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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

• All named persons associated with the study
• Patient identifiers within text, tables, or figures
• By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
PROTOCOL: SPD489-346

TITLE: A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized-withdrawal Study to Evaluate the Maintenance of Efficacy of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder

DRUG: SPD489; lisdexamfetamine dimesylate

IND: 110,503

EUDRACT NO.: 2012-004457-88

SPONSOR: Shire Development LLC and International Affiliates
725 Chesterbrook Boulevard, Wayne, PA 19087 USA

PRINCIPAL/COORDINATING INVESTIGATOR:

PROTOCOL HISTORY:
Amendment 1: Version 2.0; 30 Sep 2013
Original Protocol: Version 1.0; 21 Dec 2012

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**PROTOCOL SIGNATURE PAGE**

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<tr>
<td>PhD</td>
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Senior Director, Clinical Medicine

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**Investigator’s Acknowledgement**

I have read this protocol for Shire Study SPD489-346 Version 2.0, dated 30 Sep 2013.

**Title:** A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized-withdrawal Study to Evaluate the Maintenance of Efficacy of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor’s representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.
Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address:
(please hand print or type)

Signature: __________________________ Date: _______________
# SUMMARY OF CHANGES

## Protocol Amendments

### 1. Summary of Change(s) Since Last Version of Approved Protocol

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<tr>
<th>Description of Change</th>
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<tr>
<td>Updated the study period.</td>
<td>Synopsis</td>
</tr>
<tr>
<td>Updated the number of participating sites and countries.</td>
<td>Synopsis</td>
</tr>
<tr>
<td>Added a randomization stratification factor of region (North America vs. non-North America).</td>
<td>Synopsis</td>
</tr>
<tr>
<td>Added exploratory efficacy endpoints for change from Visit 8 (Week 12) in the Sheehan Disability Score (SDS) total score at Visit 21/ET (Week 38) and Patient Resource Utilization Questionnaire for Binge Eating Disorder (PRUQ-BED) details.</td>
<td>Synopsis</td>
</tr>
<tr>
<td>Clarified that pharmacogenomic samples should be collected at the same time as the clinical laboratory samples are collected in footnote ‘l’.</td>
<td>Schedule of Assessments</td>
</tr>
<tr>
<td>Updated assessment days for Visit 7 through Visit 22 (with the exception of Visits 9 and 22) to reflect a 14-day duration between visits.</td>
<td>Schedule of Assessments</td>
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<tr>
<td>Added additional Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) assessments to occur during the Double-blind Randomized–withdrawal Phase at Visits 10, 12, 14, 16 and 18.</td>
<td>Schedule of Assessments</td>
</tr>
<tr>
<td>Updated the visit duration between Visits 8 and 9 to 15 days.</td>
<td>Schedule of Assessments</td>
</tr>
<tr>
<td>Added the Sheehan Disability Scale as a health-related quality of life assessment.</td>
<td>Schedule of Assessments</td>
</tr>
<tr>
<td>Updated that binge eating disorder (BED) was formally added as a free-standing diagnosis per Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition® (DSM-V®).</td>
<td>1.1</td>
</tr>
<tr>
<td>Clarified that study SPD489-208 was conducted with adults with BED symptoms.</td>
<td>1.3</td>
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<tr>
<td>Added an exploratory objective of change from randomized baseline (Visit 8) in SDS total score at Visit 21/ET (Week 38).</td>
<td>2.2.3</td>
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## Protocol Amendments

### 1. Summary of Change(s) Since Last Version of Approved Protocol

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<td><strong>Description of Change</strong></td>
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<tr>
<td>Added clarification that the date of relapse should be captured in the source documentation and applicable case report form.</td>
<td>3.1</td>
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<td>Added clarification for review and documentation of contraceptive requirements for females of child-bearing potential.</td>
<td>4.4.1</td>
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<td>Added failure to meet randomization criteria and relapse criteria met as reasons for discontinuation.</td>
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<td>Changed headings for Section 6.2.3.1 to Open-label Treatment Phase and Section 6.2.3.2 to Double-blind Randomized Withdrawal Phase to reflect the written text.</td>
<td>6.2.3.1, 6.2.3.2</td>
<td></td>
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<tr>
<td>Added details for data input by the site to permit the correct assignment to strata during randomization and assessment of relapse in the Interactive Web Response System (IWRS).</td>
<td>7.1.1</td>
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<tr>
<td>Added clarification on the process of assessing abnormal electrocardiogram results.</td>
<td>7.1.2.1</td>
<td></td>
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<tr>
<td>Removed text referring to visit duration of 15 days between Visits 20 and 21.</td>
<td>7.1.5.1</td>
<td></td>
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<tr>
<td>Clarified that the Mini International Neuropsychiatric Interview-Plus (MINI-plus) will be used to establish the presence of current and lifetime comorbid Axis I conditions.</td>
<td>7.2.1</td>
<td></td>
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<tr>
<td>Clarified that binge frequency will be reviewed by the clinician with the subject to confirm reported binge episodes per day.</td>
<td>7.2.2.1</td>
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</tr>
<tr>
<td>Added new Appendix 1 for protocol history; subsequent appendices have been renumbered accordingly.</td>
<td>Appendix 1</td>
<td></td>
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EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Trial Serious Adverse Event Form within 24 hours to the Shire Pharmacovigilance Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover).

For protocol- or safety-related issues during normal business hours (8:00 AM to 5:00 PM local time per region), the investigator must contact the Premier Research Group Medical Monitor:

For sites in the Americas:

MD, Executive Director, Global Pharmacovigilance
Telephone number: [redacted]
Mobile number: [redacted]
Fax number: [redacted]
E-mail: [redacted]

For sites in Europe and Rest of World:

Dr. FFPM, Medical Director
Telephone number: [redacted]
Mobile number: [redacted]
Fax number: [redacted]
E-mail: [redacted]

For protocol- or safety-related issues outside of normal business hours, the investigator must contact the Premier Research Group Medical Monitor:

For sites in the Americas:

MD, Executive Director, Global Pharmacovigilance
Telephone number: [redacted]
E-mail: [redacted]

For sites in Europe and Rest of World:

Dr. FFPM, Medical Director
Telephone number: [redacted]
E-mail: [redacted]
PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

<table>
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<th>Origin of Product Quality Complaint</th>
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<td>North and South America</td>
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<td>European Union and Rest of World</td>
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Telephone numbers (provided for reference if needed):

Shire, Wayne, PA (USA)

or

Shire, Basingstoke, Hampshire (UK)
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<tr>
<td>ADHD</td>
<td>attention-deficit/hyperactivity disorder</td>
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<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>BED</td>
<td>binge eating disorder</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CGI-I</td>
<td>Clinical Global Impressions-Improvement</td>
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<tr>
<td>CGI-S</td>
<td>Clinical Global Impressions-Severity</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia-Suicide Severity Rating Scale</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>d-amphetamine</td>
<td>dextroamphetamine</td>
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<tr>
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<td>deoxyribonucleic acid</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<td>EDE-Q</td>
<td>Eating Disorder Examination-Questionnaire</td>
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<td>EMA</td>
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<td>EQ-5D-5L</td>
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<td>HCG</td>
<td>human chorionic gonadotropin</td>
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<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
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<td>International Conference on Harmonisation</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>IWRS</td>
<td>Interactive Web Response System</td>
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<td>Acronym</td>
<td>Definition</td>
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<td>------------</td>
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<tr>
<td>MMRM</td>
<td>mixed-effects model for repeated measures</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>PRUQ-BED</td>
<td>Patient Resource Utilization Questionnaire for Binge Eating Disorder</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<td>SAP</td>
<td>statistical analysis plan</td>
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<td>T4</td>
<td>Thyroxine</td>
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<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
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<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<td>US</td>
<td>United States</td>
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<tr>
<td>Y-BOCS-BE</td>
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## STUDY SYNOPSIS

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<td>Title of the study:</td>
<td>A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized-withdrawal Study to Evaluate the Maintenance of Efficacy of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder</td>
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<tr>
<td>Number of subjects (total and for each treatment arm):</td>
<td>Approximately 777 subjects will be screened in order to enroll approximately 412 subjects and randomize approximately 214 subjects (107 per treatment group) in a 1:1 ratio (SPD489 and placebo treatment groups) in order to have a total of approximately 72 relapses across the 2 treatment groups.</td>
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<td>Investigator(s):</td>
<td>Multicenter study to be conducted globally</td>
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<td>Coordinating Principal Investigator:</td>
<td>MD, ScD</td>
<td></td>
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<tr>
<td>Site(s) and Region(s):</td>
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<tr>
<td>Coordinating Principal Investigator Address:</td>
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<td></td>
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<td>Study period (planned):</td>
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<td>Clinical phase:</td>
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### Objectives:

**Primary:** To evaluate maintenance of efficacy based on time to relapse between SPD489 (50 or 70mg) and placebo, as measured by the number of binge days (defined as days during which at least 1 binge episode occurs) per week as assessed by clinical interview based on subject diary and Clinical Global Impression – Severity (CGI-S) scores for patients who responded to SPD489 by the end of the Open-label Treatment Phase.

(Relapse is defined as subject reports ≥2 binge days each week for 2 consecutive weeks [14 days] prior to the visit and have a ≥2 point increase in CGI-S score relative to their score at the Randomized-withdrawal Baseline Visit.)

**Secondary:**

1. To evaluate the efficacy of SPD489 as compared to placebo at Visit 21 (Week 38) on the number of binge-eating days per week as assessed by clinical interview based on subject diary.
2. To evaluate the efficacy of SPD489 as compared to placebo at Visit 21 (Week 38) on the global clinical measure of severity as measured by the CGI-S scale.
3. To evaluate the efficacy of SPD489 as compared to placebo at Visit 21 (Week 38) on the obsessive/compulsive binge eating symptoms as measured by the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE).
4. To evaluate the impact of SPD489 on a measure of the perception of health and quality of life for appraisal of clinical and economic health status as assessed by the EuroQuol Questionnaire (EQ-5D-5L), in the Open-label and Double-blind Randomized-withdrawal Treatment Phases.
5. To evaluate the safety and tolerability of SPD489 based on the occurrence of TEAEs, vitals signs results (including weight and waist circumference), clinical laboratory results, electrocardiogram (ECG) results,
and the Columbia-Suicide Severity Rating Scale (C-SSRS) results in the Open-label and Double-blind Randomized-withdrawal Treatment Phases.

6. To evaluate amphetamine withdrawal symptoms as measured by the Amphetamine Cessation Symptom Assessment (ACSA) in the Follow-up Phase.

Rationale:

The primary goal of BED treatment is to reduce or eliminate episodes of binge eating. Hypofunction of dopamine (DA) and norepinephrine (NE) systems may play a role in binge eating. Agents that facilitate DA and/or NE neurotransmission may reduce pathological overeating. Currently, there are no approved pharmacological therapies for BED. The investigational product (lisdexamfetamine dimesylate, SPD489) is a prodrug that releases pharmacologically active dextroamphetamine (d-amphetamine), which inhibits reuptake of NE and DA from the synaptic cleft and also causes the release of the 3 principal monoamine neurotransmitters (NE, DA, and serotonin). Results from a recently completed Phase 2 study (SPD489-208) support the hypothesis that treatment with SPD489 may be a potential option for treatment of moderate to severe BED.

This study is designed to assess and demonstrate the long-term maintenance of efficacy (utilizing a Randomized-withdrawal design) safety, and tolerability of SPD489 in adults (18-55) with moderate to severe BED.

Investigational product, dose, and mode of administration:

- The sponsor will provide SPD489 (lisdexamfetamine dimesylate) capsules in 30, 50, and 70mg oral dose strengths and matching placebo capsules that appear identical in size, weight, shape, and color. The 30mg dose will be utilized for titration purposes only.
- Subjects will be instructed to take 1 capsule of investigational product daily at approximately 7:00 AM (+2 hours).

Methodology:

This is a Phase 3, double-blind, randomized-withdrawal study to compare the time to relapse between SPD489 (50 or 70mg) and placebo in adults aged 18-55 years with moderate to severe BED who had responded to open-label treatment of SPD489 in the Open-label Treatment Phase. Subjects will have a screening visit conducted whereby diagnosis will be confirmed via a structured interview using the Structural Clinical Interview for DSM-IV-TR™ (SCID-I) eating disorders module and the subject-completed Eating Disorder Examination Questionnaire (EDE-Q).

Following the Screening Phase, subjects will return to the site for reassessment of eligibility criteria and to establish open-label baseline measures. Eligible subjects with the following will be enrolled in the Open-label Treatment Phase:

1. Subject reports ≥3 binge days each week during the 14 days prior to the Open-label Baseline Visit (Visit 0) as documented in the subject diary
   AND
2. Subject has a CGI-S score of ≥4

The starting titration dose in the Open-label Treatment Phase for all subjects will be SPD489 30mg/day. All subjects will have their dose force titrated to 50mg at Visit 1. Subsequent increases to 70mg/day will be made as tolerated and clinically indicated. All subjects will undergo titration to an optimal dose (50 or 70mg/day) during the Dose-optimization Period. Investigators will have the option to down-titrate a subject’s dose from 70 to 50mg in the event the 70mg dose is not tolerated. Once a dose reduction has occurred, the subject is not permitted to have their dose changed for the duration of the study. Once subjects reach an optimal dose level, this dose will be maintained until the end of the Double-blind Randomized-withdrawal Phase (Visit 21/ET). Visit 3 will be the last visit when dose changes are permitted. Subjects who are unable to tolerate investigational product will be discontinued; all eligible subjects will then proceed to the Dose-maintenance Period (Visits 5-8).
Subjects will be given the option to provide additional blood samples for exploratory research into BED, its treatment, and response to SPD489. Participation is voluntary and requires signature of a separate informed consent (pharmacogenomic) form.

Subjects who meet the following criteria at Visit 8 will be referred to as “Responders” and will be permitted to continue into the Double-blind Randomized-withdrawal Phase:

1. Subject reports ≤1 binge day each week for 4 consecutive weeks (28 days) prior to Visit 8
   AND
2. Subject has a CGI-S score of ≤2 at Visit 8

Among the Responders (meeting both criteria above), a subject having no binge days during the 4-week period is defined as achieving 4-week cessation.

Following completion of the Open-label Treatment Phase and confirmation of eligibility, subjects will enter the Double-blind Randomized-withdrawal Phase. The objective of this phase is to evaluate the maintenance of efficacy in subjects with BED who have responded to open-label treatment of SPD489. Eligible, subjects will be randomized in a 1:1 ratio to continue their optimal dose of SPD489 or be switched to placebo. Randomization will be stratified by the 4-week complete cessation status (Yes or No) at Visit 8 and region (North America vs. non-North America) in order to facilitate balance of treatment within each stratum. The duration of this phase is 26 weeks and at each study visit, efficacy and safety assessments will be measured. There will be 13 bi-weekly in-clinic visits.

**Definition of Relapse**

Relapse is determined at each visit during the Double-blind Randomized-withdrawal Phase using the following criteria:

1. Subject reports ≥2 binge days each week for 2 consecutive weeks (14 days) prior to the visit
   AND
2. Subject has a ≥2 point increase in CGI-S score relative to their score at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

A subject who meets the relapse criteria at any time point during the Randomized-withdrawal phase will immediately be discontinued from the study at the visit.

