DASOTRALINE (SEP-225289)

Protocol SEP360-322

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

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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 (SEP-225289)

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

Proposed Indication: Binge-eating Disorder

Study Centers: ~ 61 clinical sites in the United States

Planned Study Period: 35 months

Study Objectives:

Primary: To evaluate the long-term safety and tolerability of flexibly-dosed dasotraline (4, 6, or 8 mg/day) in adults with binge-eating disorder (BED) who have completed a prior dasotraline study in BED by:

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

Secondary:

- To assess potential withdrawal effects of dasotraline using the following assessments (administered during the withdrawal period):
  - Cocaine Selective Severity Assessment (CSSA)
  - Discontinuation-Emergent Signs and Symptoms (DESS) Scale
  - Symptoms of anxiety utilizing the Hamilton Anxiety Rating Scale (HAM-A)
  - Symptoms of depression utilizing the Montgomery-Asberg Depression Rating Scale (MADRS)
- To assess the abuse potential of dasotraline utilizing a comprehensive abuse potential monitoring plan (APMP)
- To evaluate the long-term effectiveness of flexibly-dosed dasotraline in the treatment of adults with BED as measured by the following:
  - Eating Disorder Examination Questionnaire (EDE-Q) modified
  - Binge-eating Clinical Global Impressions - Severity (BE-CGI-S)

– Sheehan Disability Scale (SDS) • To assess subject-reported health status using the Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12)[1]
Study Design: This is a Phase 3, 12-month, multicenter, open-label, flexibly-dosed, safety study in adults with BED. This study is projected to enroll approximately 500 subjects based on the number of subjects expected to complete treatment in the core studies (ie, SEP360-221 or SEP360-321). Informed consent will be obtained from all subjects after all procedures from the core study have been completed and before any study procedures unique to this study are performed. Safety and tolerability will be monitored throughout the study by AE reports, physical and neurological examinations, 12-lead ECG, vital signs, body weight, BMI, clinical laboratories (hematology, chemistry, urinalysis, hemoglobin A1c, and lipid panel), and C-SSRS. Effectiveness will be evaluated using the BE-CGI-S, EDE-Q modified, and SDS. Subject-reported health status will be assessed using the SF-12 (subjects from Study SEP360-221 only). Assessment of potential withdrawal effects of dasotraline will be conducted via administration of the CSSA, DESS, HAM-A, and MADRS at the end of treatment and during the 3-week study medication withdrawal period. A comprehensive Abuse Potential Monitoring Plan (APMP; see Section 24) for dasotraline designed to detect potential abuse of the compound and to more closely monitor AEs consistent with the known pharmacology for dasotraline will be implemented. An independent Data and Safety Monitoring Board (DSMB) will review safety data including data on adverse events (AEs) and serious adverse events (SAEs) at regular intervals. Subjects will self-administer study drug on an outpatient basis for 12 months, once a day at approximately the same time each morning with or without food, including on the days when clinic visits occur. Subjects meeting all inclusion and no exclusion criteria will start taking open-label study drug on Day 1, the morning following the OL Baseline visit (ie, Week 12 visit in the core study). The total daily dose will remain between 4 mg/day and 8 mg/day for the 12-month treatment period. Dasotraline will be dosed at 4 mg/day for the first 2 weeks of the study. At the Week 2 visit, the dose may be increased to 6 mg/day. Thereafter the dose may be increased or decreased by 2 mg/day, as necessary for effectiveness or tolerability reasons at the discretion of the investigator. A minimum of 8 days is required between dose increases. Dose decreases may be made at less than 8 day intervals, at the investigator's discretion, for reasons of safety or tolerability. If, in the judgment of the investigator, the subject does not tolerate the minimum required dose (4 mg/day), he or she will be discontinued from the study. All changes in study drug dose will begin the morning after the visit at which the dose change decision is made and using the new package of study drug. The study will consist of a baseline visit, 12-month open-label treatment period, and 3-week study drug withdrawal period as shown in the Study Schematic (Figure 1). During the treatment period, subjects will return to the clinic at the end of 2 and 4 weeks for clinical evaluation and thereafter will return to the clinic once every 4 weeks during the treatment period for scheduled visits. At the approximate midpoint between the scheduled monthly visits (ie, 14 ± 2 days after a visit), the site staff will contact the subject via telephone, text, or email in order to monitor for SAEs, AEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration, and upcoming visits. If necessary, an unscheduled visit can be arranged.

[1] SF-12 collected only for subjects enrolling in this study after completing core Study SEP360-221.

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

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

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

Number of Subjects (planned): This study is projected to enroll approximately 500 subjects based on the number of subjects expected to complete treatment in the core studies.

Diagnosis and Main Criteria for Subject Inclusion:

Inclusion Criteria:

1. Completion of the treatment period of a dasotraline core study (ie, SEP360-221 or SEP360-321) for the treatment of BED.
2. Subject has agreed to participate by providing written informed consent and is willing and able to comply with the protocol, in the opinion of the investigator.
3. Subject has not taken any medication other than the study drug for the purpose of controlling BED symptoms during the core study.
4. Female subject must have a negative urine pregnancy test at open-label (OL) Baseline; 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.
5. 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 22, Appendix III) 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.
6. Subject is judged by the investigator to be suitable for participation in a 12-month clinical trial involving open-label dasotraline treatment.
7. Subject can read well enough to understand the informed consent form and other subject materials.

Exclusion Criteria:

1. Subject is considered by the investigator to be at imminent risk of suicide, injury to self or to others, or damage to property.
2. Subject is considered a suicide risk in the investigator's opinion or has any previous history of suicide attempt within the past 12 months.
3. 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 OL Baseline. Subjects who answer "yes" to this question must be referred to the Investigator for follow-up evaluation.

4. Subject has a clinically significant abnormality including physical examination, vital signs, ECG, or laboratory tests that the investigator in consultation with the medical monitor considers to be inappropriate to allow participation in the study.
5. Subject has a positive urine drug screen (UDS) or breath alcohol test at OL Baseline.
6. Subject is breastfeeding.
7. Subject is at high risk of non-compliance in the investigator's opinion.

Investigational Product, Dosage and Mode of Administration:

Dasotraline 4 mg, 6 mg, and 8 mg capsules for oral administration will be supplied. Based on the flexible dosing schedule, 1 capsule of dasotraline 4 mg, 6 mg, or 8 mg will be taken once daily, at approximately the same time each morning with or without for food. Following the initial 2 weeks at 4 mg, subjects will be flexibly dosed at 4, 6, or 8 mg/day for the duration of the study.

Dose schedule and adjustment are described above under Study Design.

Duration of Treatment: 12 months

Reference Therapy, Dosage and Mode of Administration: Not applicable

Concomitant Medications:

Use of certain medications, including but not limited to the following, is prohibited throughout the study from open-label baseline through the 3-week study medication withdrawal period:

- psychostimulants
- any medications for the treatment of binge eating or other eating disorders, obesity, or weight gain
- antidepressant medications (eg, bupropion, SSRI/SNRI, Monoamine oxidase [MAO] inhibitor, tricyclic) and St. John's Wort
- medications that are CYP2B6 substrates or inhibitors or inducers of CYP2B6, eg, bupropion, cyclophosphamide, carbamazepine, etc (see Section 23, Appendix IV)
- medications for the treatment of attention deficit hyperactivity disorder (ADHD)
- corticosteroids except as noted in Section 10.3.3 and anabolic steroids
- antiepileptic medications
- benzodiazepines except for sleep or anxiety
- mood stabilizers (eg, lithium, anticonvulsants)
- antipsychotic medications
- suvorexant
- any medication that can result in either weight gain or weight loss (eg, insulin, liraglutide, diphenhydramine except topical formulations, etc) including over-the-counter and herbal products

Use of concomitant medications permitted during the study include, but are not limited to, sleep aids (with some restrictions), anxiety (with some restrictions), oral contraceptives, and limited use of

opiates.

Other Restrictions: Participation in non-pharmacologic therapy such as supportive psychotherapy, cognitive behavioral therapy or interpersonal therapy is permitted and should be documented by the investigator, to the extent possible. Any participation in a formal weight loss program such as Weight Watchers® is prohibited throughout the study.

See Section 10.3 for complete information on concomitant medications and therapies permitted during the study.

