

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-977/S037

Trade Name: Vyvanse

Generic Name: lisdexamfetamine dimesylate

Sponsor: Shire Development

Approval Date: 1/30/2015

Indication: VYVANSE is a central nervous system (CNS) stimulant indicated for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Moderate to Severe Binge Eating Disorder (BED)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-977/S037

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

APPROVAL LETTER



NDA 21977/S-036/S-037

SUPPLEMENT APPROVAL

Shire Development LLC
Attention: Kimberly McCormick, PharmD
Director, Global Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received July 24, 2014 (S-036) and August 1, 2014 (S-037), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vyvanse (lisdexamfetamine dimesylate) 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg capsules.

We acknowledge receipt of your amendments for S-037 dated:

| | | |
|--------------------|--------------------|------------------|
| August 18, 2014 | September 18, 2014 | January 5, 2015 |
| September 4, 2014 | September 25, 2014 | January 14, 2015 |
| September 9, 2014 | November 21, 2014 | |
| September 15, 2014 | December 19, 2014 | |

The Changes Being Effected supplemental new drug application, S-036, provides for the addition of “constipation” to the Postmarketing Experience, section 6.2, of the Full Prescribing Information.

The Prior Approval supplemental new drug application, S-037, provides for data supporting the safety and effectiveness of Vyvanse for the treatment of moderate to severe Binge Eating Disorder.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for this application because necessary studies are impossible or highly impracticable because there are too few patients with this disease/condition.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2868-1 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of lisdexamfetamine in the treatment of adults with binge eating disorder. This trial must be placebo-controlled, utilize a randomized withdrawal design, and include

an adequate period of stabilization with open-label treatment of lisdexamfetamine prior to double-blind randomization.

The timetable you agreed to on January 29, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: N/A (ongoing)
Study/Trial Completion: 08/2017
Final Report Submission: 02/2018

Submit clinical protocols to your IND 110503 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the

revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Hiren Patel, PharmD, Regulatory Project Manager, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
01/30/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYVANSE safely and effectively. See full prescribing information for VYVANSE.

VYVANSE® (lisdexamfetamine dimesylate) capsules, for oral use, CII
Initial U.S. Approval: 2007

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence (5.1, 9.2, 9.3)
- Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)

RECENT MAJOR CHANGES

Indications and Usage (1) 01/2015
Dosage and Administration (2) 01/2015

INDICATIONS AND USAGE

VYVANSE is a central nervous system (CNS) stimulant indicated for the treatment of (1):

- Attention Deficit Hyperactivity Disorder (ADHD)
- Moderate to Severe Binge Eating Disorder (BED)

Limitation of Use: VYVANSE is not indicated for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.

DOSAGE AND ADMINISTRATION

| Indication | Initial Dose | Titration Schedule | Recommended Dose | Maximum Dose |
|------------|--------------------|-----------------------|------------------------|---------------|
| ADHD (2.2) | 30mg every morning | 10 mg or 20 mg weekly | 30 mg to 70 mg per day | 70 mg per day |
| BED (2.3) | 30mg every morning | 20 mg weekly | 50 mg to 70 mg per day | 70 mg per day |

- Prior to treatment, assess for presence of cardiac disease (2.4)
- Severe renal impairment: Maximum dose is 50 mg/day (2.5)
- End stage renal disease (ESRD): Maximum dose is 30 mg/day (2.5)

DOSAGE FORMS AND STRENGTHS

Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients in VYVANSE (4)
- Use with monoamine oxidase (MAO) inhibitor, or within 14 days of the last MAO inhibitor dose (4, 7.2)

WARNINGS AND PRECAUTIONS

- **Serious Cardiovascular Reactions** Sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (5.2)
- **Blood Pressure and Heart Rate Increases** Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- **Psychiatric Adverse Reactions** May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use (5.4)
- **Suppression of Growth** Monitor height and weight in pediatric patients during treatment (5.5)
- **Peripheral Vasculopathy, including Raynaud's phenomenon** Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with stimulants (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) in children, adolescents, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)

Most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) in adults with BED were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Acidifying and Alkalinizing Agents Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust VYVANSE dosage accordingly (2.6, 7.1)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm (8.1)
- **Nursing Mothers:** Discontinue drug or nursing taking into consideration importance of drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2015

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy [see Warnings and Precautions (5.1, 5.2), and Drug Abuse and Dependence (9.2, 9.3)].

