased risk to subjects and will require additional monitoring. This list is a guide as to the types of events that require additional medical surveillance; it is not comprehensive and other events may be identified that require similar

medical surveillance. Subjects experiencing an event subject to additional monitoring may need to be discontinued from the study.

Table 10: Sample List of Events Subject to Additional Monitoring

Abuse and Dependence	Perceptual Effects
Drug dependence	Abnormal dreams
Drug abuse	Disinhibition
Dependence	Disorientation
Drug diversion	Dissociation
Intentional drug misuse	Feeling abnormal
Substance abuse	Hallucination (including auditory, olfactory, visual, etc.)
Mood Elevation Effects	Hyperaesthesia
Euphoric mood	Hypoaesthesia
Elevated mood	Illusion
Feeling drunk	Inappropriate affect
Sedative Effects	Mood altered
Apathy	Paraesthesia
Asthenia	Paranoia
Depressed level of consciousness	Psychotic Disorder
Fatigue	Sensory disturbance
Feeling of relaxation	Thinking abnormal
Hypokinesia	Cognitive/Motor Impairment
Indifference	Ataxia
Lethargy	Amnesia
Sedation	Aphasia
Sluggishness	Balance disorder
Somnolence	Clumsiness
Stimulant Effects	Cognitive disorder
Agitation	Confusional state
Aggression	Coordination abnormal
Anxiety	Disturbance in attention
Energy increased	Gait disturbance
Feeling jittery	Fine Motor Delay
Hypervigilance	Memory impairment
Insomnia	Mental impairment
Irritability	
Nervousness	
Psychomotor hyperactivity	
Restlessness	

Preparation of a Narrative for an Event Subject to Additional Monitoring (ESAM)

To ensure clarity and completeness of information, all Events Subject to Additional Monitoring will require the preparation of a narrative by the Investigator. This narrative will be reviewed by the medical monitor/sponsor/Investigator to determine if the subject should be discontinued from the study. A narrative summary template will be provided to the Investigators ([Attachment C](#)).

Handling of the Event Subject to Additional Monitoring (ESAM)

- Investigators will report all Events Subject to Additional Monitoring with narratives to the Medical Monitor within 24 hours ([Attachment C](#))
- The medical monitor will review all ESAM in real time and forward a copy of the report to the sponsors' Medical Director within one business day

Urine Drug Screens

The protocol incorporates exclusion criteria targeting individuals with a history of substance use disorders (eg, alcohol abuse or dependence and illicit drug abuse or dependence). The protocol includes urine drug screens at screening and at various post-randomization visits as well as providing the Investigator with the discretion to obtain random urine drug screens. Investigators will be directed to obtain urine drug screens in instances where there is known or suspected abuse of study medication and/or other substances.

ATTACHMENT A (Part 1 of 2) Medication Handling Irrregularity Instructions & Form**INSTRUCTIONS:****Medication Handling Irregularity Involving Subjects in Clinical Trials**

The form is designed to capture information about **threshold** medication handling irregularities to be used in clinical risk assessment. This form must be completed every time a threshold event occurs, within 3 business days of the event and FAXED or EMAILED to the INC medical monitor, Leslie Bauer at [1-919-882-0506](tel:1-919-882-0506) or SM_INCR_MedMon_Lab@incresearch.com.

FAX #: 1-919-882-0506

EMAIL: SM_INCR_MedMon_Lab@incresearch.com

Investigator Instructions For Each Event:

- INC's medical monitor must receive a completed Medication Handling Irregularity form by FAX or EMAIL within 3 business days of its occurrence or discovery every time a threshold medication handling irregularity occurs.
- Record any Adverse Event that was associated with, or resulted from, a medication handling irregularity, using the Electronic Case Report Form (Medidata).
- Information on concomitant medications must be recorded on the Concomitant Medication form in the electronic Case Report Form.

ATTACHMENT A (Part 2 OF 2) MEDICATION HANDLING IRREGULARITY FORM

Study No.: SEP360-321 Site No.: _____ Subject No.: _____

Date of Event Discovery: _____

Date of Event dd-mm-yyyy	Medication	Threshold	Strength of Medication	Number of Capsules

Please classify this medication handling irregularity by checking boxes 1 – 5.

- 1.
- ☐
- Drug accounting errors, not involving suspected abuse or diversion by subject.

Describe. (any missing/lost/not returned/unaccounted for blister cards/pills \geq 10% dispensed)

- 2.
- ☐
- Non-compliance with study procedures, not involving suspected abuse or diversion by subject.

Describe. (subjects who take \geq 10% more than the prescribed dose, in error)

- 3.
- ☐
- Other cases not involving suspected abuse or diversion of study drug by subject.

Describe. (other qualifying events not categorized by 1 or 2 above)

If only items 2 or 3 are checked, sign and date, and FAX or EMAIL this form to INC Research within 3 business days of its occurrence or discovery. FAX#: 1-919-882-0506 or EMAIL: SM_INCR_MedMon_Lab@incresearch.com

- 4.
- ☐
- Suspected or known abuse or diversion of study drug by subject. Please describe.

- 5.
- ☐
- Suspected abuse (nonmedical use) of alcohol, illicit substances, OTC drugs, or prescriptions obtained outside study protocol. Please describe.