Study Endpoints:

Safety Endpoints:

- The incidence of overall AEs, serious AEs (SAEs), and AEs (or SAEs) leading to discontinuation
- Clinical laboratory evaluations (serum chemistry, hematology, urinalysis)
- Clinical evaluations (vital signs including orthostatic effects, and 12-lead ECGs)
- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS
- Change and percent change in body weight and BMI
- Change in fasting lipid panel (triglycerides, total cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol)
- Change in hemoglobin A1c levels
- Change in fasting glucose levels
- Change in the symptoms of withdrawal from dasotraline from Week 52/EOT as measured by:
  - CSSA total score at Weeks 53, 54, and 55
  - DESS total score at Weeks 53, 54, and 55
  - HAM-A total score at Weeks 53, 54, and 55
  - MADRS total score at Weeks 53, 54, and 55

Effectiveness Endpoints:

- Change in EDE-Q modified global score and subscale scores (restraint, shape concern, weight concern), and Items 4-6 scores
- Change in BE-CGI-S score
- Change in SDS total score and subscale scores (school/work disability, social life disability, and family life disability)

Subject-reported Health Status Endpoints:

- Change in SF-12 two component scores (physical component, mental health component)[2]

Statistical Methods:

The safety population will include all subjects who receive at least one dose of study medication. A total of 2 analysis groups will be formed based on a subject's previous participation in the core study (previously randomized to dasotraline, previously randomized to placebo). A group that combines these 2 analysis groups also will be presented. Summary tables, wherever applicable, will be presented by analysis group, respectively. Where changes are reported, the reference will be to the pretreatment baseline from the core study, and indicated as "DB baseline". Where relevant, changes from baseline for the open-label study, defined as the Week 12 assessment in the double-blind study or the last assessment prior to the first dose of study medication in the open-label study, will also be reported, and will be referred to as the open-label study baseline or "OL baseline." Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, range, 95% confidence interval [CI] as needed) and categorical variables will be reported as frequencies and percentages. No statistical comparisons will be conducted and no inferential statistics on effectiveness and safety will be presented.

Safety Analyses: The safety data will be analyzed by analysis group based on the safety population for the open-label treatment period (for data up to the end of treatment period) and withdrawal period (for data collected during the withdrawal period), separately, as appropriate.

Treatment-emergent adverse event (TEAE) and discontinuation-emergent adverse events (DEAE) will be summarized (hereafter TEAE is referred as AE). The incidence of AEs, SAEs, and AEs leading to discontinuation due to AEs (or SAEs) will be summarized by analysis group (by presenting the number and percentage of subjects with one or more AEs in each category). The number and proportion of subjects with one or more AEs within a system organ class (SOC) or by preferred term will be presented by analysis group as well.

For laboratory tests (hematology, chemistry, urinalysis, lipid panel, hemoglobin A1c), weight, BMI, vital signs, neurological examination, and ECG parameters, descriptive statistics will be provided for observed values and changes from DB baseline and OL baseline for the continuous variables. Frequencies and percentages will be reported for categorical variables by study visit and analysis group. The markedly abnormal values for selected safety parameters will be summarized, as appropriate.

The number and percentage of subjects with suicidal ideation and/or suicidal behavior, emergence or worsening of suicidal ideation or suicidal behavior will be summarized by analysis group for the open-label treatment period, and the withdrawal period, separately.

The CSSA total score, DESS total score, MADRS total score, and HAM-A total score will be summarized by presenting descriptive statistics of observed values and changes from Week 52/EOT by treatment and visit for the withdrawal period.

Analyses for Effectiveness and Subject-reported Health Status: Descriptive statistics of observed values and changes from DB baseline and OL baseline in BE-CGI-S score, EDE-Q modified global and subscale scores (restraint, shape concern, weight concern), EDE-Q modified items 4-6 scores, SDS total score and subscale scores (school/work disability, social life disability, and family life disability), and SF-12 (subjects from Study SEP360-221) two component scores (physical component, mental

[2] SF-12 collected only for subjects enrolling in this study after completing core Study SEP360-221.

health component) will be summarized by visit and analysis group.

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

Table 2: Schedule of Assessments

Procedures		Treatment Period									
	V1E	V2E	V3E	V4E	V5E	V6E	V7E	V8E	V9E	V10E	V11E
	OL BSN[a]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36
	Day -1	Day 14 ± 3	Day 28 ± 3	Day 56 ± 3	Day 84 ± 3	Day 112 ± 3	Day 140 ± 3	Day 168 ± 3	Day 196 ± 3	Day 224 ± 3	Day 252 ± 3
Informed Consent[c]	X										
Inclusion/Exclusion Criteria	X										
Dispense Study Drug[c]	X	X	X	X	X	X	X	X	X	X	X
Study Medication Accountability		X	X	X	X	X	X	X	X	X	X
Between visit contact[d]			At the approximate midpoint between Visits 3E and 4E, Visits 4E and 5E, Visits 5E and 6E, Visits 6E and 7E, Visits 7E and 8E, Visits 8E and 9E, Visits 9E and 10E, Visits 10E and 11E, and Visits 11E and 12E.								
Demographics	X										
Physical Examination	X (carried over)				X			X			
Neurological Examination	X (carried over)							X			
Prior and Concomitant Medications	X (carried over)	X	X	X	X	X	X	X	X	X	X
Binge-eating Clinical Global Impressions of Severity (BE-CGI-S)	X (carried over)		X	X	X	X	X	X	X	X	X
Eating Disorder Examination Questionnaire (EDE-Q) modified	X[l]		X	X	X	X	X	X	X	X	X
Sheehan Disability Scale (SDS)	X (carried over)				X			X			X

Table 2: Schedule of Assessments (Continued)

		Treatment Period									
	V1E	**V2E**	**V3E**	**V4E**	**V5E**	**V6E**	**V7E**	**V8E**	**V9E**	**V10E**	**V11E**
	OL BSN[a]	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**
Procedures	**Day -1**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 56 ± 3**	**Day 84 ± 3**	**Day 112 ± 3**	**Day 140 ± 3**	**Day 168 ± 3**	**Day 196 ± 3**	**Day 224 ± 3**	**Day 252 ± 3**
Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12) for subjects from Study SEP360-221 only	X (carried over)				X			X			X
Vital Sign Measurements	X (carried over)	X	X	X	X	X	X	X	X	X	X
Weight and Body Mass Index	X (carried over)	X	X	X	X	X	X	X	X	X	X
Height	X (carried over)										
Adverse Events	X (carried over)	X	X	X	X	X	X	X	X	X	X
Serum chemistry[f]	X (carried over)				X			X			X
Lipid panel[f]	X (carried over)				X			X			X
Hemoglobin A1c	X (carried over)				X			X			X
Hematology	X (carried over)				X			X			X
Urinalysis	X (carried over)				X			X			X
Columbia – Suicide Severity Rating Scale (C-SSRS)[g]	X (carried over)	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Assessments (Continued)

		Treatment Period									
	V1E	**V2E**	**V3E**	**V4E**	**V5E**	**V6E**	**V7E**	**V8E**	**V9E**	**V10E**	**V11E**
	OL BSN[a]	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**
Procedures	**Day -1**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 56 ± 3**	**Day 84 ± 3**	**Day 112 ± 3**	**Day 140 ± 3**	**Day 168 ± 3**	**Day 196 ± 3**	**Day 224 ± 3**	**Day 252 ± 3**
Hamilton Anxiety Rating Scale (HAM-A)[h]	X (carried over)							X			
Montgomery-Asberg Depression Rating Scale (MADRS)[i]	X (carried over)							X			
Cocaine Selective Severity Assessment (CSSA)[j]											
Discontinuation-Emergent Signs and Symptoms (DESS) Scale[j]											
Urine Pregnancy Test[k] (females of child-bearing potential only)	X (carried over)		X		X		X		X		X
Urine Drug Screen	X (carried over)		X		X		X		X		X
Breath Alcohol Test	X (carried over)		X		X		X		X		X
12-Lead Electrocardiogram (ECG)	X (carried over)		X		X			X			X

Table 2: Schedule of Assessments (Continued)

Procedures	Treatment Period				Withdrawal Period		
	V12E	V13E	V14E	V15E/EOT	V16E	V17E	V18E/EOS
	Week 40	Week 44	Week 48	Week 52[b]	Week 53	Week 54	Week 55
	Day 280 ± 3	Day 308 ± 3	Day 336 ± 3	Day 364 ± 1	Day 371 ± 1	Day 378 ± 1	Day 385 ± 1
Informed Consent[c]							
Inclusion/Exclusion Criteria							
Dispense Study Drug[c]	X	X	X				
Study Medication Accountability	X	X	X	X			
Between visit contact[d]	At the approximate midpoint between Visits 12E and 13E, Visits 13E and 14E, and Visits 14E and 15E.						
Demographics							
Physical Examination				X			X
Neurological Examination				X			X
Prior and Concomitant Medications	X	X	X	X	X	X	X
Binge-eating Clinical Global Impressions of Severity (BE-CGI-S)	X	X	X	X	X	X	X
Eating Disorder Examination Questionnaire (EDE-Q) modified	X	X	X	X			
Sheehan Disability Scale (SDS)				X			X
Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12) for subjects from Study SEP360-221 only				X			X
Vital Sign Measurements	X	X	X	X	X	X	X
Weight and Body Mass Index	X	X	X	X	X	X	X
Height							
Adverse Events	X	X	X	X	X	X	X
Serum chemistry[f]				X			X
Lipid panel[f]				X			X
Hemoglobin A1c				X			X
Hematology				X			X