**Safety Follow-up**

A follow-up in-clinic visit will occur 7 days (visit window of +2 days) following the subject’s last dose of study drug to collect information on any ongoing or new adverse events (AEs), serious adverse events (SAEs), and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the investigator’s opinion, are resolved.
Inclusion Criteria:
The subject cannot be enrolled in the study before all of the following inclusion criteria (including test results) are available:

1. Subject is able to provide written, personally signed, and dated informed consent to participate in the study before completing any study-related procedures.
2. Subject is between 18-55 years of age (or age of majority if greater than 18 years of age, as defined by local regulations), inclusive, at the time of consent.
3. Subject meets the following Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – Text Revision™ (DSM-IV-TR™) criteria for a diagnosis of BED:
   - Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: eating, in a discrete period of time (e.g., within a 2-hour period) an amount of food that is definitely larger than most people would eat in a similar period of time under similar conditions, and a sense of lack of control over the eating (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
   - The binge eating episodes are associated with at least 3 of the following: eating much more rapidly than normal; eating until uncomfortably full; eating large amounts of food when not feeling physically hungry; eating alone because of being embarrassed by how much one is eating; feeling disgusted with oneself, depressed, or feeling very guilty after overeating.
   - Marked distress regarding binge eating.
   - The binge eating occurs, on average, at least 2 days a week for 6 months.
   - The episodes of binge eating do not occur exclusively during the course of bulimia nervosa or anorexia nervosa.
4. Subject has a BED diagnosis as confirmed by the eating disorder module of the SCID-I and EDE-Q.
5. Subject’s BED is of at least moderate severity with subjects reporting at least 3 binge eating days per week for the 14 days prior to the Open-label Baseline Visit (Visit 0) as documented in the subject’s binge diary. A binge day is a day during which at least 1 binge eating episode occurs.
6. Subject, who is female, must have a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the Screening Visit (Visit -1) and a negative urine pregnancy test at the Open-label Baseline Visit (Visit 0) and agrees to comply with any applicable contraceptive requirements of the protocol. Note: If Screening Visit (Visit -1) value is indeterminate, a serum β-HCG pregnancy test must be repeated and negative prior to the Open-label Baseline Visit (Visit 0) for females of child-bearing potential; serum β-HCG levels must be confirmed as stable and must not be positive for females of non-child bearing potential. Eligibility of females with indeterminate pregnancy test results should be discussed and confirmed by medical monitor.
7. Subject has a body mass index (BMI) of ≥18 and ≤45 at the Screening Visit (Visit -1) and at the Open-label Baseline Visit (Visit 0).
8. Subject must have a CGI-S score ≥4 at the Screening Visit (Visit -1) and the Open-label Baseline Visit (Visit 0).
9. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.
10. Subject is consistently able to swallow a capsule.

Exclusion Criteria
Subjects are excluded from the study if any of the following criteria are met:

1. Subject has current diagnosis of bulimia nervosa or anorexia nervosa as defined by the SCID-I eating disorders module.
2. Subject is receiving psychotherapy (e.g., supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) or weight loss support (e.g., Weight Watchers) for BED that began within the 3 months prior to the Screening Visit (Visit -1). Subjects who are receiving psychotherapy or weight loss support that was initiated ≥3 months prior to the Screening Visit (Visit -1) will be allowed to continue to receive psychotherapy or weight loss support during the study only if they agree not to make any changes in the frequency or nature of their psychotherapy or weight loss support during the course of this study.

3. Subject has used psychostimulants to facilitate fasting or dieting as a part of their BED within the 6 months prior to the Screening Visit (Visit -1).

4. Subject has a current comorbid Axis I or Axis II psychiatric disorder that is either controlled with medications prohibited in this study or is uncontrolled and associated with significant symptoms (Note: subjects with mild mood or anxiety symptoms that do not meet criteria for Axis I disorder, do not require treatment based on the investigator’s assessment, and do not confound efficacy or safety assessments in the opinion of the examining investigator may be included).

5. Subject has a lifetime history of psychosis, mania, hypomania, dementia, or ADHD.

6. Subject has other symptomatic manifestations (such as agitated states) that contraindicate treatment with SPD489 or confound efficacy or safety assessments in the opinion of the investigator.

7. Subject has Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥18 at the Screening Visit (Visit -1).

8. Subject is considered a suicide risk in the opinion of the investigator, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation are not necessarily excluded based on the assessment of the investigator.

9. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis, an infectious process requiring antibiotics or diabetes), disability, or other condition that might confound the results of safety assessments administered in the study or that might increase risk to the subject. Subject will be excluded if he or she has any additional condition(s) that in the investigator’s opinion would prohibit the subject from completing the study or would not be in the best interest of the subject to participate in the study. This would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable, asthma is not exclusionary.

10. Subject has a history of seizures (other than infantile febrile seizures), any tic disorder, or a current diagnosis and/or a known family history of Tourette’s Disorder, serious neurological disease, history of significant head trauma, dementia, cerebrovascular disease, Parkinson’s disease, or intracranial lesions.

11. Subject has known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medication.

12. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.

13. Subject has any clinically significant ECG prior to the Open-label Baseline Visit (Visit 0).

14. Subject has any clinically significant laboratory abnormality prior to the Open-label Baseline Visit (Visit 0). Subjects with hypokalemia during the Screening Visit (Visit -1) and prior to the Open-label Baseline Visit (Visit 0) will be excluded.

15. Subject has current abnormal thyroid function, defined as abnormal screening thyroid stimulating hormone (TSH) and thyroxine (T4). Treatment with a stable dose of thyroid medication for at least 3 months prior to the Screening Visit (Visit -1) is permitted.

16. Subject has recently initiated treatment with a lipid lowering medication (within the past 3 months). Treatment with a stable dose of lipid lowering medication for at least 3 months prior to the Screening Visit (Visit -1) is permitted.

17. Subject has a history of moderate or severe hypertension or has a resting average (of 3 readings) sitting systolic blood pressure >139mmHg or an average (of 3 readings) diastolic blood pressure >89mmHg at the Screening Visit (Visit -1) and/or the Open-label Baseline Visit (Visit 0). Note: Subjects with mild (Stage 1), well-controlled hypertension on a stable antihypertensive treatment regimen, defined as having
maintained the current dose for a period of at least 3 months or more at the time of the Screening Visit (Visit -1), are allowed.

18. Subject is taking any medication that is excluded (please refer to protocol for a complete list).

19. Subject has a known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients.

20. Subject has a recent history (within the past 6 months) of suspected substance abuse or dependence disorder in accordance with DSM-IV-TR criteria. Subjects with a lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence will be excluded. Nicotine dependence is not exclusionary.

21. Subject has a positive drug result at the Screening Visit (Visit -1) unless the investigator can verify that the positive result at the Screening Visit (Visit -1) is attributed to a medication that has been prescribed to the subject. In such case, medication(s) will be discontinued and verified by a negative drug result prior to the Open-label Baseline Visit (Visit 0).

22. Subject has glaucoma.

23. Subject has taken other medications that have central nervous system effects or affect performance, such as chronic use of sedating antihistamines and decongestant sympathomimetics within 7 days prior to the Screening Visit (Visit -1). Stable use of bronchodilator inhalers is not exclusionary.

24. Subject is female and pregnant or nursing.

25. Subjects who have had bariatric surgery, lap bands, duodenal stents, or other procedures for weight loss.

26. Subject has taken part in an investigational or observational study within the 30 days prior to the Screening Visit (Visit -1). Participation in a previous clinical study involving SPD489/NRP104 is excluded.

27. Subject has previously completed, discontinued, or withdrawn from this study.

Maximum duration of subject involvement in the study:

- Planned duration of Screening Phase: up to 4 weeks
- Planned duration of Open-label Treatment Phase
  - a. Dose-optimization Period: 4 weeks
  - b. Dose-maintenance Period: 8 weeks
- Planned duration of Double-blind Randomized-withdrawal Phase: 26 weeks
- Planned duration of Follow-up Phase: 1 week

Endpoints and statistical analysis:

Subject Populations

The Safety Analysis Set consists of subjects who have taken at least 1 dose of SPD489 in the Open-label Treatment Phase.

The Randomized Safety Analysis Set is defined as all subjects in the Safety Analysis Set who take at least 1 dose of investigational product in the Double-blind Randomized-withdrawal phase.

The Full Analysis Set (FAS) is defined as all subjects in the Randomized Safety Analysis Set with at least 1 post-randomization CGI-S assessment.

The summary of both safety and efficacy data for the Open-label Treatment Phase will be based on the Safety Analysis Set.

Safety analyses for the Double-blind Treatment Phase of the study will be based on the Randomized Safety Analysis Set.

Efficacy analyses for the Double-blind Treatment Phase will primarily be based on the FAS.
Primary Efficacy Endpoint

The primary efficacy endpoint is time to relapse from randomization. The investigator assesses the relapse status at each visit during the Double-blind Treatment Phase. The time of relapse is defined as the visit date when the relapse is confirmed. A subject who discontinues without meeting relapse criteria will be censored in the primary analysis.

Secondary Efficacy Endpoint(s)

- Change from Visit 8 (Week 12) to Visit 21 (Week 38) in the number of binge days per week
- CGI-S at Visit 21 (Week 38)
- Change from Visit 8 (Week 12) to Visit 21 (Week 38) in Y-BOCS-BE

Safety Endpoints

- Treatment-emergent adverse events (TEAEs)
- Vital signs
- Weight, waist circumference, and BMI
- Clinical laboratory results
- ECG
- C-SSRS
- ACSA

Health Outcomes and Outcomes Research Endpoints

- EQ-5D-5L

Exploratory Endpoints

- Change from randomized baseline (Visit 8) in Sheehan Disability Score (SDS) total score at Visit 21/ET (Week 38)
- Patient Resource Utilization Questionnaire for Binge Eating Disorder (PRUQ-BED)

Statistical Methodology for Primary Efficacy Endpoint(s)

The primary efficacy endpoint of time to relapse from randomization will be compared between the SPD489 and the placebo treatment groups using a log-rank test over the FAS, stratifying for the 4-week complete cessation status (Yes or No). The null hypothesis states that there is no between-treatment group difference in the survival functions for relapse. The 2-sided alternative states that the survival functions for relapse are different. Subjects who discontinue from the Double-blind Treatment Phase of the study without meeting relapse criteria are censored in the primary analysis. The time to relapse will be plotted graphically using the Kaplan-Meier method by treatment group. The median and quartiles of time to relapse will be calculated for each treatment group, with the proportions of relapse at 3 and 6 months after randomization estimated, with confidence intervals constructed based on the Greenwood formula.
Sample Size Justification

The sample size was determined for the primary comparison of SPD489 and placebo treatment groups using nQuery Advisor 6.0. Assuming true relapse rates of 30 and 55% for SPD489 and placebo respectively, corresponding to a hazard ratio of 0.447 for SPD489 as compared to placebo, an overall 72 subjects will need to experience relapse to provide 90% power for the 2-sided log-rank test at the 5% level of significance.

Approximately 777 subjects will be screened to enroll 412 subjects in the Open-label Treatment Phase. Assuming a 20% dropout rate in the Open-label Treatment Phase and a 65% response rate for subjects completing the Open-label Treatment Phase, a total of 214 subjects will be randomized (107 in each group). Assuming 20% of randomized subjects will discontinue before experiencing relapses, the total of 72 subjects experiencing relapse will be observed based on the assumed relapse rates of the 2 treatment groups.
## STUDY SCHEDULE

### Table 1: Schedule of Assessments

<table>
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<tr>
<th>Phase</th>
<th>Screening</th>
<th>Open-label Baseline</th>
<th>Open-label Treatment</th>
<th>Double-blind Randomized-withdrawal</th>
<th>Follow-Up</th>
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<td>Follow-Up</td>
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<tr>
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<td>-14</td>
<td>0</td>
<td>7</td>
<td>14</td>
<td>21</td>
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</table>

- Visit 8 serves as the Double-blind Randomized-withdrawal Baseline Visit.
- Subjects who complete the study will complete Visit 21. Subjects who discontinue prior to completing the study will complete the ET visit. All subjects are required to return to the clinic to complete the Follow-up Visit (Visit 22).
- Adverse events will be evaluated to ensure no change from the Open-label Baseline Visit (Visit 0) and meet the sponsor definition of responder to continue in the study.
- An abbreviated physical examination will be required to be performed if >30 days have elapsed since the Screening Visit (Visit -1).
- Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate after subjects have remained seated for a minimum of 5 minutes. Blood pressure and pulse will be taken 3 times with approximately 2 minutes in between each measurement in order to arrive at an average blood pressure and pulse.

Table 1: Schedule of Assessments
<table>
<thead>
<tr>
<th>Period</th>
<th>Phase</th>
<th>Screening</th>
<th>Open-label Baseline</th>
<th>Open-label Treatment</th>
<th>Double-blind Randomized-withdrawal</th>
<th>Follow-Up</th>
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<tr>
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<td>Dose-optimization</td>
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<td>239</td>
<td>253</td>
<td>267</td>
<td>274</td>
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</tr>
</tbody>
</table>

* A stadiometer must be used for all height measurements. Height should be measured in inches/centimeters without shoes with the subject standing on a flat surface and with chin parallel to the floor. The body should be straight but not rigid; weight (using a calibrated scale) to be measured without shoes.

* See Section 7.2.3.5 for waist circumference measurement details.

* Repeat clinical laboratory testing will be required to be performed if >30 days have elapsed since the Screening Visit (Visit -1).

* Serum β-HCG pregnancy test is to be performed on all females, regardless of child bearing potential.

* Urine pregnancy test to be conducted using a urine dipstick.

* Pharmacogenomic sample collection is optional and requires separate consent. Pharmacogenomic samples should be collected at the same time as the clinical laboratory samples are collected.

* A total of 3 ECGs will be performed at the Open-label Baseline Visit (Visit 0) with approximately 2 minutes between readings. A single ECG will be conducted at all other visits. Electrocardiogram readings should be performed after 5 minutes of rest.

* The ACSA will be administered at the Open-label Baseline Visit (Visit 0) and at the Double-blind Randomized-withdrawal Visit (Visit 8) and daily starting at Visit 21/ET and up until Visit 22/Follow-up Visit.

1. BACKGROUND INFORMATION

Lisdexamfetamine dimesylate, a prodrug of \( d \)-amphetamine, was initially developed as a once-daily treatment for ADHD. Lisdexamfetamine dimesylate itself is pharmacologically inactive, but following oral administration it is converted to \( l \)-lysine, a naturally occurring essential amino acid, and active \( d \)-amphetamine. The latter is responsible for the drug’s therapeutic activity.

SPD489 capsules (under the trade name VYVANSE®) were initially approved in the US for the treatment of ADHD in children aged 6-12 years in February 2007. Subsequently, the US approval was extended to adults aged 18-55 years (April 2008) and adolescents aged 13-17 years (November 2010). In Canada (under the trade name VYVANSE), approval was granted for children in February 2009 and extended to include adolescents and adults in November 2010. In Brazil, SPD489 capsules (under the trade name VENVANSE) were approved for the treatment of ADHD in children aged 6-12 years in July 2010.