If items 4 or 5 are checked, the investigator will:

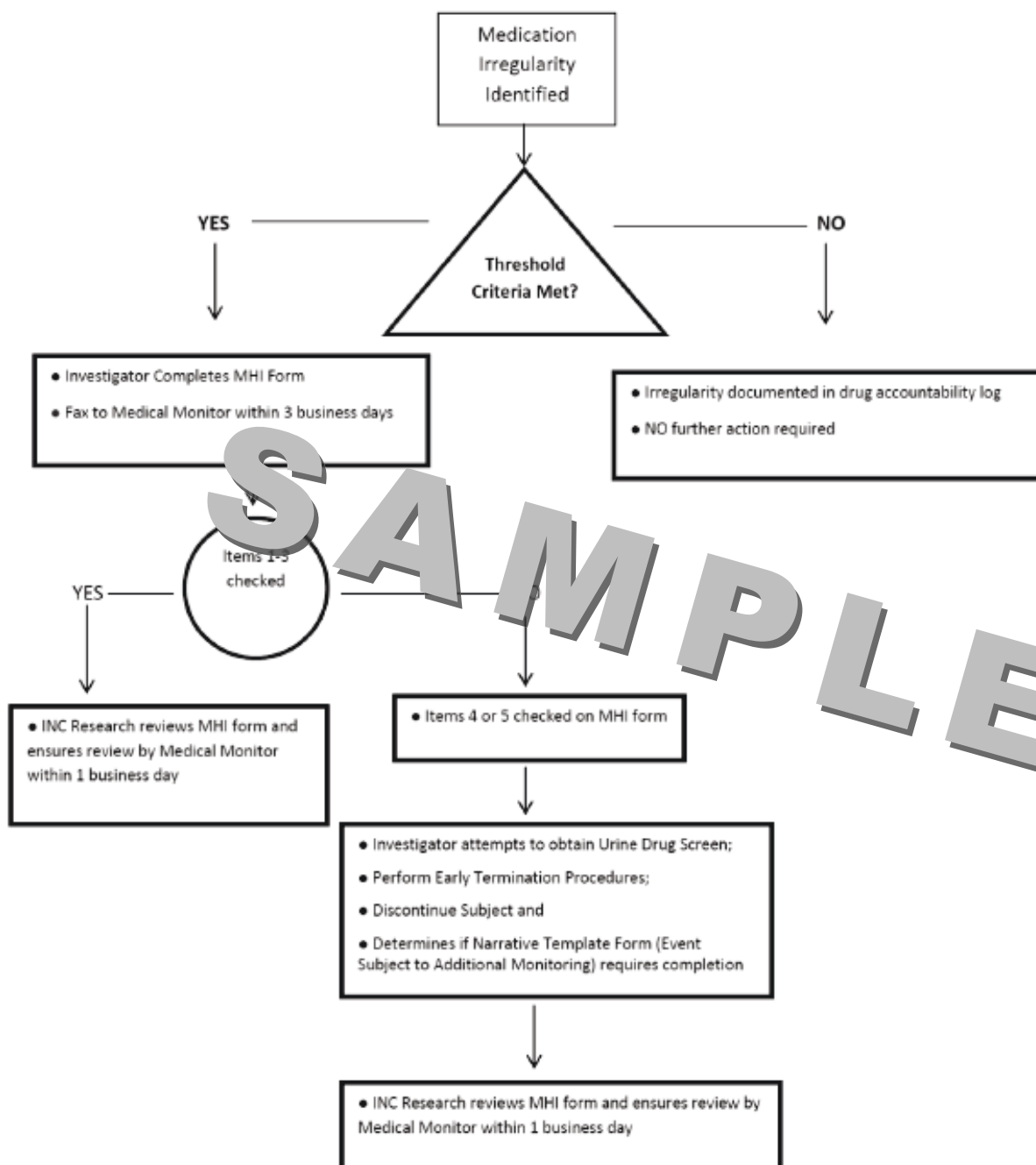
- 1) Obtain a Urine Drug Screen from the subject and document the results;
- 2) Complete Early Termination procedures, discontinue the subject from the trial;
- 3) FAX or EMAIL this form to Medical Monitor within 3 business days of its occurrence or discovery. FAX#: 1-919-882-0506 or EMAIL: SM_INCR_MedMon_Lab@incresearch.com

Investigator Signature _____

Printed Name _____

Date _____

**Please be sure to enter this data into the eCRF.

ATTACHMENT B MEDICATION HANDLING IRREGULARITY PROCESS FLOW

ATTACHMENT C EVENTS SUBJECT TO ADDITIONAL MONITORING NARRATIVE TEMPLATE FORM

Date: _____

Study No: SEP _____ Site No.: _____ Investigator Name: _____

Subject No.: _____ Subjects Initials: _____

Event term (verbatim from _____)

Coded term (from list): _____

Onset Date: _____ End Date: _____ Study Drug Start Date: _____

Related to Study Drug (Yes/No) _____ Requires Discontinuation (Yes/No) _____

Narrative description of event:

(Please use additional paper as needed – attach to this form)

Pertinent Concomitant Medications				
Drug Generic Name	Start Date	Ongoing (Y/N)	End Date	Indication

_____	_____	_____
Investigator Signature	Printed Name	Date

FAX or EMAIL to INC Research within 24 hours of site learning about ESAM.

FAX#: 1-919-882-0506 or EMAIL: SM_INCR_MedMon_Lab@incresearch.com

**Please be sure to enter this data into the eCRF.

27. APPENDIX VIII. BODY MASS INDEX DETERMINATION

Body mass index (BMI) will be calculated by measuring the subject's height and weight (both determined without subject wearing shoes) and using these measurements (in centimeters and kilograms) in the following formulae.

Formula:

$$BMI = weight (kg) \div height (m) \div height (m)$$

The entries in the following table list the BMI values for males and females of a given height and weight. Please note this table is not inclusive of all possible height and weight combinations.

Table 11: Body Mass Index (BMI) in kg/m^2 According to Height and Weight

[illegible]