Table 2: Schedule of Assessments (Continued)

Procedures	Treatment Period				Withdrawal Period		
	V12E	V13E	V14E	V15E/EOT	V16E	V17E	V18E/EOS
	Week 40	Week 44	Week 48	Week 52[b]	Week 53	Week 54	Week 55
	Day 280 ± 3	Day 308 ± 3	Day 336 ± 3	Day 364 ± 1	Day 371 ± 1	Day 378 ± 1	Day 385 ± 1
Urinalysis				X			X
Columbia – Suicide Severity Rating Scale (C-SSRS)[g]	X	X	X	X	X	X	X
Hamilton Anxiety Rating Scale (HAM-A)[h]				X	X	X	X
Montgomery-Asberg Depression Rating Scale (MADRS)[i]				X	X	X	X
Cocaine Selective Severity Assessment (CSSA)[j]				X	X	X	X
Discontinuation-Emergent Signs and Symptoms (DESS) Scale[j]				X	X	X	X
Urine Pregnancy Test[k] (females of child-bearing potential only)	X	X	X	X			X
Urine Drug Screen		X		X			X
Breath Alcohol Test		X		X			X
12-Lead Electrocardiogram (ECG)				X	X	X	X

Abbreviations: BSN = baseline; EOS = End of Study; EOT = End of Treatment; OL = open label; V = visit

[a] Week 12 in core study. Baseline assessments indicated as "carried over" are primarily performed as part of Week 12 visit in the core study and do not need to be repeated; the data will be duplicated from Week 12 visit or other visits (such as for height) in the core study.

[b] Subjects who discontinue from the study prior to completion of treatment with study drug will be asked to return to the site and complete the EOT assessments within 1 day of discontinuation and complete the Withdrawal Period visits and calls.

[c] Subjects will take the first dose of study drug in this study on Day 1 (the morning following the baseline visit); there will be no break in study drug treatment between the core study and this extension study. All study drug will be administered by the subject once a day at approximately the same time each morning including on the days when clinic visits occur.

[d] At the approximate midpoint between the scheduled monthly treatment period visits (ie, 14 ± 2 days after a visit), the site staff will contact the subject via telephone, text, or email to monitor for SAEs, AEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration and upcoming visits, following which an unscheduled visit may be scheduled, if necessary.

Footnotes continued on the next page.

[e] Informed consent will be obtained from all subjects after all procedures from the core study have been completed and before any study procedures unique to this study are performed.
[f] Subjects must be fasting for at least 8 hours (may have water) prior to the indicated laboratory tests. Visits should be scheduled in the morning.
[g] The "Since Last Visit" version will be used. 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 any time during the study must be referred to the Investigator for follow up evaluation.
[h] The Structured Interview Guide for the HAM-A (SIGH-A) will be used for the administration of the HAM-A.
[i] The Structured Interview Guide for the MADRS (SIGMA) will be used for the administration of the MADRS.
[j] 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, as necessary.
[k] Any positive urine β-hCG test should be confirmed by serum β-hCG.
[l] Carried over for subjects enrolling in this study from SEP360-321 and collected for subjects enrolling in this study from SEP360-221.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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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
AE	Adverse event
ADHD	Attention deficit hyperactivity disorder
APMP	Abuse Potential Monitoring Plan
BE-CGI-S	Binge-eating Clinical Global Impression-Severity
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CR	Controlled release
CRF	Case report form
CRO	Clinical research organization
C-SSRS	Columbia-suicide severity rating scale
CSSA	Cocaine Selective Severity Assessment
CTM	Clinical trial material
DA	Dopamine
DAT	Dopamine transporter
DB	Double-blind
DEA	Drug Enforcement Agency
DEAE	Discontinuation-emergent adverse event
DESS	Discontinuation-Emergent Signs and Symptoms
DHPG	3,4-dihydroxyphenylglycol
DMP	Data Management Plan
DNRI	Dopamine and norepinephrine reuptake inhibitor
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
EDE-Q Modified	Eating Disorder Examination Questionnaire Modified
EOT	End of treatment
ESAM	Event subject to additional monitoring
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
5-HT	5-hydroxytryptamine (serotonin)
HAM-A	Hamilton Anxiety Rating Scale
HDL	High-density lipoprotein (cholesterol)
HEENT	Head, ears, eyes, nose and throat
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IXRS	Interactive Response System
LDL	Low-density lipoprotein (cholesterol)
MADRS	Montgomery-Asberg Depression Rating Scale
MAO	Monoamine oxidase
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication Handling Irregularity
MRI	Magnetic resonance imaging
NE	Norepinephrine
NET	Norepinephrine transporter
OL	Open-label
OTC	Over-the-counter (medications)

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
PET	Positron emission tomography
PK	Pharmacokinetic(s)
POC	Point of care
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
RR	RR interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Sheehan disability Scale
SERT	Serotonin transporter
SF-12	Medical Outcomes Study 12-Item Short Form
SIGH-A	Structured Interview Guide for the HAM-A
SIGMA	Structured Interview Guide for the MADRS
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
UDS	Urine drug screen
US	United States
USP	United States Pharmacopeia
VAS	Visual analog scale
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

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.
Open-label Treatment Period	The period of the study in which the study drug is administered.
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 excess 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

Nonclinical 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.

Nonclinical 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 accumbens that form part of the reward circuit (van de Giessen-2012, van de Giessen-2013). Knockout of striatal dopamine D_2 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 nonclinical studies of drug abuse, reduced availability of dopamine D_2 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 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 D_2 receptors in the striatum (Murray-2014, Smith-2013). Down regulation of dopamine D_2 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 higher binge eating scores (Wang-2011). Additional PET studies have shown negative correlations between impulsivity and availability of dopamine $D_{2/3}$ receptors in the striatum and midbrain of humans (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 these studies show that a dysregulated dopaminergic driven reward circuit is critical to the symptomology associated with BED and suggest that therapies targeting this system may be 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. 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 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 efficacy results supported United States Food and Drug Administration (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 ADHD, blocks pre-synaptic DAT and 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 dopamine and norepinephrine reuptake inhibitor (DNRI). Dasotraline has a long time to maximum concentration ($t_{max;}$ reaches maximum concentrations approximately 10 to 12 hours after dosing) and mean apparent half-life (47.1 to 77.0 hours).

A nonclinical 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 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.

A recently completed clinical study supports dasotraline as a potentially safe and efficacious treatment option for adults with ADHD (Koblan-2015). Clinically meaningful and statistically significant treatment effects were observed at 8 mg/day. Consistent with DNRI pharmacology, the most frequent adverse events reported in the study were insomnia, decreased appetite, and dry mouth. In addition, significant dose dependent decreases were observed in appetite and weight loss. A review of previously published trials for BED suggests that decreases in appetite and weight loss are strongly associated with a reduction in binge eating frequency (Appolinario-2003, Grilo-2005, McElroy-2003B, McElroy-2006, McElroy-2007, McElroy-2012). Administration in over 1000 adult subjects in completed and ongoing studies supports the safety of dasotraline for continued evaluation.

Use of dasotraline as a potential treatment for BED is supported by research that suggests pharmacotherapies that target one or more of the neurotransmitter systems (including dopamine and norepinephrine) that have been implicated in the pathogenesis of BED may play a critical role in its management. The centrally acting effects of dasotraline on dopamine and

norepinephrine uptake combined with the results from the SEP360-201study, and the rat model study of binge eating provide further support to evaluate dasotraline as a treatment for BED.

The initial 12-week study SEP360-221 evaluates dasotraline flexibly dosed at 4, 6, or 8 mg/day and the 12-week study SEP360-321 evaluates dasotraline fixed doses of 4 or 6 mg/day as a potential treatment for BED. The current study evaluates long term safety and efficacy of dasotraline as a treatment for BED and will enroll subjects who complete treatment in Study SEP360-221 or Study SEP360-321.