Shire is investigating the efficacy and safety of SPD489 as treatment of BED in adults who meet criteria for BED without the compensatory weight loss behaviors associated with bulimia nervosa (eg, purging, laxative abuse, excessive exercise). The presumed mechanism of action of \( d \)-amphetamine is the blockade of the reuptake of DA and NE thereby increasing the availability of both of these neurotransmitters. Several lines of evidence suggest stimulants would constitute an effective treatment for BED. Growing evidence suggests that dopaminergic and noradrenergic hypofunction may play a role in BED and DA and NE are important in regulating eating behavior and reward (Wellman 2005; Palmiter 2007). Evidence from non-clinical studies show that rodents that have had their feed restricted and then binge, have a lower binding selectivity for the D2-like DA receptor in the mesoaccumben DA system (Bello and Hajnal 2006). Similarly, results from human studies show that for morbidly obese subjects there is reduced availability of the striatal DA-D2 receptor (the receptor that is associated with altered metabolic activity in prefrontal regions implicated in regulating food consumption; Wang et al. 2001; Volkow et al. 2008). Moreover, eating disorders characterized by binge eating have been associated with the hypofunctional short allele of the 3′-UTR VNTR polymorphism of the DA transporter gene (Shinohara et al. 2004).

In addition, it has been speculated that BED may represent a “reward deficiency syndrome,” where deficient tonic DA signaling promotes binge eating behavior in an attempt to restore DA function to normal levels (Blum et al. 1996, 2000, and 2008). SPD489 might relieve binge eating in BED by stabilizing a deficient DA reward system via long-term blockade of DA reuptake. Binge eating behavior was found to moderate an association between the hypofunctional 7-repeat allele of the DA D4 receptor gene and increased maximal lifetime BMI in women with seasonal affective disorder, a condition characterized by overeating, carbohydrate craving, and weight gain (Levitan et al. 2004).

Preliminary data show that agents that facilitate DA and/or NE neurotransmission may reduce pathological overeating (eg, binge eating) in animals and humans. The stimulant
methylphenidate was shown to reduce sucrose intake in an animal model of binge eating (Bello and Hajnal 2006). Draft data from a rodent binge eating model also indicate that acute administration of SPD489 reduced both normal and high palatability food (powdered chocolate) intake in a dose-dependent manner. In addition, there are preliminary reports of stimulants reducing binge eating in patients with bulimia nervosa, a condition closely related to BED (Sokol et al. 1999; Drimmer 2003), and reducing appetite in patients with BED (Davis et al. 2007). The selective NE reuptake inhibitor atomoxetine has been shown to reduce binge eating and body weight in 1 placebo-controlled study of BED in adults (McElroy et al. 2007).

The potential utility of stimulants for the treatment of BED is also suggested by growing research indicating that BED and ADHD may share common neurobiological bases. In the National Comorbidity Survey Replication, BED as well as other better-studied comorbid disorders like depressive disorders, anxiety, and impulse control disorders, was found to occur concurrently with ADHD (Hudson et al. 2007). A large percentage of patients with bulimia nervosa have ADHD (Surman et al. 2006), and conversely, girls with ADHD are at significantly greater risk for developing eating disorders (Biederman et al. 2007). Moreover, growing evidence indicates that ADHD co-occurs with obesity. It has been suggested that binge eating and a defective DA reward system may mediate this relationship (Cortese et al. 2008; Waring and Lapane 2008; Davis et al. 2006; Pagoto et al. 2009; Liu et al. 2008). Significantly, further evidence for the common biological underpinning of ADHD and BED is that these disorders might share a genetic vulnerability. For example, ADHD patients are more likely to carry the 7-repeat allele of the DA D4 receptor gene (Faraone et al. 2001). This same gene has been linked to weight gain in bulimia nervosa (Kaplan et al. 2008) and in seasonal affective disorder (Levitan et al. 2004). Polymorphisms in the DA D2 receptor gene have also been reported with all 3 disorders (Cortese et al. 2007), further suggesting a shared genetic vulnerability. Taken together, these data suggest that BED and ADHD may share a genetic causative mechanism associated with the DA system. If so, stimulants might be effective in BED via the same mechanism of action it has in ADHD (eg, by reducing impulsivity, including impulsive eating, via normalization of DA function).

As described above, amphetamine-based pharmacological therapy may be a viable option for the treatment of BED (Wellman 2005; Davis et al. 2007).

1.1 Indication and Current Treatment Options

Binge eating disorder is characterized by recurrent, distressing episodes of uncontrolled consumption of large amounts of food (binge eating) without the inappropriate compensatory weight loss behaviors of bulimia nervosa. In May 2013, BED was formally added as a free-standing diagnosis under DSM-V. Binge eating disorder is an important public health problem; with a lifetime prevalence of about 2-3% (Hudson et al. 2007). Binge eating disorder can be a chronic disease and associated with psychopathology, obesity, reduced quality of life, and disability. Binge eating disorder is the most common eating disorder (Hudson et al. 2007).
Several psychological interventions and SSRIs have been shown to reduce binge eating behaviors (Brownley et al. 2007; McElroy et al. 2012). Additionally, topiramate (antiepileptic) and sibutramine (SNRI) have been shown to decrease binge eating symptoms, but each is associated with AEs of concern (cognitive impairment for topiramate and increased blood pressure and pulse for sibutramine). There is no currently approved pharmacological treatment to treat BED and to date there are no published studies assessing the long term efficacy of pharmacological treatment in BED. As such, treatments that are effective in treating the multiple symptom domains of BED with acceptable safety profiles are needed.

1.2 Product Background and Clinical Information

The chemical structure of lisdexamfetamine dimesylate (SPD489) is presented in Figure 1.

**Figure 1: Chemical Structure of Lisdexamfetamine Dimesylate (SPD489)**

\[
\text{Chemical Structure of Lisdexamfetamine Dimesylate (SPD489)}
\]

Additional information can be found in the current SPD489 Investigator’s Brochure.

1.3 Overall Risk/Benefit Assessment

The safety and efficacy of SPD489 for the treatment of ADHD has been rigorously demonstrated in children, adolescents, and adults with ADHD. SPD489 has also been studied in adults with major depressive disorder and negative symptoms of schizophrenia in addition to 1 study in adults with BED (SPD489-208), with no evidence of new or unique safety findings in any of these populations.

It is noted that stimulant medications, including SPD489, cause modest increases in mean blood pressure and pulse. As a result, stringent inclusion and exclusion criteria, review of medical history and regular cardiovascular monitoring have been included in order to mitigate any potential risk. Further, subjects with a current comorbid psychiatric disorder, either controlled with a prohibited medication or uncontrolled with significant symptoms; subjects with ADHD or a lifetime history of amphetamine, cocaine, or other stimulant abuse; subjects who have moderate to severe depressive symptoms at entry (MADRS total score ≥18) are all excluded.

Finally, the potential improvement in BED symptoms with SPD489 treatment, the safety profile of SPD489, and the appropriate subject inclusion and safety monitoring procedures included in Study SPD489-346 are considered sufficient conditions to support the investigation of SPD489 as a treatment of BED.
2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Despite growing recognition of the consequences of BED, there is no approved pharmacological treatment. Several psychological interventions and SSRIs have been shown to reduce binge eating in BED (Brownley et al. 2007; McElroy et al. 2012). The antiepileptic topiramate and the SNRI sibutramine have been shown to decrease binge eating symptoms, but each is associated with problematic adverse events (cognitive impairment for topiramate and increased blood pressure and pulse for sibutramine). Novel treatments that are effective for the multiple symptom domains of BED with acceptable safety profiles are greatly needed. The investigational product (lisdexamfetamine dimesylate, SPD489) is a prodrug that releases pharmacologically active d-amphetamine, which inhibits reuptake of NE and DA from the synaptic cleft and also causes the release of the 3 principal monoamine neurotransmitters (NE, DA, and serotonin). In the binge eating clinical development program, 1 Phase 2 study (SPD489-208) of 11 week duration has been completed and on the primary efficacy analysis, robust efficacy was demonstrated for SPD489. BED can be a chronic condition. To date no pharmacotherapy studies have been performed in the targeted population to demonstrate maintenance of efficacy. The randomized-withdrawal design can be used to demonstrate maintenance of effect as discussed in the ICH Guideline E10. The randomized-withdrawal design may offer an advantage over traditional parallel-group studies because placebo may not be suitable for a long-term study due to ethical concerns and the potential for high dropout rates.

The proposed study design will effectively evaluate the maintenance of efficacy of SPD489, using a clinically interpretable definition of relapse based on the number of binge days/week and the CGI-S rating scale, utilizing a randomized-withdrawal design.

2.2 Study Objectives

2.2.1 Primary Objective

To evaluate maintenance of efficacy based on time to relapse between SPD489 (50 or 70mg) and placebo, as measured by the number of binge days (defined as days during which at least 1 binge episode occurs) per week as assessed by clinical interview based on subject diary and CGI-S scores for patients who responded to SPD489 by the end of the Open-label Treatment Phase.

Relapse is defined as subject reports ≥2 binge days each week for 2 consecutive weeks (14 days) prior to the visit and have a ≥2 point increase in CGI-S score relative to their score at the Randomized-withdrawal Baseline Visit.
2.2.2 Secondary Objectives

1. To evaluate the efficacy of SPD489 as compared to placebo at Visit 21 (Week 38) on the number of binge-eating days per week as assessed by clinical interview based on subject diary.

2. To evaluate the efficacy of SPD489 as compared to placebo at Visit 21 (Week 38) on the global clinical measure of severity as measured by the CGI-S scale.

3. To evaluate the efficacy of SPD489 as compared to placebo at Visit 21 (Week 38) on the obsessive/compulsive binge eating symptoms as measured by the Y-BOCS-BE.

4. To evaluate the impact of SPD489 on a measure of the perception of health and quality of life for appraisal of clinical and economic health status as assessed by the EQ-5D-5L, in the Open-label and Double-blind Randomized-withdrawal Phases.

5. To evaluate the safety and tolerability of SPD489 based on the occurrence of TEAEs, vital signs results (including weight and waist circumference), clinical laboratory results, ECG results, and the C-SSRS results in the Open-label and Double-blind Randomized-withdrawal Treatment Phases.

6. To evaluate amphetamine withdrawal symptoms as measured by the ACSA in the Follow-up Phase.

2.2.3 Exploratory Objectives

To explore the following:

1. The change from randomized baseline (Visit 8) in SDS total score at Visit 21/ET (Week 38).

2. To explore the utilization of healthcare resources in subjects with moderate to severe BED using the PRUQ-BED in the Open-label and Double-blind Treatment Phases.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

Study SPD489-208 was a Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study enrolling adults 18-55 years of age who had been diagnosed with BED according to DSM-IV-TR™ criteria. The primary objective of the study was to evaluate the efficacy of SPD489 30, 50, and 70mg compared to placebo in the treatment of BED at Week 11 as measured by the number of binge days per week as assessed by clinical interview based on patient diary.
In study SPD489-208, SPD489 50 and 70mg were statistically superior to placebo on the primary efficacy endpoint. The primary efficacy endpoint was defined as the change from baseline to Visit 8 (Week 11) on log (number of binge days per week + 1). The SPD489 30mg dose was numerically better than placebo but did not achieve statistical significance. Consistent patterns of results were seen across the majority of secondary endpoints. Study SPD489-208 demonstrated dose response both clinically and statistically for the primary endpoint. Based on the Study SPD489-208 results, 30mg/day will be used as a titration dose in this study with subjects being individually titrated, based on efficacy and tolerability, to achieve an optimized dose (50 or 70mg/day) during the Dose-optimization Period.

This is a Phase 3, double-blind, randomized-withdrawal study to compare the time to relapse between SPD489 (50 or 70mg) and placebo in adults aged 18-55 years with moderate to severe BED who had responded to SPD489 in the Open-label treatment phase.

The study will have 4 phases as outlined below and in Figure 2:

- **Screening Phase**
  - Up to 4 weeks

- **Open-label Treatment Phase**
  - Dose-optimization Period – 4 weeks
  - Dose-maintenance Period – 8 weeks

- **Double-blind Randomized-withdrawal Phase**
  - 26 weeks

- **Follow-up Phase**
  - 1 week

This study includes a 4-week Dose-optimization Period during which subjects are titrated to an optimal dose of investigational product, based on both efficacy and side effects (see Section 7 for a detailed description of each phase).

Subjects who meet the following criteria at Visit 8 will be referred to as “Responders” and will be permitted to continue into the Double-blind Randomized-withdrawal Phase:

1. Subject reports \( \leq 1 \) binge day each week for 4 consecutive weeks (28 days) prior to Visit 8

   AND

2. Subject has a CGI-S score of \( \leq 2 \) at Visit 8

Among the Responders (meeting both criteria above), a subject having no binge days during the 4-week period is defined as achieving 4-week cessation.
Relapse is determined at each visit during the Double-blind Randomized-withdrawal Phase using the following criteria:

1. Subject reports ≥2 binge days each week for 2 consecutive weeks (14 days) prior to each visit

AND

2. Subject has a ≥2 point increase in CGI-S score relative to their score at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

A subject who meets the relapse criteria at any time point during the Double-blind Randomized-withdrawal Phase will immediately be discontinued from the study at the visit and the actual “Date of Relapse” should be recorded in source documentation as well as the applicable CRF.
Figure 2: Study Design Flow Chart
3.2 Duration

The Subject Completion Date is defined as the date of the last visit or last scheduled assessment, in most cases, for a subject participating in the study. The subject’s maximum duration of participation is expected to be approximately 43 weeks.

The Study Completion Date is defined as the date the final subject in the study, across all sites, was examined or received an intervention for the purposes of final collection of data (last subject in-clinic visit). Note that this date is used to ascertain timing for study results posting.

3.3 Sites and Regions

This study is a multicenter study to be conducted globally in approximately 5 countries at approximately 60 sites.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below (including test results).

1. Subject is able to provide written, personally signed, and dated informed consent to participate in the study before completing any study-related procedures.
2. Subject is between 18-55 years of age (or age of majority if greater than 18 years of age, as defined by local regulations), inclusive, at the time of consent.
3. Subject meets the following DSM-IV-TR criteria for a diagnosis of BED:
   - Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: eating, in a discrete period of time (eg, within a 2-hour period) an amount of food that is definitely larger than most people would eat in a similar period of time under similar conditions, and a sense of lack of control over the eating (eg, a feeling that one cannot stop eating or control what or how much one is eating).
   - The binge eating episodes are associated with at least 3 of the following: eating much more rapidly than normal; eating until uncomfortably full; eating large amounts of food when not feeling physically hungry; eating alone because of being embarrassed by how much one is eating; feeling disgusted with oneself, depressed, or feeling very guilty after overeating.
- Marked distress regarding binge eating.
- The binge eating occurs, on average, at least 2 days a week for 6 months.
- The episodes of binge eating do not occur exclusively during the course of bulimia nervosa or anorexia nervosa.

4. Subject has a BED diagnosis as confirmed by the eating disorder module of the SCID-I and EDE-Q.

5. Subject’s BED is of at least moderate severity with subjects reporting at least 3 binge eating days each week for the 14 days prior to the Open-label Baseline Visit (Visit 0) as documented in the subject’s binge diary. A binge day is a day during which at least 1 binge eating episode occurs.

6. Subject, who is female, must have a negative serum β-HCG pregnancy test at the Screening Visit (Visit -1) and a negative urine pregnancy test at the Open-label Baseline Visit (Visit 0) and agrees to comply with any applicable contraceptive requirements of the protocol. Note: If Screening Visit (Visit -1) value is indeterminate, a serum β-HCG pregnancy test must be repeated and negative prior to the Open-label Baseline Visit (Visit 0) for females of child-bearing potential; serum β-HCG levels must be confirmed as stable and must not be positive for females of non-child bearing potential. Eligibility of females with indeterminate pregnancy test results should be discussed and confirmed by medical monitor.