1 INDICATIONS AND USAGE

VYVANSE[®] is indicated for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) [see Clinical Studies (14.1)]
- Moderate to Severe Binge Eating Disorder (BED) [see Clinical Studies (14.2)].

Limitation of Use:

VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established [see Warnings and Precautions (5.2)].

2 DOSAGE AND ADMINISTRATION

2.1 General Instructions for Use

Take VYVANSE by mouth in the morning with or without food; avoid afternoon doses because of the potential for insomnia. VYVANSE may be administered in one of the following ways:

- Swallow VYVANSE capsules whole, or
- Open capsules, empty and mix the entire contents with yogurt, water, or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder. The contents should be mixed until completely dispersed. Consume the entire mixture **immediately**. It should not be stored. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass or container once the mixture is consumed. Do not take anything less than one capsule per day, and a single capsule should not be divided.

2.2 Dosage for Treatment of ADHD

The recommended starting dose is 30 mg once daily in the morning in patients ages 6 and above. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum dose of 70 mg/day. Patients may be maintained on their optimal dose [see Clinical Studies (14.1)].

2.3 Dosage for Treatment of Moderate to Severe BED

The recommended starting dose is 30 mg/day to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 to 70 mg/day. The maximum dose is 70 mg/day [see *Clinical Studies (14.2)*]. Discontinue VYVANSE if binge eating does not improve.

2.4 Important Information Prior to Dosing

Prior to treating children, adolescents, and adults with CNS stimulants, assess for the presence of cardiac disease (e.g., a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) [see *Warnings and Precautions (5.2)*].

To reduce the abuse of CNS stimulants including VYVANSE, assess the risk of abuse, prior to prescribing. After prescribing, keep careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and re-evaluate the need for VYVANSE use [see *Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)*].

2.5 Dosage in Patients with Renal Impairment

In patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m²), the maximum dose should not exceed 50 mg/day. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m²), the maximum recommended dose is 30 mg/day [see *Use in Specific Populations (8.6)*].

2.6 Dosage Modifications due to Drug Interactions

Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust VYVANSE dosage accordingly [see *Drug Interactions (7.1)*].

3 DOSAGE FORMS AND STRENGTHS

Capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg)

Capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg)

Capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg)

Capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg)

Capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg)

Capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg)

Capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg)

4 CONTRAINDICATIONS

VYVANSE is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports [*see Adverse Reactions (6.2)*].
- Concurrent administration of monoamine oxidase inhibitors (MAOI) or administration of VYVANSE within 14 days of the last MAOI dose. Hypertensive crisis can occur [*see Drug Interactions (7.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Drug Abuse and Dependence (9.2, 9.3)*].

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during VYVANSE treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode.

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing VYVANSE. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

5.5 Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including VYVANSE. In a 4-week, placebo-controlled trial of VYVANSE in patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the VYVANSE groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height [*see Adverse Reactions (6.1)*].

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including VYVANSE, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling

- Serious Cardiovascular Reactions [*see Warnings and Precautions (5.2)*]
- Blood Pressure and Heart Rate Increases [*see Warnings and Precautions (5.3)*]
- Psychiatric Adverse Reactions [*see Warnings and Precautions (5.4)*]
- Suppression of Growth [*see Warnings and Precautions (5.5)*]
- Peripheral Vasculopathy, including Raynaud's phenomenon [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Attention Deficit Hyperactivity Disorder

The safety data in this section is based on data from the 4-week parallel-group controlled clinical studies of VYVANSE in pediatric and adult patients with ADHD [see *Clinical Studies (14.1)*].

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials

In the controlled trial in patients ages 6 to 12 years (Study 1), 9% (20/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/72) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of VYVANSE-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)].

In the controlled trial in patients ages 13 to 17 years (Study 4), 4% (10/233) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

In the controlled adult trial (Study 7), 6% (21/358) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequent adverse reactions leading to discontinuation (i.e. leading to discontinuation in at least 1% of VYVANSE-treated patients and at a rate at least twice that of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