4.3. Risk-Benefit Assessment

Overall, in previous clinical studies dasotraline was generally safe and well tolerated. The pharmacokinetic (PK) and safety profiles observed in adults from completed clinical studies support evaluation of dose levels of 4 – 8 mg/day in adults with BED.

Most adverse events in completed clinical studies were mild to moderate in intensity, and included headache, dizziness, insomnia, tachycardia, and nausea. Dose dependent increases in the incidence of insomnia and weight loss were observed, consistent with DNRI pharmacology. A total of 13 serious adverse events (SAEs) have been reported in 9 subjects receiving dasotraline. Across the 8 completed clinical studies evaluating dasotraline, the rate of discontinuations as a result of treatment-emergent adverse events (TEAEs) was low. The highest rate of discontinuations due to TEAEs was in the SEP360-201 adult ADHD study (11.2% and 29.7% of subjects treated with dasotraline 4 and 8 mg/day, respectively), primarily due to insomnia. In general, the side-effect profile of dasotraline, based on available data, appears comparable with other medications used in the treatment of ADHD and suggests it may be well tolerated in patients with BED. A flexible dose design to reach the 8 mg dose will be implemented in this study to facilitate management of safety and tolerability issues.

The results from the human abuse liability study indicate dasotraline has minimal abuse potential and is unlikely to be recreationally abused. All doses of dasotraline (8, 16, 36 mg) demonstrated significantly lower drug liking scores than methylphenidate (40, 80 mg) and were no greater than placebo. The most frequently reported abuse potential adverse events were insomnia and dizziness in subjects with major depressive disorder (MDD) and insomnia and suicidal ideation in adults with ADHD. 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 a comprehensive Abuse Potential Monitoring Plan (APMP) for dasotraline designed to detect potential abuse of the compound and to more closely monitor adverse events (AEs) consistent with the pharmacology of the compound will be implemented for this study (Section 24, Appendix V).

Additionally, a Data and Safety Monitoring Board (DSMB) will be established for this study. The DSMB will review safety data including AEs and SAEs at regular intervals.

Results from the adult ADHD study and the rat model of binge-eating combined with dasotraline's DNRI pharmacology, and extended PK profile suggest dasotraline may prove safe and efficacious in the treatment of patients with BED. Although drugs targeting disturbances in dopaminergic transmission may translate to therapeutic benefit in BED, the efficacy and safety of dasotraline in this indication is currently being evaluated.

5. STUDY OBJECTIVES

5.1. Primary Objectives

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

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

5.2. Secondary Objectives

The secondary objects are:

- To assess potential withdrawal effects of dasotraline using the following assessments (administered during the withdrawal period):
  - Cocaine Selective Severity Assessment (CSSA)
  - Discontinuation-Emergent Signs and Symptoms (DESS) Scale
  - Symptoms of anxiety utilizing the Hamilton Anxiety Rating Scale (HAM-A)
  - Symptoms of depression utilizing the Montgomery-Asberg Depression Rating Scale (MADRS)
- To assess the abuse potential of dasotraline utilizing a comprehensive abuse potential monitoring plan (APMP)
- To evaluate the long-term effectiveness of flexibly-dosed dasotraline in the treatment of adults with BED as measured by the following:
  - Eating Disorder Examination Questionnaire (EDE-Q) modified
  - Binge-eating Clinical Global Impressions - Severity (BE-CGI-S)
  - Sheehan Disability Scale (SDS)
- To assess subject-reported health status using the Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12)[3]

[3] SF-12 collected only for subjects enrolling in this study after completing core Study SEP360-221.

6. STUDY ENDPOINTS

6.1. Safety Endpoints

The safety endpoints include:

- The incidence of overall AEs, serious AEs, and AEs or SAEs leading to discontinuation
- Clinical laboratory evaluations (serum chemistry, hematology, urinalysis)
- Clinical evaluations (vital signs including orthostatic effects, and 12-lead ECGs)
- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS
- Change and percent change in body weight and BMI
- Change in fasting lipid panel (triglycerides, total cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol)
- Change in hemoglobin A1c levels
- Change in fasting glucose levels
- Change in the symptoms of withdrawal from dasotraline from Week 52/end of treatment (EOT) as measured by
  - CSSA total score at Weeks 53, 54, and 55
  - DESS total score at Weeks 53, 54, and 55
  - HAM-A total score at Weeks 53, 54, and 55
  - MADRS total score at Weeks 53, 54, and 55

6.2. Effectiveness Endpoints

The effectiveness endpoints include:

- Change in EDE-Q modified global score, subscale scores (restraint, shape concern, weight concern), and Items 4-6 scores
- Change in BE-CGI-S score
- Change in SDS total score and subscale scores (school/work disability, social life disability, and family life disability)

6.3. Subject-reported Health Status Endpoints

The subject-reported health status endpoints include:

- Change in SF-12 two component scores (physical component, mental health component)[4]

[4] SF-12 collected only for subjects enrolling in this study after completing core Study SEP360-221.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

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

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

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

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

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

All changes in study drug dose will begin the morning after the visit at which the dose change decision is made and using the new package of study drug.

The study will consist of a baseline visit, 12-month open-label treatment period, and 3-week study drug withdrawal period as shown in the Study Schematic (Figure 1). During the treatment period, subjects will return to the clinic at the end of 2 and 4 weeks for clinical evaluation and thereafter will return to the clinic once every 4 weeks during the treatment period for scheduled visits. At the approximate midpoint between the scheduled monthly visits (ie, 14 ± 2 days after a

visit), the site staff will contact the subject via telephone, text, or email in order to monitor for SAEs, AEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration, and upcoming visits. If necessary, an unscheduled visit can be arranged.

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

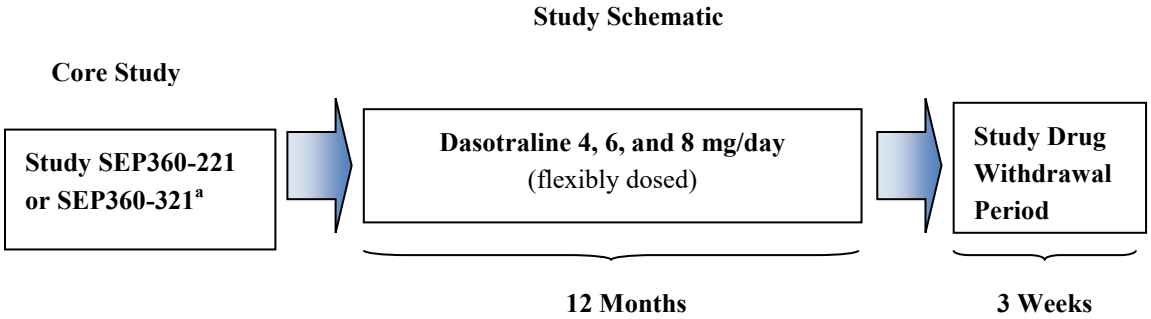
A window of ± 1 day will be allowed for each weekly clinic visit and telephone call during the study medication withdrawal period.

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

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2, Schedule of Assessments, and Section 11, Study Assessments.

If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic



[a] There will be no break in study drug treatment between the core study and this extension study.

7.2. Treatment Assignment and Blinding

This is a non-randomized open-label study. All subjects receive flexibly-dosed dasotraline (4, 6, or 8 mg/day).

7.3. Rationale

7.3.1. Rationale for the Study Design

This is an open-label study to evaluate the long-term safety and effectiveness of flexibly-dosed dasotraline consistent with the intended long-term use of the compound in this population.

7.3.2. Rationale for the Dosages

The dosages to be used in this study (4, 6, or 8 mg/day) are the same as those administered in the core study SEP360-221. Doses of 4 and 6 mg are administered in the core study SEP360-321.

7.3.3. Rationale for the Study Population

Subjects in this study will have met BED eligibility requirements in the core study and not have taken any medication other than study drug for the purpose of controlling BED symptoms during the core study.

7.3.4. Rationale for the Endpoints

The safety assessments and their timing are considered appropriate to assess the long-term safety of dasotraline, taking into account known pharmacology and adverse events based on previous studies. The symptom, functional, and quality of life assessments were selected to assess the potential effectiveness of dasotraline on these parameters.

7.3.5. 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 2 weeks for the first month, every 4 weeks for the remainder of treatment, and every week during the study drug withdrawal period, (ii) during the treatment period a window of ± 3 days for each bi-weekly or monthly clinic visit and a window of ± 1 day for each weekly clinic visit starting at Week 52, (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, and (iv) monitoring of data collection for adherence during the study.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

A subject who fulfills all of the following criteria may be included in the study.