7. Subject has a BMI of ≥18 and ≤45 at the Screening Visit (Visit -1) and the Open-label Baseline Visit (Visit 0).

8. Subject must have a CGI-S score >4 at the Screening Visit (Visit -1) and the Open-label Baseline Visit (Visit 0).

9. Subject is willing and has an understanding and ability to fully comply with study procedures and restrictions defined in this protocol.

10. Subject is consistently able to swallow a capsule.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has current diagnosis of bulimia nervosa or anorexia nervosa as defined by the SCID-I eating disorders module.

2. Subject is receiving psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) or weight loss support (eg, Weight Watchers) for BED that began within the 3 months prior to the Screening Visit (Visit -1). Subjects who are receiving psychotherapy or weight loss support that was initiated ≥3 months prior to the Screening Visit (Visit -1) will be allowed to continue to receive psychotherapy or weight loss support during the study only if they agree not to make any changes in the frequency or nature of their psychotherapy or weight loss support during the course of this study.

3. Subject has used psychostimulants to facilitate fasting or dieting as a part of their BED within the 6 months prior to the Screening Visit (Visit -1).
4. Subject has a current comorbid Axis I or Axis II psychiatric disorder that is either controlled with medications prohibited in this study or is uncontrolled and associated with significant symptoms (Note: subjects with mild mood or anxiety symptoms that do not meet criteria for Axis I disorder, do not require treatment based on the investigator’s assessment, and do not confound efficacy or safety assessments in the opinion of the examining investigator may be included).

5. Subject has a lifetime history of psychosis, mania, hypomania, dementia, or ADHD.

6. Subject has other symptomatic manifestations (such as agitated states) that contraindicate treatment with SPD489 or confound efficacy or safety assessments in the opinion of the investigator.

7. Subject has MADRS total score \( \geq 18 \) at the Screening Visit (Visit -1).

8. Subject is considered a suicide risk in the opinion of the investigator, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation are not necessarily excluded based on the assessment of the investigator.

9. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis, an infectious process requiring antibiotics or diabetes), disability, or other condition that might confound the results of safety assessments administered in the study or that might increase risk to the subject. Subject will be excluded if he or she has any additional condition(s) that in the investigator’s opinion would prohibit the subject from completing the study or would not be in the best interest of the subject to participate in the study. This would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable, asthma is not exclusionary.

10. Subject has a history of seizures (other than infantile febrile seizures), any tic disorder, or a current diagnosis and/or a known family history of Tourette’s Disorder, serious neurological disease, history of significant head trauma, dementia, cerebrovascular disease, Parkinson’s disease, or intracranial lesions.

11. Subject has known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medication.

12. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.

13. Subject has any clinically significant ECG prior to the Open-label Baseline Visit (Visit 0).

14. Subject has any clinically significant laboratory abnormality prior to the Open-label Baseline Visit (Visit 0). Subjects with hypokalemia during the Screening Visit (Visit -1) and prior to the Open-label Baseline Visit (Visit 0) will be excluded.

15. Subject has current abnormal thyroid function, defined as abnormal screening TSH and T4. Treatment with a stable dose of thyroid medication for at least 3 months prior to the Screening Visit (Visit -1) is permitted.

16. Subject has recently initiated treatment with a lipid lowering medication (within the past 3 months). Treatment with a stable dose of lipid lowering medication for at least 3 months prior to the Screening Visit (Visit -1) is permitted.
17. Subject has a history of moderate or severe hypertension or has a resting average (of 3 readings) sitting systolic blood pressure >139mmHg or an average (of 3 readings) diastolic blood pressure >89mmHg at the Screening Visit (Visit -1) and/or Open-label Baseline Visit (Visit 0). Note: Subjects with mild (Stage 1), well-controlled hypertension on a stable antihypertensive treatment regimen, defined as having maintained the current dose for a period of at least 3 months or more at the time of the Screening Visit (Visit -1), are allowed.

18. Subject is taking any medication that is excluded (See Section 5.1 for additional details and Table 2 for a complete list).

19. Subject has a known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients.

20. Subject has a recent history (within the past 6 months) of suspected substance abuse or dependence disorder in accordance with DSM-IV-TR criteria. Subjects with a lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence will be excluded. Nicotine dependence is not exclusionary.

21. Subject has a positive drug result at the Screening Visit (Visit -1) unless the investigator can verify that the positive result at the Screening Visit (Visit -1) is attributed to a medication that has been prescribed to the subject. In such case, medication(s) will be discontinued and verified by a negative drug result prior to the Open-label Baseline Visit (Visit 0).

22. Subject has glaucoma.

23. Subject has taken other medications that have central nervous system effects or affect performance, such as chronic use of sedating antihistamines and decongestant sympathomimetics within 7 days prior to the Screening Visit (Visit -1). Stable use of bronchodilator inhalers is not exclusionary.

24. Subject is female and pregnant or nursing.

25. Subjects who have had bariatric surgery, lap bands, duodenal stents, or other procedures for weight loss.

26. Subject has taken part in an investigational or observational study within the 30 days prior to the Screening Visit (Visit -1). Participation in a previous clinical study involving SPD489/NRP104 is excluded.

27. Subject has previously completed, discontinued, or withdrawn from this study.
4.3 Randomization Criteria (Evaluated at the Double-blind Randomized-withdrawal Baseline Visit; Visit 8)

A subject must meet all criteria below to be eligible for randomization.

1. Subject reports \( \leq 1 \) binge day each week for 4 consecutive weeks (28 days) prior to the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

AND

2. Subject has a CGI-S score of \( \leq 2 \) at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

In addition, subject has had no changes since the Open-label Baseline Visit (Visit 0) in physical examination, clinical laboratory, ECG, or vital signs results that would preclude treatment with SPD489. If clinical laboratory or ECG results are received at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8) that in the opinion of the investigator would preclude treatment with SPD489, the subject will be discontinued from the study.

4.4 Reproductive Potential

Contraception requirements should be reviewed at every study visit and documented in the CRF and source documents.

4.4.1 Female Contraception

Sexually active females of child-bearing potential should be using an acceptable form of contraception. Females of child-bearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and \( \geq \) age 51 years)
- Surgically sterile (having undergone 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of child-bearing potential with a negative urine and/or serum β-HCG pregnancy test. Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception should be used with condoms at all times for the following:

- Intrauterine devices
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the Screening Visit (Visit -1), plus condoms. Note: if subject becomes sexually active during the study, they should use 1 of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

For females of child-bearing potential, contraceptive requirements are to be reviewed at every study visit and documented in the source.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The withdrawal of a subject from investigational product by the investigator should be discussed, where possible, with the medical monitor before the subject stops investigational product.

If investigational product is discontinued, regardless of the reason, the final evaluations are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified Visit 21/ET and the Follow-up Visit (Visit 22). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded on the CRF and source documents.

Subjects who discontinue will not be replaced.

4.5.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject’s medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.
Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Failure to meet randomization criteria*
- Relapse criteria met**
- Other (must be specified on the CRF).

In addition, during the Open-label Treatment Phase of the study, subjects will be withdrawn due to lack of response if the subject does not meet the protocol defined response criteria as follows at Visit 8:

1. Subject reports \( \leq 1 \) binge day each week for 4 consecutive weeks (28 days) prior to Visit 8

AND

2. Subject has a CGI-S score of \( \leq 2 \)

Furthermore, in the Double-blind Randomized-withdrawal Phase of the study, subjects will be withdrawn if the subject meets the protocol defined relapse criteria as follows:

1. Subject reports \( \geq 2 \) binge days each week for 2 consecutive weeks (14 days) prior to the visit

AND

2. Subject has a \( \geq 2 \) point increase in CGI-S score relative to their score at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

* Failure to meet randomization criteria can only be chosen as a reason for discontinuation at Visit 8.

** Relapse criteria met can only be chosen as a reason for discontinuation during the Double-blind Randomized-withdrawal Phase.
4.5.2 Subjects ‘Lost to Follow-up’ Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). One of these documented attempts must include a written communication sent to the subject’s last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 30 days prior to the Screening Visit (Visit -1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

5.1 Prior Treatment

Prior treatment includes all treatment (including herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days of and discontinued prior to the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate CRF page.

No psychoactive medications will be allowed during the study. Treatments excluded from this study are detailed in Table 2. Further, any psychoactive medications not listed within Table 2 used within 5 half-lives of the Screening Visit (Visit -1) are exclusionary.

<table>
<thead>
<tr>
<th>Table 2: Prior Treatments and Common Excluded Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigational compounds</strong></td>
</tr>
<tr>
<td><strong>Sedatives, anxiolytics, antipsychotics</strong></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
</tr>
</tbody>
</table>
### Table 2: Prior Treatments and Common Excluded Medications

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychostimulants, amphetamines and amphetamine-like agents</td>
<td>Use of sympathomimetics, appetite suppressants (i.e., phentermine, sibutramine, modafinil, methylphenidate, amphetamine, and pemoline) within 6 months prior to the Screening Visit (Visit -1) will exclude the subject from this study. Use of caffeine and tobacco will not exclude the subject. Use of cough/cold preparations containing stimulants/sympathomimetic agents within 7 days prior to the Screening Visit (Visit -1) will exclude the subject from the study.</td>
</tr>
<tr>
<td>Clonidine and guanfacine</td>
<td>Use of clonidine or guanfacine within 30 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Norepinephrine reuptake inhibitors</td>
<td>Norepinephrine reuptake inhibitors, such as atomoxetine (STRATTERA®, Lilly), are not allowed. Use of atomoxetine within 30 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Sedative-hypnotics and benzodiazepines</td>
<td>Use of sedative-hypnotics and benzodiazepines within 30 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Antihistamines (centrally and peripherally active)</td>
<td>The chronic use of sedating antihistamines (as a single preparation or in combination) is not permitted. Use of sedating antihistamines within 7 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Herbal preparations/other medications</td>
<td>Use of any herbal preparations/other medications that would confound safety or efficacy assessments is prohibited. Use of herbal preparations/other medications within 7 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Use of melatonin within 7 days prior to the first visit of this study is not permitted.</td>
</tr>
<tr>
<td>Over-the-counter medications and weight loss therapies</td>
<td>Use of over-the-counter weight loss therapies or prescription weight loss therapies including but not limited to sibutramine (MERIDIA®, Abbot),lorcaserin hydrochloride (BELVIQ®, Eisai), phentermine and topiramate extended-release (QSYMIA™, Vivus) or lipase inhibitors orlistat (XENICAL®, Roche) within 30 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Use of narcotics within 30 days prior to the Screening Visit (Visit -1) will exclude the subject from this study.</td>
</tr>
<tr>
<td>Psychoactive medications</td>
<td>No psychoactive medications will be allowed during the study and use within 5 half-lives of the Screening Visit (Visit -1) are exclusionary.</td>
</tr>
</tbody>
</table>

### 5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.
5.2.1 Permitted Treatment

Treatments not listed in Table 2 above are permitted during the study.

The following therapies are permitted during the study:

- Stable dose of thyroid medication, provided the same dose has been used for at least 3 months prior to the Screening Visit (Visit -1)
- Stable regimen of bronchodilator inhalers for well-controlled, mild asthma is permitted. (Note: Chronic use of oral corticosteroids is prohibited.)
- Any medications that do not affect blood pressure, heart rate, or the central nervous system and which are considered necessary for the subject’s welfare, may be administered at the discretion of the investigator
- Non-sedating antihistamines such as fexofenadine (ALLEGRA®, Sanofi Aventis), loratadine (CLARITIN®, Schering Plough), and cetirizine hydrochloride (Zyrtec®, McNeil-PPC)
- Narcotics prescribed for an acute condition (Note: Chronic use of narcotics is not permitted.)
- Over-the-counter non-stimulant cold remedies
- Hormonal contraceptives for sexually active females of child-bearing potential administered according to the package insert. All hormonal contraceptives should have been initiated 30 days prior to the Screening Visit (Visit -1).
- Stable dose of lipid-lowering medication, provided the same dose was used for at least 3 months prior to the first dose of investigational product
- A stable dose of antihypertensive therapy with well-controlled mild hypertension for at least 3 months prior to the Screening Visit (Visit -1).
- Psychotherapy (eg, cognitive behavior therapy, interpersonal therapy) or weight loss support (eg, Weight Watchers) for BED that began ≥3 months prior to the Screening Visit (Visit -1). Initiation or changes are not permitted during the study.

5.2.2 Prohibited Treatment

Prior and concomitant treatments excluded from this study are detailed in Table 2.
6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The investigational product is SPD489 (lisdexamfetamine dimesylate), which will be provided as 30, 50, and 70mg capsules. Additional information is provided in the SPD489 Investigator’s Brochure which is provided under separate cover.

The reference product will be matching placebo that capsules. All investigational and reference product will appear identical, to protect the study blind.

Capsules should be taken whole and not crushed, chewed, or cut.

6.1.1 Blinding the Treatment Assignment

After completion of the Open-label Treatment Phase, the actual treatment given to individual subjects is determined by a randomization schedule. A randomization schedule will be prepared to assign eligible subjects to 1 of 2 treatment groups with an allocation ratio of 1:1 (SPD489 or placebo), stratified by 4-week cessation status (Yes or No) at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8) and region (North America vs. non-North America). The associated treatment assignments giving details of individual subject treatment are automatically defined by the IWRS. At each visit, subjects will be supplied bottles of investigational product that have been individually allocated by IWRS, and instructed to take 1 capsule every morning.

All investigational product (SPD489 or placebo) will appear identical, in order to protect the study blind.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An IWRS will be employed in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, site-assignments, subject randomization, returns, and emergency unblinding of the investigational product.

The IWRS provider will provide a user manual and training to each site, with detailed instruction on use of the IWRS.
6.2.2 Allocation of Subjects to Treatment

The Randomized-withdrawal Phase is the double-blind, placebo-controlled portion of the study. The actual treatment given to individual subjects is determined by a randomization schedule, automatically assigned by the IWRS.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

At Visit 8 (the Double-blind Randomized-withdrawal Baseline Visit), a unique 4-digit randomization number corresponding to investigational product allocated to the subject is assigned to each subject by the IWRS, once eligibility for the double-blind Randomized-withdrawal Phase has been determined. The allocation ratio of 1:1 (SPD489 or placebo) will be used for the randomization, stratified by the 4-week complete cessation status (Yes or No) at Visit 8 and region (North America vs. non-North America) to facilitate balance of treatment within each stratum.

6.2.3 Dosing

Subjects will be instructed to take 1 capsule each morning at approximately 7:00 AM (±2 hours).

6.2.3.1 Open-label Treatment Phase

Subjects will enter the Dose-optimization Period and begin treatment with an SPD489 dose of 30mg/day. The 30mg dose will be used for titration purposes only. At Visit 1 all subjects will be titrated to a dose of 50mg/day. Subsequent increases to 70mg/day will be made as tolerated and clinically indicated. All subjects will undergo titration to an optimal dose (50 or 70mg/day) during the Dose-optimization Period.

<table>
<thead>
<tr>
<th>Table 3: SPD489 Dose-optimization Period Schedule</th>
</tr>
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<tbody>
<tr>
<td>Week 0 (Visit 0)</td>
</tr>
<tr>
<td>30mg</td>
</tr>
<tr>
<td>Week 1 (Visit 1)</td>
</tr>
<tr>
<td>50mg</td>
</tr>
<tr>
<td>Week 2 (Visit 2)</td>
</tr>
<tr>
<td>50 or 70mg</td>
</tr>
<tr>
<td>Week 3 (Visit 3)</td>
</tr>
<tr>
<td>50 or 70mg</td>
</tr>
</tbody>
</table>

Investigators will have the option to down-titratre a subject’s dose from 70 to 50mg in the event the 70mg dose is not tolerated. Visit 3 will be the last visit when dose changes are permitted. Once a dose reduction has occurred, the subject is not permitted to have their dose changed and it will be maintained until the end of the Double-blind Randomized-withdrawal
Phase (Visit 21/ET). Subjects who are unable to tolerate investigational product will be discontinued.

Following enrollment into the Open-label Treatment Phase, at all weekly visits, all subjects will continue taking SPD489 and will be evaluated after approximately 7 days (±2 days) for safety and efficacy.

6.2.3.2 Double-blind Randomized Withdrawal Phase

Following completion of the Open-label Treatment Phase and confirmation of eligibility for randomization, subjects will enter the Double-blind Treatment Phase. If eligible, subjects will be randomized using a 1:1 allocation ratio to continue on their optimal dose of SPD489 or placebo. If a subject does not meet the responder criteria at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8) as detailed in Section 7.1.4.3, they will be discontinued from the study.

6.2.4 Unblinding the Treatment Assignment

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor as soon as possible after the investigator has been unblinded.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code and the reason for breaking the code are recorded in the IWRS and the source documents. Upon breaking the blind, the subject is to be withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the CRO and sponsor. Code break access will be provided to the investigator/designated person at the site and the CRO medical monitor for the study.
6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product container.

A computer-generated label is applied to the investigational product. All investigational product is labeled with a minimum of the protocol number, pack number (if applicable), dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number or packing reference, the statements ‘For clinical trial use only’, and/or ‘CAUTION: New Drug- Limited by Federal (or US) Law to Investigational Use’ and ‘Keep out of reach of children’, and the sponsor's name and address.

Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record a unique subject identifier.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name.

Additional labels may not be added without the sponsor’s prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

- 9-count high density polyethylene bottles with child-resistant closures, for the weekly visits during the Dose-optimization Period
- 16-count high density polyethylene bottles with child-resistant closures, for the 2-weekly visits in the Dose-maintenance and Randomized-withdrawal Phases.

Bottle counts dispensed may vary depending on specific country or region regulations.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.
6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

All controlled-substance investigational product for the sponsor’s studies must be stored in a securely locked, substantially constructed room or cabinet according to all applicable local, state, and/or national laws. Limited, controlled access to these investigational products must be maintained, as well as chain of custody, for all investigational product movement.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct
supervision of the investigator. This delegation must be documented in the applicable study
degression of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable
study delegation of authority form) will dispense the investigational product only to subjects
included in this study following the procedures set out in the study protocol. Each subject
will be given only the investigational product carrying his/her treatment assignment. All
dispensed medication will be documented on the CRFs and/or other investigational product
record. The investigator is responsible for assuring the retrieval of all study supplies from
subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be
removed from the site where originally shipped without prior knowledge and consent by the
sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national
laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and
distribution procedures and records provided that the blind of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned
investigational product, and empty/used investigational product packaging are to be sent to a
nominated contractor on behalf of the sponsor. Investigational product being returned to the
sponsor’s designated contractors must be counted and verified by clinical site personnel and
the sponsor (or designated CRO). For unused supplies where the original supplied
tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and
the labeled amount is to be documented in lieu of counting. Shipment return forms, when
used, must be signed prior to shipment from the site. Validated electronic return systems
(ie, IRT) do not require a shipment form. Returned investigational product must be packed in
a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to
return any investigational product prior to shipment. Shipment of all returned investigational
product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile
investigational products delivered with those used and returned. All investigational products
must be accounted for and all discrepancies investigated and documented to the sponsor’s
satisfaction.

6.5 Subject Compliance

Subjects must be instructed to bring their unused investigational product and empty/used
investigational product packaging to every visit. Drug accountability must be assessed at the
container/packaging level for unused investigational product that is contained within the
original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count
level for opened containers/packaging. The pharmacist/nominated person will record details
on the drug accountability form.
Subject compliance must be assessed by the investigator. Subjects who have taken 80-100% of the investigational product are regarded as being compliant with the study protocol. Compliance will be assessed at each on-treatment visit after the Open-label and Double-blind baseline phases.

7. STUDY PROCEDURES

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (see Table 1) and must be referred to in conjunction with the instruction provided in this section. Clinician-completed rating scales and assessments that are conducted at multiple visits (eg, CGI-S, CGI-I, Y-BOCS-BE, C-SSRS) should be completed by the same rater whenever possible.

Throughout the Dose-optimization Period, visits should be scheduled every 7 days with reference to the Open-label Baseline Visit (Visit 0). There is a ±2 day window for each visit; however, the visit window is not a factor when calculating the next visit date. For example, Visit 2 will occur 14 days (±2 days) after the Open-label Baseline Visit (Visit 0), regardless of when Visit 1 occurred.

Throughout the Dose-maintenance Period, visits should be scheduled every 14 days with reference to the Open-label Baseline Visit (Visit 0). There is a ±2 day window for each visit; however, the visit window is not a factor when calculating the next visit date. For example, Visit 7 will occur 70 days (±2 days) after the Open-label Baseline Visit (Visit 0), regardless of when Visit 6 occurred.

Visit 8 (Week 12) should occur 77 days after the Open-label Baseline Visit (Visit 0) with a +1 day visit window. This gives a 15-day interval from Visit 7 to allow for a full 14 days of diary data to be recorded and collected.

Throughout the Double-blind Randomized-withdrawal Phase, visits should be scheduled every 14 days with reference to the Open-label Baseline Visit (Visit 0). There is a ±2 day window for each visit; however, the visit window is not a factor when calculating the next visit date. For example, Visit 10 will occur 105 days (±2 days) after the Open-label Baseline Visit (Visit 0), regardless of when Visit 9 occurred.

The Follow-up Visit (Visit 22) should be scheduled 7 days following the last dose with a +2 day visit window.

7.1 Study Schedule

See Table 1 for study procedures.
7.1.1 Interactive Web Response System for Subject Tracking/Data Collection

An IWRS will be used to track consented subjects, screen failures, enrolled and randomized subjects (those meeting all eligibility criteria), subjects’ visits, completed subjects, discontinued subjects, and Follow-up Visit (Visit 22) information. Section 6.2.1 discusses use of the IWRS to also manage investigational product.

At the Screening Visit (Visit -1), the investigator or designee will access the IWRS to record subject-specific information (eg, subject identification number, date of birth, etc) to allow the sponsor and the CRO to track the number of subjects consenting at each site.

At the Open-label Baseline Visit (Visit 0), the investigator or designee will again access the IWRS to either document the subject as a screen failure or as enrolled, and to obtain details regarding the investigational product (eg, treatment assignment) for enrolled subjects.

At Visits 1-20, the investigator or designee will access the IWRS to obtain details regarding the investigational product.

For Visits 6-20, the investigator or designee will also be prompted to enter the number of binge days over a given period of time as well as the CGI-S score to allow the correct assignment to strata during randomization (Visit 8 only) and to help determine subject relapse (Visits 9-20).

Additionally, as each subject completes Visit 21/ET, the investigator or designee will access IWRS to record the visit.

At the Follow-up Visit (Visit 22), the investigator or designee will access the IWRS to record visit completion.

The IWRS provider will provide a user manual and training to each site with detailed instructions on the use of the IWRS.

7.1.2 Screening Phase

Subjects will be screened at Visit -1 to establish eligibility for study participation. The minimum duration of the screening phase is 14 days and the maximum duration of the Screening Phase is 28 days.

The principal investigator or his/her designee must obtain written informed consent from the subject prior to any study-related procedures.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s).
Subjects cannot be rescreened once they have been designated as a screen failure. Reassessment of subjects who failed specific criteria is not allowed.

7.1.2.1 Screening Visit (Visit -1)

Table 1 details all procedures to be completed at the Screening Visit (Visit -1) and should serve as the primary section of the protocol regarding visit-specific study procedures. Additional clarification on the procedures performed during the Screening Visit (Visit -1) is provided below:

- For subjects agreeing to a pharmacogenomic sample (see Section 7.2.4.1):
  - Subject will sign an additional genomic research informed consent form
  - The physician/clinician will collect all samples using the collection kit provided, and mail the kit as per instructions
  - Subjects who do not consent to provide a pharmacogenomic sample are still eligible to participate in the main study.

- All AEs occurring after signature of informed consent must be recorded in the source documents and CRF.

- Twelve-lead ECG will be performed after 5 minutes of rest. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject. The ECG tracing will be sent to the central reader for analysis. Upon review of the report from the central reader, results from central reader will be reported as normal or abnormal, the investigator will re-evaluate the clinical significance of the ECG in light of other safety data for the subject. Following assessment by the central reader, if abnormal results are confirmed clinically significant by the investigator, the investigator, in consultation with the appointed CRO medical monitor, will confirm the subject’s eligibility to participate in this study. Subjects with abnormal and clinically significant results are not eligible to enroll.

- Body mass index should be calculated using 1 of the following formulae:

  \[
  \text{BMI} = \frac{\text{Weight in pounds} \times 703}{(\text{Height in inches})^2}
  \]

  \[
  \text{BMI} = \frac{\text{Weight in kilograms}}{(\text{Height in meters})^2}
  \]

  Body mass index values may be computed using the formula provided or by using an approved online calculator as referenced in external site documentation.

Subjects will record their eating history in their diaries on a daily basis.
7.1.3 Open-label Baseline Visit (Visit 0)

Once the screening central clinical laboratory tests and 12-lead ECG results have been obtained in addition to repeat assessments (if required), subjects will return to the site for the Open-label Baseline Visit (Visit 0).

Inclusion/exclusion criteria will be re-evaluated at the Open-label Baseline Visit (Visit 0) to ensure subjects continue to meet all eligibility criteria (where applicable). All eligible subjects will be administered SPD489.

Subjects will be considered eligible to enroll into the Open-label Treatment Phase if they meet the following criteria at the Open-label Baseline Visit (Visit 0):

1. Subject reports \( \geq 3 \) binge days each week during the 14 days prior to the Open-label Baseline Visit (Visit 0) as documented in the subject diary

AND

2. Subject has a CGI-S score of \( \geq 4 \)

Table 1 outlines all procedures to be conducted during the Open-label Baseline Visit (Visit 0) with further clarification provided below:

- Urine pregnancy test using a urine dipstick will be performed by site personnel. Results must be recorded on the source documents and CRF. Results must be negative for the female subject to be enrolled in the study. If the result is positive the subject may not continue in the study and the process outlined in Section 8.1.6 must be followed.

- Subjects will be dispensed a 9-count bottle of investigational product to cover them until their next scheduled visit (Visit 1). Subjects will be instructed to take a 1 capsule of investigational product daily. Dosing will begin the morning following the Open-label Baseline Visit (Visit 0). See Section 6.2.3 for full investigational product dosing instructions.

7.1.4 Open-Label Treatment Phase

7.1.4.1 Dose-Optimization Period (Visits 1-4 / Weeks 1-4)

During this period, subjects will return to the site for evaluations of safety and efficacy as outlined in Table 1. Further clarification for these visits is outlined below:

- Scales are to be completed by the same rater whenever possible

- At each visit during the Dose-optimization Period, subjects must return any empty, partially used, or unused bottles of investigational product, to permit drug accountability and compliance to be assessed
Subjects will be dispensed a 9-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule of investigational product daily. Dosing will begin the morning following each visit. See Section 6.2.3 for full investigational product dosing instructions.

Throughout the Dose-optimization Period, subjects may attend the clinic for unscheduled visits to address any medical needs that arise between scheduled visits.

7.1.4.2 Dose-Maintenance Period (Visits 5-8 / Weeks 6-12)

Following the Dose-optimization Period, subjects will continue daily morning treatment with their optimized dose of SPD489.

Table 1 outlines the procedures to be completed at each visit during the Dose-maintenance Period. Additional clarification on the procedures to be performed during the Dose-maintenance Period is provided below:

- Scales are to be completed by the same rater whenever possible
- At each visit during the Dose-maintenance Period, subjects must return any empty, partially used, or unused bottles of investigational product, to permit drug accountability and compliance to be assessed
- Subjects will be dispensed a 16-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule of investigational product daily. Dosing will begin the morning following each visit.

Throughout the Dose-maintenance Period, subjects may attend the clinic for unscheduled visits to address any medical needs that arise between scheduled visits.

7.1.4.3 Double-Blind Randomized-Withdrawal Baseline Visit (Visit 8 / Week 12)

Subjects who meet both of the following criteria at Visit 8 will be referred to as “Responders” and will be eligible to continue into the Double-blind Treatment Phase:

1. Subject reports ≤1 binge day each week for 4 consecutive weeks (28 days) prior to the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

AND

2. Subject has a CGI-S score of ≤2 at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

Among the responders (meeting both criteria above), a subject having no binge days during the 4-week period is defined as achieving 4-week cessation.
7.1.5 Double-Blind Randomized-Withdrawal Phase (Visits 9-20 / Weeks 14-36)

Following completion of the Open-label Treatment Phase and confirmation of eligibility, subjects will enter the Double-blind Randomized-withdrawal Phase. If eligible, subjects will be randomized using a 1:1 allocation ratio to continue on their optimal dose of SPD489 or placebo. If a subject does not meet the responder criteria at Visit 8, they will not be able to move into the Double-blind Randomized-withdrawal Phase of the study. Visit 9 should occur at least 15 days after Visit 8 in order to capture 14 complete days of diary history.

Relapse is determined by the investigator at each visit during the Double-blind Treatment Phase using the following criteria:

1. Subject reports $\geq 2$ binge days each week for 2 consecutive weeks (14 days) prior to each visit

   AND

2. Subject has a $\geq 2$ point increase in CGI-S score relative to their score at the Double-blind Randomized-withdrawal Baseline Visit (Visit 8)

A subject who meets the relapse criteria at any time point during the Double-blind Randomized-withdrawal Phase will be immediately discontinued from the study and all early termination procedures will be completed.

Table 1 outlines the procedures to be completed at each visit during the Dose-maintenance Period. Additional clarification on the procedures to be performed during the Dose-maintenance Period is provided below:

- Scales are to be completed by the same rater whenever possible
- At each visit during the Double-blind Randomized-withdrawal Phase, subjects must return any empty, partially used, or unused bottles of investigational product, to permit drug accountability and compliance to be assessed
- Subjects will be dispensed a 16-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule of investigational product daily. Dosing will begin the morning following each visit.

Throughout the Double-blind Randomized-withdrawal Phase, subjects may attend the clinic for unscheduled visits to address any medical needs that arise between scheduled visits.

7.1.5.1 Final Visit (Visit 21/ET / Week 38)

All subjects completing the study, those who have decided to withdraw early, and those who have been withdrawn, will be asked to return for the final safety and efficacy assessments scheduled for Visit 21/ET. Table 1 lists the procedures to be completed at Visit 21/ET and should serve as the primary point of reference regarding visit-specific study procedures.
Further clarification on the procedures performed during Visit 21/ET is provided below:

- The ACSA should be completed by the subject daily starting at Visit 21/ET up to and including the day of Visit 22/Follow-up Visit.
- A serum $\beta$-HCG pregnancy test is to be performed on all females, regardless of child-bearing potential, at this visit. Results must be recorded in the source documents as well as the CRF. If test results are positive, the process outlined in Section 8.1.6 must be followed.
- For subjects who have consented to a pharmacogenomic sample (see Section 7.2.4.1):
  - The physician/clinician will collect additional samples using the collection kit provided and mail the kit as per instructions.
- Unused investigational product and empty containers will be collected to calculate medication compliance.
- As each subject completes this visit, the investigator or designee will access IWRS to record the visit.