1. Completion of the treatment period of a dasotraline core study (ie, SEP360-221 or SEP360-321) for the treatment of BED.
2. Subject has agreed to participate by providing written informed consent and is willing and able to comply with the protocol, in the opinion of the investigator.
3. Subject has not taken any medication other than the study drug for the purpose of controlling BED symptoms during the core study.
4. Female subject must have a negative urine pregnancy test at open-label (OL) Baseline; 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.
5. 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 22, Appendix III) 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.
6. Subject is judged by the investigator to be suitable for participation in a 12-month clinical trial involving open-label dasotraline treatment.
7. Subject can read well enough to understand the informed consent form and other subject materials.

8.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded in the study.

1. Subject is considered by the investigator to be at imminent risk of suicide, injury to self or to others, or damage to property.
2. Subject is considered a suicide risk in the investigator's opinion or has any previous history of suicide attempt within the past 12 months.
3. 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 OL Baseline. Subjects who answer "yes" to this question must be referred to the Investigator for follow up evaluation.
4. Subject has a clinically significant abnormality including physical examination, vital signs, ECG, or laboratory tests that the investigator in consultation with the medical monitor considers to be inappropriate to allow participation in the study.
5. Subject has a positive urine drug screen (UDS) or breath alcohol test at OL Baseline.

6. Subject is breastfeeding.
7. Subject is at high risk of non-compliance in the investigator's opinion.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

The study medication is described in Table 5.

Table 5: Study Medication

Attribute	Study Medication		
Product name	Dasotraline 4.0 mg	Dasotraline 6.0 mg	Dasotraline 8.0 mg
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.

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, 6 mg, or 8 mg capsules (7 days + 3 extra days).

9.2.2. Labeling Description

All packaging for the study medication will be labeled with:

- Protocol number
- Sponsor's name and address
- Content (eg, number of capsules)
- 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 permitted to 15°C to 30°C (59°F - 86°F) but must still be reported to CRO. The subject will be instructed to store the study medication at room temperature.

9.4. Dispensing of Study Drug

An Interactive Response System (IXRS) will be used to manage subject 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 on which medication number to assign to a subject. Each subject will be dispensed two or four 10-day blister cards per scheduled visit depending on the timing of the next scheduled visit (see Table 2).

Subjects will self-administer the study drug on an outpatient basis.

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the study drug in a secure location and for maintaining adequate records of drug disposition that includes 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/ clinical research organization (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 or designee on an ongoing basis must maintain a study drug inventory record of supplied, received, dispensed, and returned study drug 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

10.1.1. Dose or Dosage for Study Drug

Dasotraline 4 mg, 6 mg, or 8 mg 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 months. 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.

10.1.2. Dose Adjustment Criteria

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

All changes in study drug dose will begin the morning after the visit at which the dose change decision is made and using the new package of study drug.

10.2. Treatment Compliance

Compliance with study drug will be monitored closely and determined at each visit during treatment. Subjects will be instructed to bring all unused study drug 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 subject, 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 drug for the effectiveness of treatment and for the successful outcome of the study.

10.3. Concomitant Medications and Therapies

The following information on all medication administered between open-label baseline through the 3-week study medication withdrawal period or at 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 coding dictionary is provided in the Data Management Plan (DMP). All medications will be coded using World Health Organization Drug Dictionary (WHO-DD). Information on the concomitant mediations carried over from the core-study will be described in the DMP.

10.3.1. Prohibited Medications

Use of certain medications, including but not limited to the following, is prohibited throughout the study from open-label baseline through the 3-week study medication withdrawal period:

- 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] inhibitor, tricyclic) and St. John's Wort
- medications that are CYP2B6 substrates or inhibitors or inducers of CYP2B6, eg, bupropion, cyclophosphamide, carbamazepine, etc (see Section 23, Appendix IV)
- medications for the treatment of ADHD
- corticosteroids except as noted in Section 10.3.3 and anabolic steroids
- antiepileptic medications
- benzodiazepines except for sleep or anxiety
- mood stabilizers (eg, lithium, anticonvulsants)
- antipsychotic medications
- suvorexant
- any medication that can result in either weight gain or weight loss (eg, insulin, liraglutide, diphenhydramine except topical formulations, etc) including over-the-counter and herbal products

10.3.2. Prohibited Therapies

Any participation in a formal weight loss program such as Weight Watchers® is prohibited 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:

- Corticosteroids: Topical and intra-nasal corticosteroids. Other formulations of corticosteroid may be permitted following consultation with the Medical Monitor
- 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 permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Lorazepam should be used sparingly, when clinically required, per investigator judgment
  - 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
- Medications used for the treatment of anxiety/agitation and insomnia (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other)
- Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor
- Medications for short-term treatment of a medical condition (no more than 10 days) are allowed following consultation with the Medical Monitor
- Subjects who require treatment with more than 1 of the restricted concomitant medications (including other antipsychotics or anxiolytics [lorazepam or equivalent above protocol-specified limits]) will be discontinued (as appropriate) from the study
- Contraceptives (see Section 22, Appendix III)

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

10.3.4. Permitted Therapies

Participation in non-pharmacologic therapy, such as supportive psychotherapy, cognitive behavioral therapy or interpersonal therapy is permitted and should be documented by the investigator, to the extent possible.

10.3.5. Contraception Requirements

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, as

described in Section 22, Appendix III, from informed consent through the end of the study. Note: Continued use of an effective and medically acceptable form of birth control is recommended for 30 days after study completion or premature discontinuation from the study.

10.4. Guidance for Overdose

There is no overdose experience with dasotraline in humans. Signs and symptoms of overdose in nonclinical 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).

10.5. Cautions

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

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 EDE-Q modified, BE-CGI-S, MADRS, SDS, HAM-A, CSSA, DESS, and SF-12 rating scales. 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

Visits 1E, 2E, 3E, 4E, 5E, 6E, 7E, 8E, 9E, 10E, 11E, 12E, 13E, and 14E (as applicable[a])	**Visits 15E/End of Treatment, Visits 16E, 17E, and 18E/End of Study (as applicable[a])**
EDE-Q modified (by subject)	EDE-Q modified (by subject)
SDS (by subject)	SDS (by subject)
MADRS	MADRS
C-SSRS	C-SSRS
BE-CGI-S	BE-CGI-S
SF-12[b] (by subject)	SF-12[b] (by subject)
HAM-A	HAM-A
	CSSA
	DESS

[a] As applicable, see Table 2, schedule of assessments, and Section 11.5.
[b] SF-12 collected only for subjects enrolling in this study after completing core Study SEP360-221.

11.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics including date of birth, sex, ethnicity, race, and subject ID number from the core study will be collected at the OL Baseline visit. Weight, BMI, physical and brief neurological examination results will be carried over from Week 12 in the core studies.

11.2. Safety Assessments

11.2.1. 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 will be monitored throughout the study at all visits including telephone, text, or email assessments.

Information on AEs carried over from the core-study will be described in the DMP.

11.2.2. Clinical Laboratory Tests

The 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. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Any POC (point of care) kits that are performed on site by study personnel rather than in a lab- must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.2.3. 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 sample collection and performance of an ECG, whenever possible.

11.2.4. Electrocardiograms (ECGs)

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 by a centralized cardiac safety vendor 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 interval, and QRS duration.

11.2.5. Physical and Neurological Examinations

Clinically significant physical and neurological examination findings, as judged by the investigator, after baseline (carried over) 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.

11.2.6. Safety Scales

11.2.6.1. 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 the "Since Last Visit" version of the C-SSRS.

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 any time during the study must be referred to the Investigator for follow-up evaluation.

11.2.6.2. 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.

Subjects will be instructed by the site staff regarding the appropriate way to take their pulse.

11.2.6.3. 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.

11.2.6.4. 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.

11.2.6.5. 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. Effectiveness Assessments

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

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).

Convergent findings from confirmatory factor analyses of item data 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.

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

The BE-CGI-S (Busner & McElroy, 2012; based on Guy-1976) asks the clinician one question: *"Considering your total clinical experience with the adult Binge Eating Disorder (BED) 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.

11.4. Other Assessments and Scales

11.4.1. Short Form-12 Health Survey (SF-12)

The SF-12 is a 12-item self-report questionnaire that is a subset of the SF-36 Health Survey. The survey captures physical and mental health. There are 8 subscales including: Physical functioning, Role-physical, Bodily pain, General health, Vitality, Social Functioning, Role-emotional, Mental health. The responses are reported on a 3 or 5 point Likert scale, depending on the question. The SF-12 is collected only for subjects enrolling in this study after completing Study SEP360-221.