7.1.6  Follow-Up Phase

7.1.6.1  Follow-up Visit (Visit 22 / Week 39)

The Follow-up Visit (Visit 22) for this protocol is 7 days following the last dose of investigational product with a +2 day visit window.

All subjects will be asked to return for this final clinic visit in order to collect information on any ongoing or new AEs, SAEs, and concomitant medications. In addition, the CGI-I and C-SSRS will be carried out. Appropriate follow-up should continue until all safety concerns, in the investigator’s opinion, have resolved (see Section 8.1).

As each subject completes the Follow-up Visit, the investigator or designee will access IWRS to record the visit.

If a subject refuses to return to the site for the Follow-up Visit, the site personnel will initiate a follow-up telephone call 7-9 days after a subject’s last dose of investigational product. During this telephone call, the site personnel will collect all information on any ongoing or new AEs or SAEs, and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the investigator’s opinion, are resolved. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1).
7.1.7 Additional Care of Subjects after the Study

There is no planned additional care for subjects after the trial. The investigator will discuss the available BED treatment options for subjects as they complete the study.

7.2 Study Evaluations and Procedures

7.2.1 Evaluations for Binge Eating and Psychiatric Disorders

The principal investigator or a sub-investigator who is experienced in psychiatric evaluations will determine a diagnosis of BED based on the SCID-I Eating Disorders Module H and review of EDE-Q as well as establish the presence of current and lifetime comorbid Axis I conditions as based on the MINI-Plus. The psychiatric evaluations will be carried out by a clinician or trained mental health professional with experience of these instruments and who is qualified to establish a psychiatric diagnosis. This would include physicians, nurse practitioners, or licensed psychologists. Individuals performing these interviews must be pre-approved by the sponsor or designee. See Table 1 for time points of assessments.

7.2.1.1 Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – Text Revision

The SCID-I is a semi-structured interview for making DSM-IV-TR Axis I diagnoses using DSM-IV-TR criteria. It has been developed to increase diagnostic reliability through standardization of the assessment process, to increase diagnostic validity by facilitating the application of the DSM-IV-TR diagnostic criteria, and by systematically probing for symptoms that might otherwise be overlooked. The SCID-I Eating Disorders Module H is administered for this study in a single setting. In this study, it will be conducted at the Screening Visit (Visit -1) only, to confirm a diagnosis of BED.

The title, version, and date of the SCID-I scale used in this study are detailed in Appendix 5.

7.2.1.2 Mini International Neuropsychiatric Interview-Plus

The MINI-Plus is a structured interview for the major Axis I psychiatric disorders in DSM-IV-TR and ICD-10. In this study, it will be conducted at the Screening Visit (Visit -1) only, to exclude comorbid Axis I disorders.

The title, version, and date of the MINI-Plus scale used in this study are detailed in Appendix 5.
7.2.1.3 Montgomery-Åsberg Depression Rating Scale

The MADRS is a measurement of depressive illness severity consisting of 10 items. Each of the 10 items is scored using a 7-point rating scale (0-6), worded with anchors at the even anchor points (0, 2, 4, 6). Higher scores indicate increasing depressive symptoms. Ratings can be added to form an overall score (range 0-60). Cut-off points include 0-6 (symptom absent), 7-19 (mild depression), 30-34 (moderate depression), and 35-60 (severe depression). The scale will be administered at the Screening Visit (Visit -1) only, as an eligibility assessment.

The title and date of the MADRS used in this study are detailed in Appendix 5.

7.2.1.4 Eating Disorder Examination-Questionnaire

The EDE-Q is a 28-item questionnaire measuring eating pathology and is derived directly from the Eating Disorder Examination Interview (Fairburn and Cooper 1993). The EDE-Q focuses on the past 28 days to assess the main behavioral (eating and purging) and attitudinal features of eating disorders. The EDE-Q contains 4 subscales: Restraint, Eating Concern, Weight Concern, and Shape Concern. In this study, it will be conducted at the Screening Visit (Visit -1) only, to confirm a diagnosis of BED.

The title, version, and date of the EDE-Q used in this study are detailed in Appendix 5.

7.2.2 Efficacy

Every effort should be made to ensure efficacy assessments for each subject are completed by the same rater throughout the study. Raters of all scales must be medically responsible, experienced clinicians who are pre-approved by the sponsor or designee, and who are trained in administering each scale.

7.2.2.1 Subject Daily Diary

Binge eating information will be captured daily via a self-report paper diary and collected by the site at each visit. Binge frequency will be reviewed by the clinician with the subject to confirm reported binge episodes per day.

The binge diary will capture the number of binges per day, total hours per day spent binging, type of binge (at mealtime or at another time other than mealtime), and a description of the binge (amounts and types of foods). All of the above information is reported by the subject at each study visit; the investigator reviews the diary and confirms whether each recorded eating episode is a binge as reported by the subject. The number of confirmed binge episodes per day is collected on the CRF. Investigators will be trained on the proper evaluation of a binge episode to allow for diary assessment standardization.
The title, version, and date of the subject daily diary used in this study are detailed in Appendix 5.

7.2.2.2 Clinical Global Impressions Rating Scales

The Clinical Global Impressions rating scales permit a global evaluation of a subject’s condition, severity, and improvement over time. The CGI-S is performed at each visit to rate the severity of a subject’s condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) and includes a ‘not assessed’ option. The CGI-I is performed at each visit post-baseline to rate the improvement of a subject’s condition on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) and includes a ‘not assessed’ option.

The title and date of the CGI-S and CGI-I scales used in this study are detailed in Appendix 5.

7.2.2.3 Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating

The Y-BOCS-BE is a modified version of the Yale-Brown Obsessive Compulsive Scale used in previous pharmacotherapy studies with BED that measures the obsession of binge eating thoughts and compulsiveness of binge eating behaviors. The scale is a clinician-rated, 10-item scale, each item rated from 0 (no symptoms) to 4 (extreme symptoms). The scale includes questions about the amount of time the subject spends on obsessions, how much impairment or distress they experience, and how much resistance and control they have over these thoughts. As well, the same types of questions are asked about compulsions (ie, time spent, interference, etc). The results can be interpreted based on the score. A score of 0-7 is sub-clinical; 8-15 is mild; 16-23 is moderate; 24-31 is severe; and 32-40 is extreme. The title of the Y-BOCS-BE used in this study is detailed in Appendix 5.

7.2.3 Safety

The name and address of each third party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator’s and sponsor’s files.

7.2.3.1 Medical and Medication History

The investigator will perform a complete medical history at the Screening Visit (Visit -1), including a medication history, and record all information gathered. The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of diagnosis.
Medical history must include, but is not limited to:

- Age
- Sex
- Race
- Ethnicity
- Recent use of medication
- Smoking status
- Lifetime history of pharmacological and non-pharmacological treatment of BED including lifetime history of psychological/weight loss interventions
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases.

7.2.3.2 Physical Examination (Including Height and Weight)

A full physical examination will be performed at the Screening Visit (Visit -1) and Visit 21/ET by a qualified individual, licensed in his/her respective state/province (eg, physician, physician assistant, or a nurse practitioner). A full physical examination is composed of a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological.

Any abnormalities or changes in intensity noted during the review of body systems should be documented in the source documents and reported in the CRF.

If a new clinically significant finding occurs (ie, not noted at screening) after the screening examination, it must be captured as an AE. In addition, resolution of any clinically significant abnormal findings that have been reported as an AE during the study will be noted in the medical record and in the CRF.
Height will be captured at the Screening Visit (Visit -1). A stadiometer must be used for all height measurements. Height should be measured in inches/centimeters without shoes with the subject standing on a flat surface and with chin parallel to the floor. The body should be straight but not rigid. The subject’s height should be recorded as accurately as possible using the stadiometer.

Weight will be captured at all visits. The same calibrated scale must be used for all weight measurements. Weight may be measured in pounds or kilograms without shoes, and should be recorded as accurately as possible.

7.2.3.3 Adverse Event Collection

At each study visit, and to avoid bias in eliciting AEs, subjects will be questioned in a general, non-leading way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). This information should be collected prior to completion of assessments at all study visits.

In addition, any symptoms/conditions reported during assessments and deemed clinically significant by the investigator will be assessed as AEs. Adverse events are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.6. (Please see Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.4 Vital Signs

Measurements of vital signs (sitting systolic and diastolic blood pressure, pulse, oral or tympanic temperature, and sitting respiratory rate) will be performed at each visit by a trained individual. At every visit, blood pressure, pulse, temperature, and respiratory rate will be obtained after subjects have remained seated for a minimum of 5 minutes.

Blood pressure will be determined by automated cuff (the same unit and the same arm should be used throughout the study). A blood pressure cuff appropriate for the subject’s arm length and girth should be used for all blood pressure measurements. The cuff should be approximately two-thirds the length/width of the subject’s arm (from elbow to shoulder). All blood pressure measurements should be performed throughout the study using the apparatus provided by the central ECG vendor. The automated cuff will obtain 3 measurements with approximately 2 minutes in between each collection for blood pressure and pulse and report the average of the 3 measurements for each parameter. The 3 individual measurements and the averaged reading should be recorded in the source documents and CRF.

Any clinically significant deviations in vital signs in the opinion of the investigator from the Open-label Baseline Visit (Visit 0) will be recorded as an AE.
7.2.3.5 Waist Circumference

Waist circumference measurements will be performed at the time points specified in Table 1. To ensure the proper measurement, the subject must stand erect and remove any excess clothing. Waist circumference measurements may be taken with a tape measure. Start at the top of the hip bone and then bring the tape all the way around so that it is level with the navel. Wrap the tape measure completely around the subject’s waist and obtain the measurement making sure that the tape is parallel with the floor. Waist circumference may be measured in inches or centimeters.

7.2.3.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory’s normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject’s clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

A central laboratory will perform all testing with the exception of the urine pregnancy test, which will be performed at the site. The name and address of the central laboratory for this study will be maintained in the investigator’s files at each site as well as in the trial master file at the CRO/sponsor.

The investigator should assess any out-of-range clinical laboratory values (high or low) for clinical significance on the original clinical laboratory report.
The following clinical laboratory assessments will be performed:

**Biochemistry**

Blood samples (~8.5mL) for biochemistry will be taken at the Screening Visit (Visit -1) and Visits 7, 14, and 21/ET to assess the following parameters.

- **Total cholesterol, HDL, LDL, and triglycerides**
- **Calcium**
- **Aspartate transaminase (AST)**
- **Uric acid**
- **Phosphorus**
- **Blood urea nitrogen (BUN)**
- **Alanine transaminase (ALT)**
- **Total bilirubin**
- **Sodium**
- **Creatinine**
- **Alkaline phosphatase**
- **Glucose**
- **Potassium**
- **Albumin**
- **Gamma-glutamyl transferase (GGT)**
- **Total protein**
- **Thyroid stimulating hormone (TSH)**
- **Creatine phosphokinase (CPK)**
- **Hemoglobin A1c (HbA1c)**
- **Lactate dehydrogenase (LDH)**
- **C-reactive protein (CRP)**
- **Insulin**
  - **Leptin**
  - **Ghrelin**

If a subject has a result for TSH that meets the reflex criterion, the central laboratory will perform a free T4 reflex test to confirm the initial result. For TSH, the reflex criterion is defined as <0.4 or >4.0 μIU/mL.

Upon receipt of the reflex test results, the investigator, in conjunction with the CRO medical monitor, will evaluate the suitability for the subject to participate in the study.

**Hematology**

Blood samples (~3mL) for hematology will be taken at the Screening Visit (Visit -1) and Visits 7, 14, and 21/ET to assess the following parameters.

- **Hemoglobin**
  - **Neutrophils**
- **Hematocrit**
  - **Lymphocytes**
- **Red blood cells (RBC)**
  - **Monocytes**
- **Platelet count**
  - **Eosinophils**
- **White blood cell (WBC) count – total and differential**
  - **Basophils**
- **Mean corpuscular hemoglobin concentration (MCHC)**
  - **Bands**
- **Mean corpuscular hemoglobin (MCH)**
  - **Mean corpuscular volume (MCV)**
Urinalysis
Urinalysis
Urine samples (~10mL) will be collected at the Screening Visit (Visit -1) and Visits 7, 14, and 21/ET for urinalysis to assess the following parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>pH</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>Urobilinogen</td>
</tr>
<tr>
<td>Blood</td>
<td>Color</td>
</tr>
<tr>
<td>Ketones</td>
<td>Leukocyte esterase</td>
</tr>
<tr>
<td>Protein</td>
<td>Nitrite</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
</tr>
</tbody>
</table>

If urinalysis detects protein and/or blood, microscopic examination will be conducted. The microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.3.7 Pregnancy Test

A serum β-HCG pregnancy test will be performed on all females at the Screening Visit (Visit -1) and at the end of the study (Visit 21/ET), or if pregnancy is suspected, or on withdrawal of the subject from the study. Serum required to perform this screen will be obtained from the biochemistry sample already being collected for all subjects.

A urine pregnancy test using a urine dipstick will be conducted at the Open-label Baseline Visit (Visit 0) for all female subjects and will continue to be performed monthly for the duration of the study (see Table 1).

Entry into the study and continued participation is contingent on a negative result at the Screening Visit (Visit -1) and the Open-label Baseline Visit (Visit 0). Note: If Screening Visit value is indeterminate, a serum β-HCG pregnancy test must be repeated and negative prior to the Open-label Baseline Visit (Visit 0) for females of child-bearing potential; serum β-HCG levels have to be confirmed stable and not positive for females of non-child bearing potential. Eligibility of females with indeterminate pregnancy test results should be discussed and confirmed by a medical monitor. Additional urine pregnancy tests may be performed at the investigator’s discretion.

In case of pregnancy, see Section 8.1.6.

7.2.3.8 Urine Drug Screen

A urine drug screen will be conducted at the Screening Visit (Visit -1). Urine samples (~10mL) will be collected for this testing.
The urine drug screen will test for the following drugs/drug classes.

- Cocaine metabolites
- Cannabinoids
- Phencyclidine
- Barbiturates
- Benzodiazepines
- Propoxyphene
- Opiates
- Methadone
- Methaqualone
- Methamphetamine
- Amphetamine

7.2.3.9 Electrocardiogram

Twelve-lead ECGs will be performed at the Screening Visit (Visit -1), Open-label Baseline Visit (Visit 0), Visit 4, Double-blind Randomized-withdrawal Baseline Visit (Visit 8), Visit 9, Visit 12, Visit 16, and at Visit 21/ET. To ensure appropriate intervals are recorded, a total of 3 ECGs will be performed at the Open-label Baseline Visit (Visit 0) with approximately 2 minutes between readings. A single ECG will be conducted at all other visits.

All ECGs will be performed using the central ECG provider’s equipment and will be sent to the central ECG provider electronically. The name and location of the central ECG provider will be maintained in the investigator’s files at each study site as well as in the trial master file at the CRO/sponsor.

The initial interpretation of the ECG, normal or abnormal and clinical significance, will be performed at the site by the investigator or another medically qualified designee immediately after collection to ensure the safety of each subject. Electrocardiogram tracings will then be evaluated by a cardiologist at a central ECG reading vendor and returned to the site with a determination of normal or abnormal. Upon review of each report from this vendor, the investigator will re-evaluate the clinical significance of the ECG while taking into consideration all other safety data available for the subject.

Although a central ECG reader is being used for this study, the eligibility of the subject is based on the investigator’s assessment of the ECG. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed CRO medical monitor, reconfirms subject eligibility to continue.

All ECGs transmitted to the central ECG reader will be analyzed. If the central ECG reader receives more than the protocol-specified number of ECGs at any visit, the first interpretable ECG(s) will be analyzed as the scheduled ECG(s) for that visit. Any additional ECGs transmitted will be reported on the CRF as additional ECGs for that respective visit. All ECGs (scheduled and unscheduled) are transmitted to the central reader and they are all captured in the database.
7.2.3.10 Columbia-Suicide Severity Rating Scale

The C-SSRS (Posner et al. 2009) is a semi-structured interview that was developed to assess suicidal ideations and behaviors. The interview and rating for the C-SSRS must be completed by a clinician who has been successfully trained by sponsor or designee to rate this scale.

The interview is initiated with 5 (yes/no) questions, presented in ascending order of severity, about suicidal ideation. The most severe type of ideation was rated (based on 5- and 6-point Likert scales) for frequency, duration, controllability, deterrents, and reason.

If the answer to the first 2 ideation questions is “yes”, the clinician asks the third, fourth, and fifth ideation questions. If the answer to the first 2 ideation questions is “no”, the clinician proceeds to the questions (see below) that address suicidal behavior.

Four yes/no questions assess suicidal behavior (categorized as actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behaviors) and 1 yes/no question assesses non-suicidal self-injurious behavior. Lethality (actual, potential) is assessed for actual suicidal attempts. One additional question collects completed suicide yes or no.

Two versions of the C-SSRS are used in this study: The “Baseline” version will be administered at the Screening Visit (Visit -1). The “Since Last Visit” version will be completed at all other visits for all of the subjects in this study.

The titles, versions, and dates of the C-SSRS used in this study are detailed in Appendix 5.

7.2.3.11 Suitability of Subject to Remain in the Study

Following completion of the C-SSRS at each clinic visit up to and including Visit 21/ET (Week 38), a clinician who is medically responsible for the subject, should assess whether it remains in the best interest of the subject to participate in or continue in the study and that it is safe for the subject to do so. As part of the assessment of the subject’s suitability to remain in the study, the investigator should assess the subject’s current potential for suicide, suicidal ideation, self-harm, or harm to others. The investigator should make this assessment by conducting a clinical interview with the subject and by reviewing all other relevant sources available, including results of the C-SSRS. Active suicidal ideation is defined as any non-specific suicidal thoughts, ideation with any methods without intent, ideation with some intent to act without a specific plan, or ideation with specific plan and intent. Passive suicidal ideation is defined as any thoughts about a wish to be dead without any thoughts of actually killing themselves.

The investigator should also ensure that there is appropriate documentation of this suitability assessment in the subject’s source notes. As part of this assessment, if appropriate, the investigator should discuss risk factors for suicide with the subject. Where a subject has suffered an accidental injury, the investigator should ensure that this was a true accidental injury, rather than an episode of self-harming or a suicide attempt.
The subject’s source notes should clearly document that the assessment of continued suitability, including an assessment of the subject’s current potential risk of suicide, suicidal ideation (active or passive), feelings of hopelessness, drug use, self-harm, or harm to others, has taken place and should contain the decision on whether the subject is suitable to continue in the study.

The investigator should pay particular attention to a positive score for Questions 4 and/or 5 on the C-SSRS or any suicidal behavior. If a subject is found to meet these criteria they must undergo further evaluation to ensure that they are not in any way at risk. This evaluation and decision should also be clearly documented in the subject’s source notes and discussed with a medical monitor.

As part of routine good clinical care, subjects will be provided with 24-hour emergency contact details in case of an emergency situation where the subject feels that they are acutely at risk. In addition, subjects who are recruited into the study will be advised of the location of their closest hospital.

7.2.3.12 Amphetamine Cessation Symptom Assessment

The ACSA is a self-completed scale for the assessment of withdrawal symptoms. The scale has 16 symptom items rated on a 5-point scale ranging from 0 (not at all) to 4 (extremely).

The ACSA will be administered at the Open-label Baseline Visit (Visit 0), Double-blind Randomized-withdrawal Baseline Visit (Visit 8), and daily starting at Visit 21/ET up until Visit 22/Follow-up Visit.

The title of the ACSA scale used in this study is included in Appendix 5.

7.2.4 Others

7.2.4.1 Pharmacogenomic Sampling

Shire intends to apply genomic research across the SPD489 development program. The intent of this exploratory research is to aid in biomarker development, design, and interpretation of clinical studies, exploration of guided treatment strategies and to increase disease understanding.

To support these aims, subjects will have the option to provide additional blood samples for DNA (8.5mL), RNA (2.5mL), and protein (4.0mL) at the Screening Visit (Visit -1) and RNA (2.5mL) and protein (4.0mL) at Visit 7 and at Visit 21/ET.

Donation of samples is optional, non-participation has no impact on participation in the main study, and requires a separate informed consent. To ensure subject confidentiality, samples
will be stored and analyzed in a de-identified format. Samples will be stored in biorepositories for up to 15 years.

Samples from subjects who are screened but not subsequently enrolled into the study will be destroyed.

The scope of any present and/or future research will be restricted to candidate gene/proteins/markers related to responses to SPD489, BED and its treatment. Based on the outcome of ongoing research, the following pre-defined gene variants may be assessed in relation to BED and its treatment with SPD489:

<table>
<thead>
<tr>
<th>Table 4: Pharmacogenomic Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
</tr>
<tr>
<td>Dopamine transporter (DAT, SLC6A3)</td>
</tr>
<tr>
<td>Dopamine receptor DRD2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Norepinephrine transporter (SLC6A2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>COMT</td>
</tr>
<tr>
<td>OPRM1</td>
</tr>
<tr>
<td>Dopamine Receptor DRD1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Dopamine Receptor DRD4</td>
</tr>
</tbody>
</table>

Any associations of interest may be replicated in the Phase 3 program. A validation analysis plan may be pre-specified prior to Phase 3 data un-blinding to define prospective analysis of the marker(s) of interest on samples collected within the study.

Beyond this, samples will be biobanked for potential future exploratory analysis which will be restricted to increasing our understanding of BED, and its treatment and response to SPD489.
only. Any future analysis beyond the defined genes will be performed as exploratory research and reported separately from the main clinical study report. Biobanked samples will be retained for a maximum of 15 years.

Results may be used internally to help support the design of additional clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. The sponsor has no obligation to perform this additional exploratory research.

Subjects have the right to withdraw consent from this additional component, with no impact on participation in the main study. Any results generated will not be made available, unless required to do so by law. Subjects can request results of any analysis on their samples, although it won’t be possible to interpret these. No record of participation in this pharmacogenomics portion of the protocol or any results derived from it should be recorded in the subject’s personal medical records. A record of participation in the pharmacogenomics portion of the protocol will, however, be captured in the study-specific source documentation records.

The intent of this research is not to return results to subjects, unless required to do so by law. Subjects can request return of individual results, but it will not be possible to interpret these. No record of participation in any pharmacogenomic research, or any results derived from it should be recorded in a subject’s personal medical records.

Any results of this exploratory research will be reported separately from the main clinical study report. Results may be used internally to help support the design of additional clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. The sponsor has no obligation to perform this additional exploratory research.

For additional information and details see Appendix 6.

7.2.4.2 Health-related Quality of Life Assessments

7.2.4.2.1 EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire

The EQ-5D-5L is one of the most widely used generic index measures of health-related quality of life. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses. The EQ-5D-5L will be completed at Screening (Visit -1), Open-label Baseline Visit (Visit 0), Visit 4 (Week 4), Visit 8 (Week 12), and Visit 21/ET.

The title, version, and date of the EQ-5D-5L used in this study are detailed in Appendix 5.
7.2.4.2.2 Sheehan Disability Scale

The SDS is a composite of 3 self-rated items designed to evaluate the extent to which illness symptoms impact a subject’s life. Subjects rate the extent to which their illness has impacted their work, social life, and family life/home responsibilities on an 11-point continuum from 0=no impairment to 10=most severe. There are ranges within each continuum of mild (1-3), moderate (4-6), and marked (7-9). The SDS will be completed at the Open-label Baseline Visit (Visit 0), Visit 4 (Week 4), Visit 8 (Week 12), Visit 10 (Week 16), Visit 12 (Week 20), Visit 14 (Week 24), Visit 16 (Week 28), Visit 18 (Week 32), and Visit 21/ET (Week 38).

The title and date of the SDS used in this study are detailed in Appendix 5.

7.2.4.3 Healthcare Resource Utilization Assessments

7.2.4.3.1 Patient Resource Utilization Questionnaire for Binge Eating Disorder

The PRUQ-BED has been developed by the Shire Health Economics Outcomes Research team to assess long-term economic outcomes. It collects utilization of healthcare resources reported by the study subjects. The types of healthcare resources collected by this instrument are: outpatient visits, clinical laboratory tests, emergency room visits, length, and reasons for hospitalization, and productivity measures (presenteeism and absenteeism). The PRUQ-BED has 2 versions: the baseline version and the follow-up version. The “Baseline” version will be administered at the Open-label Baseline Visit (Visit 0). The follow-up version should be used for all other administrations as described in Table 1.

The title, version, and date of the PRUQ-BED used in this study are detailed in Appendix 5.
7.2.5 Volume of Blood to be Drawn From Each Subject

Table 5: Volume of Blood to be drawn From Each Subject

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Sample Volume (mL)</th>
<th>Number of Samples</th>
<th>Total Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical chemistry and β-HCG(^a)</td>
<td>8.5</td>
<td>4</td>
<td>34.0</td>
</tr>
<tr>
<td>Hematology</td>
<td>3</td>
<td>4</td>
<td>12.0</td>
</tr>
<tr>
<td><strong>Total mL for Safety</strong></td>
<td></td>
<td></td>
<td><strong>46.0</strong></td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>8.5</td>
<td>1</td>
<td>8.5</td>
</tr>
<tr>
<td>RNA</td>
<td>2.5</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>Protein</td>
<td>4.0</td>
<td>3</td>
<td>12.0</td>
</tr>
<tr>
<td><strong>Total mL for Pharmacogenomics</strong></td>
<td></td>
<td></td>
<td><strong>28.0</strong></td>
</tr>
<tr>
<td><strong>Total mL (if pharmacogenomic sample is collected)</strong></td>
<td></td>
<td></td>
<td><strong>74.0</strong></td>
</tr>
</tbody>
</table>

\(^a\) β-HCG testing for females only.

During this study, it is expected that approximately 46.0mL of blood will be drawn from all subjects, regardless of sex. For subjects who consent to providing voluntary samples for pharmacogenomic analysis, an additional 28.0mL blood will be taken (ie, 74.0mL in total).

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that 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 temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.6. This includes events occurring during the screening phase of
the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject’s health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

**Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

**Moderate:** A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

**Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related”. Otherwise, if there is any valid reason, even if undetermined or untested, for
suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related”. The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

<table>
<thead>
<tr>
<th>Term</th>
<th>Relationship Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject’s medical condition, other therapies, or accident.</td>
</tr>
<tr>
<td>Not Related</td>
<td>The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.</td>
</tr>
</tbody>
</table>

### 8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

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

### 8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

### 8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of
deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.6.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Pharmacovigilance Department using the Shire Investigational and Marketed Products Pregnancy Report Form. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Trial Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Trial Serious Adverse Event Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as
described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one’s state of consciousness or get high) in a manner that may be detrimental to the individual and/or society

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 70mg of SPD489 in the Open-label Treatment Phase and 1 capsule of the investigational product during the Double-blind Treatment Phase.

- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

### 8.2 Serious Adverse Event Procedures

#### 8.2.1 Reference Safety Information

The reference for safety information for this study is the SPD489 Investigator’s Brochure which the sponsor has provided under separate cover to all investigators.

#### 8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event. Note: The
24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents. Note: Fax or e-mail the form to the Shire Pharmacovigilance Department; source documents are not to be sent unless requested.

8.2.3 Serious Adverse Event Definition

A **Serious Adverse Event (SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term ‘life-threatening’ in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. 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; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.6, and must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.
In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

### 8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

### 8.2.6 Fatal Outcome

Any SAE that results in the subject’s death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject’s death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject’s death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product).

### 8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and the Clinical CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/EU central ECs of related, unexpected SAEs. Notifications will also be sent to local IRBs/ECs in accordance with all applicable local guidelines and regulations.

In addition the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SPD489 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.
9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators’ authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator’s meeting. It is expected that site personnel will complete the CRF entry within 3 business days of the subject’s visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO’s data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. Statistical analyses will be primarily performed in SAS® version 9.1 or higher. Other software, if utilized, will be specified in the SAP.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study
information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

For efficacy and safety analyses, the Visit 21/ET value is defined as the last valid available assessment during the Double-blind Randomized-withdrawal Phase, and will be summarized similar to scheduled visits.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or Data Monitoring Committee in this study.

9.6 Sample Size Calculation and Power Considerations

The sample size was determined for the primary comparison of SPD489 and placebo treatment groups using nQuery Advisor 6.0. Assuming true relapse rates of 30 and 55% for SPD489 and placebo respectively, corresponding to a hazard ratio of 0.447 for SPD489 as compared to placebo, an overall 72 subjects will need to experience relapse overall to provide 90% power for the 2-sided stratified log-rank test at the 5% level of significance.

Approximately 777 subjects will be screened to enroll 412 subjects in the Open-label Treatment Phase. Assuming a 20% dropout rate in the Open-label Treatment Phase and a 65% response rate for subjects completing the Open-label Treatment Phase, a total of 214 subjects will be randomized (107 in each treatment group). Assuming 20% of randomized subjects will discontinue before experiencing relapses, the total of 72 subjects experiencing relapses will be observed based on the assumed relapse rates of the 2 treatment groups.

9.7 Study Population

The Safety Analysis Set consists of subjects who have taken at least 1 dose of SPD489 in the Open-label Treatment Phase.

The Randomized Safety Analysis Set is defined as all subjects in the Safety Analysis Set who take at least 1 dose of investigational product in the Double-blind Randomized-withdrawal Phase.

The Full Analysis Set (FAS) is defined as all subjects in the Randomized Safety Analysis Set with at least 1 post-randomization CGI-S assessment.
The summary of both safety and efficacy data for the Open-label Treatment Phase will be based on the Safety Analysis Set.

Safety analyses for the Double-blind Treatment Phase of the study will be based on the Randomized Safety Analysis Set.

Efficacy analyses for the Double-blind Treatment Phase will primarily be based on the FAS.

### 9.8 Efficacy Analyses

#### 9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is time to relapse (see Section 7.1.5) from randomization. The investigator assesses the relapse status at each visit during the Double-blind Treatment Phase. The time of relapse is defined as the visit date when the relapse is confirmed.

The primary efficacy endpoint of time to relapse from randomization will be compared between the SPD489 and the placebo treatment groups using a stratified log-rank test over the FAS, stratifying for the 4-week complete cessation status (Yes or No).