11.5. Study Visits and Assessments

11.5.1. Open-label Baseline: Visit 1E (Day -1)

Subjects will be evaluated at the Open-label Baseline Visit to determine their eligibility to enroll in the study. The following study-related procedures will be performed at Open-label Baseline:

- Obtain informed consent
- Review inclusion/exclusion criteria
- Demographics
- Administer EDE-Q modified (Subjects from Study SEP360-221 only)
- Dispense study drug (First dose taken the following day on Day 1)

Results for the following study-related procedures will be carried over from the core study Week 12 visit, and do not need to be performed for the Open-label Baseline visit:

- Physical and neurological examinations
- Vital signs, weight, and BMI
- ECG
- Scales: BE-CGI-S, SDS, SF-12 (Subjects from Study SEP360-221 only), C-SSRS, HAM-A, MADRS, and EDE-Q modified (Subjects from Study SEP360-321 only)
- Clinical laboratories (serum chemistry, lipid panel, hemoglobin A1c, hematology, urinalysis), UDS, and urine pregnancy test for females of child bearing potential
- Breath alcohol test

AEs and concomitant medications ongoing at the Week 12 visit in the core study will be carried over. Other data such as height will be carried over from other visits in the core study.

Further information on data carried over from the core study will be addressed in the DMP.

11.5.2. Treatment Period (Visits 2E – 15E; Weeks 2 – 52)

Approximate midpoint between monthly Visits 3E and 4E, Visits 4E and 5E, Visits 5E and 6E, Visits 6E and 7E, Visits 7E and 8E, Visits 8E and 9E, Visits 9E and 10E, Visits 10E and 11E, Visits 11E and 12E, Visits 12E and 13E, Visits 13E and 14E, and Visits 14E and 15E (ie, 14 ± 2 days after visit) a member of the study site staff will contact the subject/parent/legal guardian via telephone, text, or email between monthly visits according to the timeline in Table 2. These contacts will be used to collect AEs, and concomitant medications, as well as to remind subjects about adherence to study drug administration and upcoming visits, following which an unscheduled visit may be scheduled, if necessary. The date and time of these contacts will be documented in the CRF.

11.5.2.1. Visit 2E: Week 2 (Day 14 ± 3)

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Record AEs
- Administer C-SSRS

- Perform study medication accountability
- Dispense study medication

11.5.2.2. Visit 3E (Week 4; Day 28 ± 3), Visit 5E (Week 12; Day 84 ± 3), Visit 7E (Week 20 Day 140 ± 3), Visit 9E (Week 28; Day 196 ± 3), Visit 11E (Week 36; Day 252 ± 3), and Visit 13E (Week 44 Day 308 ± 3)

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Perform physical examination (Visit 5E, Week 12, only)
- Perform ECG (Visit 3E, Week 4; Visit 5E, Week 12; and Visit 11E, Week 36 only)
- Record AEs
- Administer Scales:
- EDE-Q modified, SDS (Visit 5E, Week 12; and Visit 11E, Week 36, only), C-SSRS, BE-CGI-S, and SF-12 (Visit 5E, Week 12; and Visit 11E, Week 36 only; Subjects from Study SEP360-221 only)
- Collect samples for clinical laboratories (serum chemistry, lipid panel, hemoglobin A1c, hematology, urinalysis) (Visit 5E, Week 12; and Visit 11E, Week 36 only)
- Collect samples for UDS and urine pregnancy test for females of child bearing potential
- Perform breath alcohol test
- Perform study medication accountability
- Dispense study medication

11.5.2.3. Visit 4E (Week 8; Day 56 ± 3), Visit 6E (Week 16; Day 112 ± 3), Visit 8E (Week 24; Day 168 ± 3), Visit 10E (Week 32; Day 224 ± 3), Visit 12E (Week 40; Day 280 ± 3), and Visit 14E (Week 48; Day 336 ± 3)

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Perform physical examination (Visit 8E, Week 24, only)
- Perform neurological examination (Visit 8E, Week 24, only)
- Perform ECG (Visit 8E, Week 24, only)
- Record AEs

- Administer Scales: SDS (Visit 8E, Week 24, only), EDE-Q modified, C-SSRS, BE-CGI-S, SF-12 (Visit 8E, Week 24, only; Subjects from Study SEP360-221 only), HAM-A (Visit 8E, Week 24, only), and MADRS (Visit 8E, Week 24, only)
- Collect samples for clinical laboratories (serum chemistry, lipid panel, hemoglobin A1c, hematology, urinalysis) (Visit 8E, Week 24, only)
- Collect samples for urine pregnancy test for females of child bearing potential (Visit 12E, Week 40 and Visit 14E,Week 48 only)
- Perform study medication accountability
- Dispense study medication

11.5.2.4. Visit 15E/End of Treatment (Week 52; Day 364 ± 1)

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
- Administer Scales: EDE-Q modified, SDS, MADRS, C-SSRS, BE-CGI-S, SF-12 (Subjects from Study SEP360-221 only), HAM-A, CSSA, and DESS
- Collect Samples for clinical laboratories (serum chemistry, lipid panel, hemoglobin A1c, hematology, urinalysis), UDS and urine pregnancy test for females of child bearing potential
- Perform breath alcohol test
- Perform study medication accountability

11.5.3. Withdrawal Period

All subjects, including those who complete treatment and those who discontinue treatment, will complete weekly in-clinic visits during the 3 week study medication withdrawal period. In addition to the weekly 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 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, as necessary.

11.5.3.1. Visit 16E (Week 53; Day 371 ± 1[5]) and Visit 17E (Week 54; Day 378 ± 1[6])

The following study related procedures will be performed:

- Record concomitant medications
- Collect vital signs and weight
- Perform ECG
- Record AEs
- Administer Scales: MADRS, C-SSRS, BE-CGI-S, HAM-A, CSSA, and DESS

11.5.3.2. Visit 18E/End of Study (Week 55; Day 385 ± 1[7])

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
- Administer Scales: MADRS, C-SSRS, BE-CGI-S, HAM-A, CSSA, DESS, SDS, SF-12 (Subjects from Study SEP360-221 only)
- Collect Samples for clinical laboratories (serum chemistry, lipid panel, hemoglobin A1c, hematology, urinalysis), UDS, and urine pregnancy test for females of child bearing potential
- Perform breath alcohol test

[5] For Early terminating subjects 7 days post last dose ± 1 day

[6] For Early Terminating subjects 14 days post last dose ± 1 day

[7] For Early Terminating subjects 21 days post last dose ± 1 day

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment.

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 the time the informed consent is obtained to the last study visit.

Lack of effectiveness 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 (ie, a patient is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death)
- 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 an 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.

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 site. 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 at OL Baseline is indicated as clinically significant and is not covered by the inclusion criteria in Section 8.1, 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 at the Follow-up Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized.

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 ECG that persists 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 AEs must be collected and recorded in the subject's study records/source documents, in accordance with the Investigator's normal clinical practice, and on the CRF. All AEs will be followed up 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 2 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 medication stopped temporarily
- **Drug Withdrawn** – Study medication stopped permanently
- **Dose Reduced**
- **Dose Increased**
- **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-medication administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after study-medication administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study medication.
  - **Definite** - occurred in a reasonable time after study-medication administration and cannot be explained by concurrent drugs or underlying disease. The AE 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 from the time that informed consent is signed 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 medication. SAEs occurring from the time of informed consent through 14 days following last dose of the study medication also must be recorded on the CRF and the data recorded should match 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 PPD-PVG if considered at least possibly related to the study medication.

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

In addition to the initial 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 site staff becoming aware of the event. The SAE report 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 sites 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 site.

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.

If a pregnancy is reported for the study subject's partner, the Sponsor's representative will provide instructions on how to collect pregnancy information in accordance with local requirements. Proper consent to collect the partner's information will be obtained before the collection of any information.

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 site staff becoming aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study medication 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. 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 effectiveness 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 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. 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 11.5.2.4), as soon as possible following discontinuation of study drug, and complete the study medication withdrawal assessments and visits (Section 11.5.3).

13.3. 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).
- Protocol violation (specify).
- Pregnancy.
- Withdrawal by subject (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.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time while ensuring that early termination does not compromise subjects' safety or well-being. In particular, a site that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the site 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 after consultation with the Sponsor.

In the event of study or site termination, subjects who discontinue study medication before completion will be asked to return to the site and complete the EOT visit assessments (Section 11.5.2.4) as soon as possible after discontinuation of study drug and complete the study medication withdrawal visits and calls (Section 11.5.3).

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

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

15.2. Analysis Populations

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

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

All effectiveness and safety evaluations will be summarized by analysis group based on the safety population and withdrawal population separately, when applicable.