The null hypothesis states that there is no between-treatment group difference in the survival functions for relapse. The 2-sided alternative states that the survival functions for relapse are different. The null hypothesis will be rejected if the statistical analysis results in a 2-sided p-value less than or equal to 0.05 from the log-rank test comparing 2 survival functions. Subjects who discontinue from the Double-blind Treatment Phase of the study without meeting relapse criteria are censored in the primary analysis. The time to relapse will be plotted graphically using the Kaplan-Meier method by treatment group. The median and quartiles of time to relapse will be calculated for each treatment group, with the proportions of relapse at 3 and 6 months after randomization estimated, with confidence intervals constructed based on the Greenwood formula.

Sensitivity analysis to be used in the assessment of primary endpoints will be described in detail in the SAP. Such analysis will include but are not limited to:

- Repeating the primary analysis based the alternative definition for relapse as reporting ≥2 binge days each week for 2 consecutive weeks (14 days) prior to a visit, without the CGI-S requirement

#### 9.8.2 Secondary Efficacy Endpoints

Due to the removal of subjects with relapse events impacting the numbers of subjects over time in the study, there are no Key Secondary endpoints.
Secondary efficacy endpoints are:

- Change from Visit 8 (Week 12) to Visit 21 (Week 38) in the number of binge days per week
- CGI-S at Visit 21/ET (Week 38)
- Change from Visit 8 (Week 12) to Visit 21 (Week 38) in Y-BOCS-BE

The change from Visit 8 (Week 12) to Visit 21 (Week 38) in the number of binge days per week will be analyzed over the FAS using an MMRM analysis over all post-baseline visits during the Double-blind Randomized-withdrawal Phase, with change from Visit 8 (Week 12) in number of binge days per week as the outcome variable; treatment group, visit, and their interaction as factors; baseline binge days per week as a covariate; and its interaction with visit also in the model.

For the Double-blind Randomized-withdrawal Phase, a covariate-adjusted Cochran-Mantel-Haenszel test (Stokes et al. 2000) with a modified ridit score will be conducted over the FAS on CGI-S, adjusting for Visit 8 (Week 12) CGI-S as the covariate.

The change from Visit 8 (Week 12) in Y-BOCS-BE will be compared between the SPD489 group and the placebo group using the MMRM method, with treatment group, visit, and their interaction as factors; the respective value at the randomized baseline (Visit 8) as a covariate; and its interaction with visit also in the model.

The summarization on EQ-5D-5L data is detailed in Section 9.10.1.

**9.8.3 Exploratory Efficacy Endpoints**

The change from Visit 8 (Week 12) in SDS total score at Visit 21/ET (Week 38) during the Double-blind Randomized Withdrawal Phase will be compared between the SPD489 group and the placebo group using the MMRM method, with treatment group, visit, and their interaction as factors; the respective value at the randomized baseline (Visit 8) as a covariate; and its interaction with visit also in the model.

The summarization on PRUQ-BED data is detailed in Section 9.10.2.

**9.9 Safety Analyses**

Safety data in the Open-label Treatment Phase will be presented over the Safety Analysis Set and the Double-blind Randomized-withdrawal Phase will be presented over the Randomized Safety Analysis Set by treatment group. The safety data collected at the Open-label Baseline Visit (Visit 0) (Screening if not collected at the Open-label Baseline Visit [Visit 0]) will be used as the baseline for safety analyses over the duration of the study. In addition, the values of vital signs, weight, and ECG collected at Visit 8 (Week 12) will be used as the
randomization baseline and will be used for summaries for the Double-blind Randomized-withdrawal Phase.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that start or deteriorate on or after the date of the first dose of investigational product, and no later than 3 days following the last dose of investigational product. However, any subjects who die during the study (ie, the date of death is between the date of first dose of investigational product and the date of study discontinuation entered by the site, inclusive), all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose, and will be included in the TEAE summaries. All summaries of AEs will be based on TEAEs unless specified otherwise.

If severity or relationship to investigational product is missing for an AE which occurred post administration of investigational product, the event will be regarded as severe and related to investigational product, respectively.

The number and percent of subjects with TEAEs will be calculated by system organ class and preferred term, and presented for all patients in the Open-label Treatment Phase and by treatment group in the Double-blind Randomized-withdrawal Phase. The severity of the TEAEs, the relationship to investigational product (as assessed by the investigator), TEAEs causing discontinuation of investigational product, SAEs, and SAEs resulting in death will be similarly presented.

Vital signs (temperature, weight, systolic and diastolic blood pressure, pulse, and respiratory rate) and ECG results will be descriptively summarized for the Open-label Treatment Phase and for the Double-blind Randomized-withdrawal Phase by treatment group for each post Open-label Baseline Visit. Potentially clinically important values for vital signs and ECG results will be defined in the SAP. Number and percent of subjects with potentially clinically important values will be presented by treatment group.

The change and the percent change in body weight, waist circumference, and BMI will be summarized by post Open-label Baseline Visit over the Safety Analysis Set for the Open-label Treatment Phase and will be summarized by treatment group over Randomized Safety Analysis Set for the Double-blind Randomized-withdrawal Phase. In addition, the change and percent change from Visit 8 (Week 12) in body weight, waist circumference, and BMI will be summarized over Randomized FAS for the Double-blind Randomized-withdrawal Phase by treatment group.

Clinical laboratory test results will be descriptively presented overall for the Open-label treatment Phase over the Safety Analysis Set and by treatment group for each visit during the Double-blind Randomized-withdrawal Phase over the Randomized Safety Analysis Set. Clinical laboratory test results will be descriptively presented by treatment group for each visit. Shifts of clinical laboratory abnormality from the Open-label Baseline Visit (Visit 0) to Visit 21/ET will be presented. Potentially clinically important laboratory ranges will be defined in the SAP. Number and percent of subjects with potentially clinically important
laboratory values during the Open-label Treatment Phase will be presented. The Double-blind Randomized-withdrawal Phase will be presented by treatment group.

Any positive findings in C-SSRS data will be descriptively summarized for the Open-label Treatment Phase and by treatment group for the Double-blind Randomized-withdrawal Phase.

The ACSA will be summarized descriptively at the Open-label Baseline Visit (Visit 0), Double-blind Randomized-withdrawal Baseline Visit (Visit 8), and daily starting at Visit 21/ET, through the Follow-up Visit at the end of the study.

9.10 Other Analyses

No other analyses are planned in this study.

9.10.1 Health-related Quality of Life Analyses

The EQ-5D-5L will be summarized for each item at the Open-label Baseline Visit (Visit 0), Visit 4 (Week 4) and Visit 8 (Week 12) for the Open-label treatment phase, and at Visit 8 (Week 12) and Visit 21/ET by treatment group for the Double-blind Randomized-withdrawal Phase.

9.10.2 Healthcare Resource Utilization Analyses

The PRUQ-BED data will be descriptively summarized and listed at the Open-label Baseline Visit (Visit 0), Visit 4 (Week 4), Visit 6 (Week 8), and Visit 8 (Week 12) for the Open-label Treatment Phase and will be descriptively summarized by treatment group at the Randomized-withdrawal Baseline Visit (Visit 8), Visit 10 (Week 16), Visit 12 (Week 20), Visit 14 (Week 24), Visit 16 (Week 28), Visit 18 (Week 32), Visit 20 (Week 36), Visit 21/ET (Week 38) for the Double-blind Randomized-withdrawal Phase.

10. SPONSOR’S AND INVESTIGATOR’S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third party vendor (eg, CRO) used in this study will be maintained in the investigator’s and sponsor’s files, as appropriate.
10.1 Sponsor’s Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects’ medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary. Copies will also be provided to MOH/ECs in accordance with all applicable local guidelines and regulations.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators’ names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the
end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor/CRO will provide the ECs with a copy of the same summary in accordance with all applicable local guidelines and regulations.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator’s Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator’s responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject’s consent, inform them of the subject’s participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).
10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate/study monitor will verify the contents of the completed CRF against the source data, per the monitoring plan. Further instruction on completion of the CRF and source document verification will be detailed in the CRF completion guidelines and monitoring plan, respectively. If the data are unclear or contradictory, queries are sent for corrections or verification of data.
10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject’s medical file, subject diary cards, original clinical laboratory, and ECG reports.

All key data must be recorded in the subject’s medical records.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject’s medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54.2(b) (1998).
In consideration of participation in the study, the sponsor pays the investigator or nominated payee the sums set out in the payment schedule attached to the investigator agreement.

10.2.4 Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject’s legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject’s rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject’s legally-authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject’s study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC’s written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.
10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the Sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SPD489; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects’ identities.
Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies—containing subjects’ unique identifying number, relevant medical records, and possibly initials and dates of birth—will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results / Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor’s proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term “publication” refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor’s confidential information shall be submitted for publication without the sponsor’s prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal
investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor’s presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.
11. REFERENCES


12. APPENDICES
## APPENDIX 1 PROTOCOL HISTORY

<table>
<thead>
<tr>
<th>Document</th>
<th>Date</th>
<th>Global/Country/Site Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Protocol</td>
<td>21 Dec 2012</td>
<td>Global</td>
</tr>
</tbody>
</table>
APPENDIX 2 CONTACT LIST

The coordinating principal investigator name/contact details and the details of other investigators are provided in a separate document.
APPENDIX 3 INVESTIGATOR’S BROCHURE

The current investigator’s brochure for SPD489 will be provided under separate cover.
Please refer to section 307.50 of the DSM-IV-TR: Eating Disorder Not Otherwise Specified for additional information on binge eating disorder.

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

1. Eating, in a discrete period of time (eg, within a 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar conditions.
2. A sense of lack of control over the eating (eg, a feeling that one cannot stop eating or control what or how much one is eating).

B. The binge eating episodes are associated with at least 3 of the following:

1. Eating much more rapidly than normal.
2. Eating until uncomfortably full.
3. Eating large amounts of food when not feeling physically hungry.
4. Eating alone because of being embarrassed by how much one is eating.
5. Feeling disgusted with oneself, depressed, or feeling very guilty after overeating.

C. Marked distress regarding binge eating

D. The binge eating occurs, on average, at least 2 days a week for 6 months

E. The binge eating is not associated with the regular use of inappropriate compensatory behaviors (eg, purging, fasting, excessive exercise) and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.
## APPENDIX 5  SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

<table>
<thead>
<tr>
<th>Full Title of Scale/Assessment</th>
<th>Version</th>
<th>Date Issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) Section 307.50 of the DSM-IV-TR: Eating Disorder Not Otherwise Specified for additional information on binge eating disorder</td>
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<tr>
<td>The Mini International Neuropsychiatric Interview (MINI) Plus</td>
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<tr>
<td>Eating Disorder Examination Questionnaire (EDE-Q)</td>
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<td>Columbia-Suicide Severity Rating Scale (C-SSRS)</td>
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</tr>
<tr>
<td></td>
<td>Since Last Visit</td>
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<td>Clinical Global Impressions - Severity of Illness</td>
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</tr>
<tr>
<td>Clinical Global Impressions - Global Improvement</td>
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<tr>
<td>Montgomery–Åsberg Depression Rating Scale (MADRS)</td>
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<tr>
<td>Yale-Brown Compulsive Scale Modified for Binge Eating (Y-BOCS-BE)</td>
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<td>N/A</td>
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<td>Patient Resource Utilization Questionnaire for Binge Eating Disorder (PRUQ-BED)- Baseline and Follow-up</td>
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<td>21 Dec 2010</td>
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<tr>
<td>EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L)</td>
<td>V. 2.0</td>
<td>2009</td>
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<td>Sheehan Disability Scale (SDS)</td>
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<td>Amphetamine Cessation Symptom Assessment (ACSA)</td>
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<td>Subject Daily Diary</td>
<td>V 1.0</td>
<td>31 Jul 2012</td>
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A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.
APPENDIX 6 PHARMACOGENOMIC SAMPLING

Shire intends to apply genomic research across the SPD489 development program to explore how genomic variations may affect the clinical parameters associated with and response to SPD489 (and any background products, comparators and concomitant medications), and potentially the basis of the indications under study in the protocol, in this case BED. Collection of appropriate samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies, biomarker guided treatment strategies and a better understanding of disease etiology which may lead to new therapeutic approaches.

Exploratory research is currently ongoing into variants in genes selected from the literature for their potential involvement in response to SPD489, BED and its treatment (as detailed in Section 7.2.4.1, Table 4). Any associations of interest may be replicated in the Phase 3 program. A validation analysis plan may be pre-specified prior to Phase 3 data unblinding to define prospective analysis of the marker(s) of interest on samples collected within the study.

Beyond this, samples will be biobanked for potential future exploratory analysis which will be restricted to increasing our understanding of BED, its treatment and response to SPD489 only. Any future analysis beyond the defined genes will be performed as exploratory research and reported separately from the main clinical study report. Biobanked samples will be retained for a maximum of 15 years.

Samples will be taken at Visit -1 (DNA, RNA, and protein), Visits 8 and 21/ET, (RNA and protein). Blood volumes required per sample are: DNA 8.5mL; RNA 2.5mL; protein 4.0mL. Note: only a single sample is required for DNA. Samples may only be collected from subjects who provide separate informed consent, as detailed in the laboratory manual. Samples collected from subjects at enrollment visit who are not subsequently enrolled into the study will be destroyed.

Samples will be labeled with the study protocol number, the subject’s study identification number and information related to the sample (ie, sample type [DNA, RNA, protein]), study visit, tube number (where multiple aliquots are collected). No personal identifiers will be recorded on the sample labels.

Subjects terminating early from the study due to AE, tolerability, or drug-related issues should, where possible, be approached for their remaining protocol-defined samples at the earliest possible time. Unscheduled samples should be labeled with free text capturing study protocol number, subject’s study identification number, and information related to the sample (RNA or protein, sampling date, and time). Samples will be shipped to and stored at biorepositories as detailed in the laboratory manual. DNA, RNA, and protein will be extracted from the samples only when, and if, any separate exploratory research will be undertaken.
As an added level of security, samples will be recoded with a new, unique number at the biorepository laboratory. This unique number is the only code used in any subsequent analysis and will be used to link a sample to a subject and to ensure that the subject’s identity remains confidential.

A link file linking the first and second codes will be kept in a secure place at the sponsor, with restricted access. This will be in a secure environment outside of the clinical study database and separate to any analysis results. This file will be used to identify the relevant samples for analysis, facilitate correlation of any results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. No record of participation in this pharmacogenomics portion of the protocol, or any results derived from it, should be captured in the subject’s personal medical records. A record of participation in the pharmacogenomics portion of the protocol will, however, be captured in the study-specific source documentation.

The sponsor, sponsor’s representatives, biorepositories, and any specialty laboratories will be blinded to the subject’s identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. The link will also be destroyed at the same time as any remaining sample(s) are destroyed. Any results already generated on the samples will not be removed from any analyses that have already been performed.

Participation in this portion of the study is optional and does not impact the subject’s eligibility for participation in the main clinical study protocol. Subjects may continue to participate in the primary study if they refuse to provide a blood sample or if they withdraw their samples.

Results of the genetic analyses may contribute to the global understanding of BED and its treatment and may be used internally to help support the design of additional clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. Any results generated will be for exploratory research purposes only and will not be made available unless required by law (ie, to regulatory authorities). Subjects can request results of any analysis on their samples, although it will not be possible to interpret these.