15.3. Data Analysis

Unless otherwise specified, safety data will be presented separately by analysis group for the open-label treatment period (for data collected up to the end of open-label treatment period) and withdrawal period (for data collected during the withdrawal period), as appropriate. Since this is an uncontrolled open-label extension, no statistical comparisons will be conducted and no inferential statistics on effectiveness and safety will be presented.

15.3.1. Analysis Group

A total of 2 analysis groups will be formed based on a subject's previous participation in the core studies (ie, subjects previously randomized to dasotraline and subjects previously randomized to placebo). Group "All-Das" that combines these 2 analysis groups will be also presented. Summary tables, wherever applicable, will be presented by above analysis group, respectively.

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

- All-Das: all subjects combined

Subjects continued from Study SEP360-221 will be further grouped into 2 analysis subgroups. In summary table they will be labeled as follows (ie, with one additional pooled group: 221-Das):

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

Subjects continued from Study SEP360-321 will be further grouped into 3 analysis subgroups. In summary table they will be labeled as follows (ie, with 2 additional pooled groups: All Das-Das and 321-Das):

- Pbo-Das: previously randomized to placebo
- Das4-Das: previously randomized to dasotraline 4 mg/day
- Das6-Das: previously randomized to dasotraline 6 mg/day
- All Das-Das: previously randomized to dasotraline (4 mg/day or 6 mg/day)
- 321-Das: subjects continued from study SEP360-321

Results will be presented by analysis subgroup as needed for limited analyses, wherever applicable.

15.3.2. Definitions of Assessments

The following definitions will be used for assessments:

- Double-blind (DB) Baseline (ie, Baseline assessment of the double-blind study [core study]): the last assessment made on or before double-blind randomization as described in the core protocols;
- OL Baseline (ie, Endpoint assessment of the double-blind treatment period of core study) or Baseline assessment of the open-label study (SEP360-322): the last assessment made during the double-blind treatment period, as described in the core protocols;
- Week 52 Endpoint/Withdrawal Baseline: the last post-OL Baseline assessment made prior to or at Week 52 visit.
- Withdrawal Endpoint: the last post-Withdrawal Baseline assessment made prior to or at Week 55 visit.

Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation [SD], median, range, 95% confidence interval [CI] as needed). Where changes are reported, the reference will be to “DB Baseline”. Where relevant, changes from “OL Baseline” will also be reported.

15.3.3. Safety Analysis

The CSSA and DESS, which are used to assess physical dependence and withdrawal symptoms, are collected only at the Week 52 endpoint and in the withdrawal period; all other safety data are to be collected in both treatment period and withdrawal period and will be presented by analysis group for the open-label treatment period and withdrawal period, separately, as appropriate.

15.3.3.1. Adverse Events

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

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

A discontinuation-emergent adverse event (DEAE) is defined as an AE which has an onset after the last dose date of study drug through the Week 55 visit (ie, the last study visit in the withdrawal period).

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

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

The AEs also will be summarized by system organ class (SOC) and preferred term (PT) by presenting the number and percentage of subjects with each AE category. The incidence of AEs (by preferred term, grouped by SOC, and presented by analysis group) 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 incidence of AEs of special interest, including but not limited to neuropsychiatric-related and cardiovascular-related AEs, will be summarized by analysis group. For time to the earliest onset of insomnia, Kaplan-Meier curves will be plotted by analysis group.

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

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

The number and percentage of subjects with suicidal ideation and/or suicidal behavior, emergence or worsening of suicidal ideation or suicidal behavior will be summarized by analysis group for the open-label treatment period and the withdrawal period, separately.

15.3.3.3. Other Safety Assessments

Other safety assessments, including but not limited to laboratory values, ECG, vital signs, weight, BMI, and neurological exam, will be summarized as below. BMI at a study visit will be derived per weight assessed at each open-label study visit and the height collected at Screening in the core studies.

Treatment Period

Descriptive statistics will be provided for observed values and changes from DB baseline and OL baseline by study visit and analysis group for continuous variables; for categorical variables. Frequencies and percentages by study visit and analysis group will be reported. In addition, for selected parameters of laboratory values, ECG, vital signs, and weight, the number and percentage of subjects with markedly abnormal values will be presented.

Withdrawal Period

Descriptive statistics of continuous variables will be provided for observed values and changes from Week 52 Endpoint by study visit and analysis group; for categorical variables, frequencies and percentage by study visit and analysis group will be reported.

15.3.3.4. Physical Dependence and Withdrawal Symptoms

For continuous data used to assess physical dependence and withdrawal symptoms (ie, CSSA total score, DESS total score, MADRS total score, and HAM-A total score), descriptive statistics of the observed values and changes from Week 52 Endpoint will be summarized by analysis group and visit for the withdrawal period.

15.3.3.5. Concomitant Medications

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

15.3.4. Analyses for Effectiveness and Subject-Reported Health Status

For BE-CGI-S score, EDE-Q modified global score and subscales scores (restraint, shape concern, weight concern), EDE-Q modified items 4-6 scores, SDS total score and subscale scores, and SF-12 (subjects from Study SEP360-221 only) physical component and mental health component scores, descriptive statistics (N, mean, SD, median, range) of observed values will be summarized by analysis group at DB baseline, OL baseline (when applicable), each scheduled assessment in the treatment period, and Week 52 Endpoint. In addition, similar summary statistics as described above and 95% CI of changes from DB baseline and OL baseline will be presented. Confidence intervals will be based on means and standard deviations estimated without adjustment for any center or baseline effects.

For time to early discontinuation, Kaplan-Meier curves will be plotted by analysis group.

15.3.5. Interim Analysis

No interim analysis is planned.

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

16.1. Data Collection/Electronic Data Capture (EDC)

The results from 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 electronic data capture (EDC) system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11, Medidata Rave®. The SDS, C-SSRS, EDE-Q modified, MADRS, BE-CGI-S, HAM-A, CSSA, DESS, and SF-12 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
Inclusion/Exclusion Criteria	A
Dispense Study Drug	A, D
Study Medication Accountability	A
Between visit contact	A
Demographics	A
Physical Examination	A
Neurological Examination	A
Prior and Concomitant Medications	A
Binge-eating Clinical Global Impressions of Improvement (BE-CGI-S)	A
Eating Disorder Examination Questionnaire (EDE-Q) modified	A
Sheehan Disability Scale (SDS)	A
Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12)	A
Vital Sign Measurements	A
Weight and Body Mass Index	A
Height	A
Adverse Events	A
Serum chemistry	B

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

Protocol Step	Computerized System Type or Description
Lipid panel	B
Hemoglobin A1c	B
Hematology	B
Urinalysis	B
Columbia – Suicide Severity Rating Scale (C-SSRS)	A
Hamilton Anxiety Rating Scale (HAM-A)	A
Montgomery-Asberg Depression Rating Scale (MADRS)	A
Cocaine Selective Severity Assessment (CSSA)	A
Discontinuation-Emergent Signs and Symptoms (DESS) Scale	A
Urine Pregnancy Test (females of child-bearing potential only)	A
Urine Drug Screen	A
Breath Alcohol Test	A
12-Lead Electrocardiogram (ECG)	C
Statistical analysis	SAS®, version 9.1.3 or higher

A = EDC (Medidata Rave®); B = LIMS; C = Core Lab Over-read; D = IXRS.
Abbreviations: EDC = electronic data capture; IXRS = Interactive Response System; LIMS = laboratory information management system.

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 informed consent form (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.

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). 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 (see Section 19).

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) will be obtained for all participating 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 approval must be obtained and also forwarded to the Sponsor. The IRB must supply the Sponsor a list of the IRB membership, and a statement to confirm that the IRB is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB 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 chairman or designee identify the IRB 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 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 continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at

intervals not to exceed one year or as otherwise specified by the IRB. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB 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 before submission to the IRB. 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 approval. The Sponsor/CRO may submit informed consent forms to a central IRB for review and approval or favorable opinion contingent upon prior the 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 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 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 and initials 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.

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. 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, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB 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 immediately/within five business days of the occurrence, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the site must arrange for retention of study records at the site for at least 15 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor standard operating procedures (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 site 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, 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 before 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, SEP360-322, Version 4.00, "An Open-label, Flexibly-dosed, Multicenter, Extension Study of Dasotraline to Evaluate Long-term Safety and Tolerability in Adults with 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, Breath Alcohol Test, Urine Pregnancy Test (in female subjects of child-bearing potential only), Serum Pregnancy Test (in female subjects with a positive urine pregnancy test).

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. ACCEPTABLE CONTRACEPTIVE PROCEDURES FOR AND DURING THE STUDY

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, spermicidal condom).

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.

23. APPENDIX IV. 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
ifosphamide		phenobarbital
ketamine		phenytoin
meperidine		rifampin
methadone		
nevirapine		
propafol		
selegiline		
sorafenib		

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24. APPENDIX V. 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 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 8: Checklist of Events Subject to Additional Monitoring Terms

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 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 1 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 baseline and at various post-baseline 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 Irregularity 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 by the investigator every time a threshold event occurs, at the time of event and FAXED within 3 business days to the contact provided.

FAX #: XXX-XXX-XXXX

For clinical trials ut[illegible] dasotraline, the threshold criteria for medication irregularities are any one of the following:

- 10% or [illegible] dispe[illegible]rug is [illegible]r used in excess of prescribed dose or is unaccounted for; a[illegible]
- Suspected abuse or diversion of [illegible]so[illegible]n [illegible]and/o[illegible]
- Suspected abuse of any other substance including [illegible]cohol, illic[illegible]ubstance[illegible] over-the-counter (OTC) medications or prescription drugs.

Any instance of medication handling irregularity may further be classified as an eve[illegible]bject to additional monitoring (ESAM).

Investigator Instructions For Each Event:

- The contact must receive a completed Medication Handling Irregularity form by FAX within 3 business days of its occurrence or discovery every time a threshold medication handling irregularity occurs. The Medication Handling Irregularity form should include a thorough description of the threshold event; additional pages may be used, if necessary.
- Record any Adverse Event that was associated with, or resulted from, a medication handling irregularity, using the Case Report Form.
- Information on concomitant medications must be recorded under Concomitant Medication in the Case Report Form.
- Complete additional procedures, as instructed, on the Medication Handling Irregularity form.

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

Study No.: _____ Site No.: ___ ___ ___ Subject No.: ___ ___ ___ ___ ___

Date of Event Discovery: _____

Date of Event dd-mm-yyyy	Medication Meeting Threshold (for DB Studies Record Possible Medication Name Even If It May Be Placebo, Active or Comparator)	Strength of Medication	Number of Capsules

Please classify this m[illegible] ca[illegible] handling irregularity by checking one of the following boxes 1 – 5.

1 ◯ Drug accoun[illegible] er[illegible] not inv[illegible] suspected abuse or diversion by subject.
Describe eve[illegible] nd us[illegible] it[illegible] al page[illegible] ce[illegible]
2 ◯ Non-compliance with study p[illegible] ce[illegible] not i[illegible] g[illegible] cted al[illegible] or diversion by subject.
Describe event here and use additional pag[illegible] if [illegible].
3 ◯ Other cases not involving suspected abuse or diversion [illegible] study [illegible] oject.
Describe event here and use additional pages, if necessary.
4 ◯ Suspected or known abuse or diversion of study drug. Describe.
Describe event here and use additional pages, if necessary.
5 ◯ Suspected abuse (nonmedical use) of alcohol, illicit substances, OTC drugs or prescription drugs obtained outside study protocol.

Describe event here and use additional pages, if necessary.

If items 1, 2 or 3 are checked, the investigator will sign and have this form FAXED to the contact within 3 business days of its occurrence or discovery. FAX#: XXX-XXX-XXXX

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

Obtain a Urine Drug Screen from the subject;

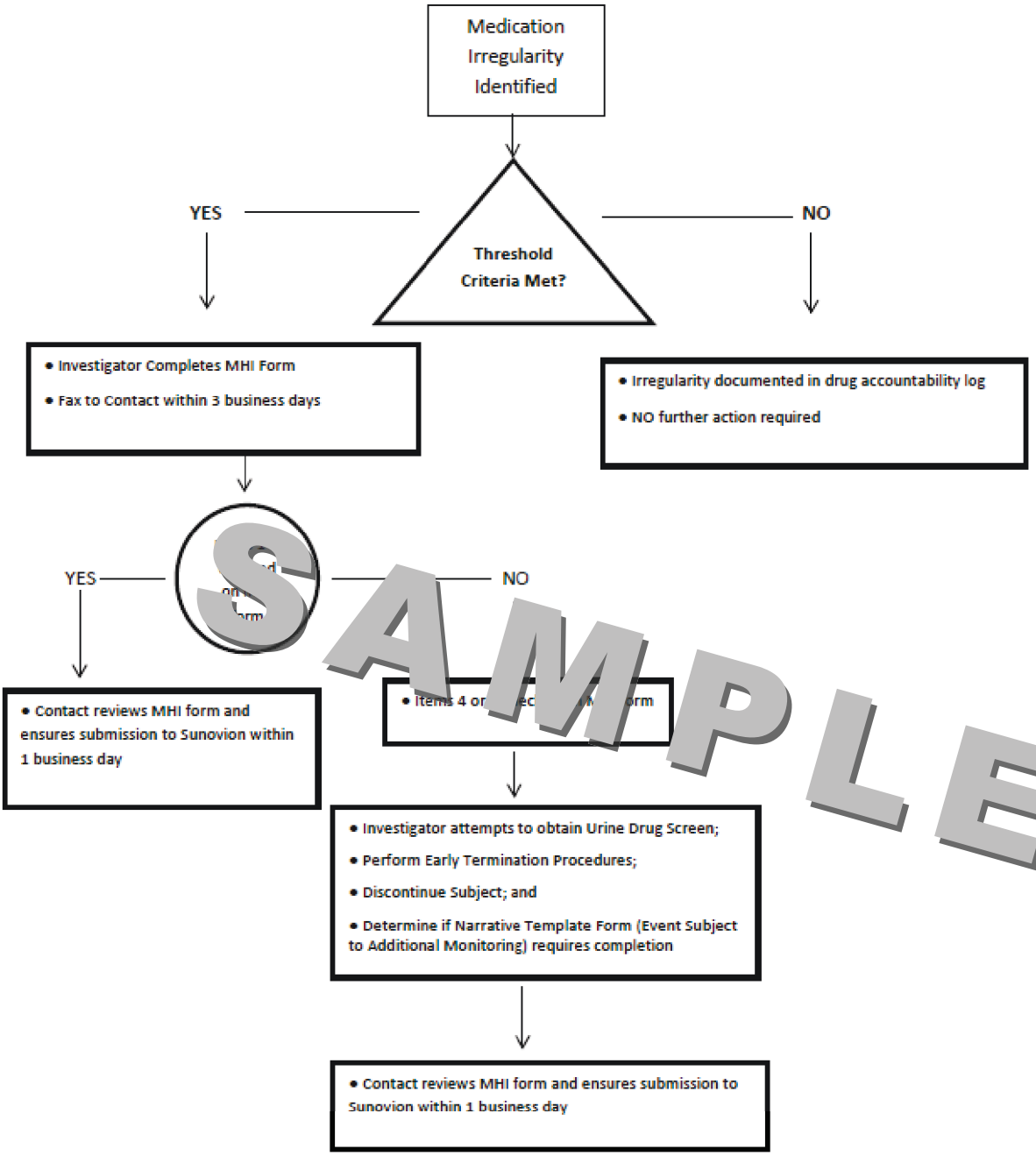
Complete Early Termination procedures and discontinue the subject from the trial;

Determine if Narrative Template Form (Event Subject to Additional Monitoring) requires completion;

FAX this form to the contact provided within 3 business days of its occurrence or discovery.

FAX#: XXX-XXX-XXXX

ATTACHMENT B MEDICATION HANDLING IRREGULARITY PROCESS FLOW



ATTACHMENT C EVENTS SUBJECT TO ADDITIONAL MONITORING NARRATIVE TEMPLATE FORM

Investigator will report all Events Subject to Additional Monitoring with narratives to the contact provided within 24 hours. FAX#: XXX-XXX-XXXX

Date: _____ Original Report ☐ Supplemental Report ☐

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

Subject No.: _____ Subjects Initials: _____Treatment:_____

Event term (verbatim from _____

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

Related to Study Drug (check one):	
	Not related
	Unlikely
	Possible
	Probable
	Definite

Action taken with Study Drug (check one):	
	Study Drug Interrupted
	Study Drug Withdrawn
	Study Drug Dose Reduced
	Study Drug Dose Increased
	Study Drug Dose Not Changed
	Study Drug Interrupted

Provide Narrative description of event on reverse side; use additional pages, if necessary. Provide a thorough description of the circumstances of the event. Supplemental information may be submitted on additional forms.

Pertinent Concomitant Mediations (also record on Concomitant Medication CRF)				
Drug Generic Name	**Start Date**	**Ongoing (Y/N)**	**End Date**	**Indication**

_____ _____ _____

Investigator Signature **Printed Name** **Date**