The most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More Among VYVANSE Treated Patients with ADHD in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years (Study 1), adolescent patients ages 13 to 17 years (Study 4), and adult patients (Study 7) treated with VYVANSE or placebo are presented in Tables 1, 2, and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Children (Ages 6 to 12 Years) with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)

| | VYVANSE (n=218) | Placebo (n=72) |
|----------------------|--------------------|-------------------|
| Decreased Appetite | 39% | 4% |
| Insomnia | 23% | 3% |
| Abdominal Pain Upper | 12% | 6% |

| | | |
|------------------|-----|----|
| Irritability | 10% | 0% |
| Vomiting | 9% | 4% |
| Weight Decreased | 9% | 1% |
| Nausea | 6% | 3% |
| Dry Mouth | 5% | 0% |
| Dizziness | 5% | 0% |
| Affect lability | 3% | 0% |
| Rash | 3% | 0% |
| Pyrexia | 2% | 1% |
| Somnolence | 2% | 1% |
| Tic | 2% | 0% |

Table 2 Adverse Reactions Reported by 2% or More of Adolescent (Ages 13 to 17 Years) Patients with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)

| | VYVANSE (n=233) | Placebo (n=77) |
|--------------------|--------------------|-------------------|
| Decreased Appetite | 34% | 3% |
| Insomnia | 13% | 4% |
| Weight Decreased | 9% | 0% |
| Dry Mouth | 4% | 1% |

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 7)

| | VYVANSE (n=358) | Placebo (n=62) |
|--------------------------|--------------------|-------------------|
| Decreased Appetite | 27% | 2% |
| Insomnia | 27% | 8% |
| Dry Mouth | 26% | 3% |
| Diarrhea | 7% | 0% |
| Nausea | 7% | 0% |
| Anxiety | 6% | 0% |
| Anorexia | 5% | 0% |
| Feeling Jittery | 4% | 0% |
| Agitation | 3% | 0% |
| Increased Blood Pressure | 3% | 0% |
| Hyperhidrosis | 3% | 0% |
| Restlessness | 3% | 0% |
| Decreased Weight | 3% | 0% |
| Dyspnea | 2% | 0% |

| | | |
|----------------------|----|----|
| Increased Heart Rate | 2% | 0% |
| Tremor | 2% | 0% |

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on VYVANSE and 0% on placebo; decreased libido was observed in 1.4% of subjects on VYVANSE and 0% on placebo.

Weight Loss and Slowing Growth Rate in Pediatric Patients with ADHD

In a controlled trial of VYVANSE in children ages 6 to 12 years (Study 1), mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 1 pound weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received VYVANSE over 12 months suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentiles at baseline and 12 months were 60.9 and 47.2, respectively). In a 4-week controlled trial of VYVANSE in adolescents ages 13 to 17 years, mean weight loss from baseline to endpoint was -2.7, -4.3, and -4.8 lbs., respectively, for patients receiving 30 mg, 50 mg, and 70 mg of VYVANSE, compared to a 2.0 pound weight gain for patients receiving placebo.

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d- to l-enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 pounds and -2.8 pounds, respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment [*see Warnings and Precautions (5.5)*].

Weight Loss in Adults with ADHD

In the controlled adult trial (Study 7), mean weight loss after 4 weeks of therapy was 2.8 pounds, 3.1 pounds, and 4.3 pounds, for patients receiving final doses of 30 mg, 50 mg, and 70 mg of VYVANSE, respectively, compared to a mean weight gain of 0.5 pounds for patients receiving placebo.

Binge Eating Disorder

The safety data in this section is based on data from two 12 week parallel group, flexible-dose, placebo-controlled studies in adults with BED [see *Clinical Studies 14.2*]. Patients with cardiovascular risk factors other than obesity and smoking were excluded.

Adverse Reactions Associated with Discontinuation of Treatment in BED Clinical Trials

In controlled trials of patients ages 18 to 55 years, 5.1% (19/373) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2.4% (9/372) of placebo-treated patients. No single adverse reaction led to discontinuation in 1% or more of VYVANSE-treated patients.

The most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) reported in adults were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety.

Adverse reactions reported in the pooled controlled trials in adult patients (Study 10 and 11) treated with VYVANSE or placebo are presented in Table 4 below.

Table 4 Adverse Reactions Reported by 2% or More of Adult Patients with BED Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo in 12-Week Clinical Trials (Study 10 and 11)

| | VYVANSE (N=373) | Placebo (N=372) |
|-----------------------------------|----------------------------|----------------------------|
| Dry Mouth | 36% | 7% |
| Insomnia ¹ | 20% | 8% |
| Decreased Appetite | 8% | 2% |
| Increased Heart Rate ² | 7% | 1% |
| Feeling Jittery | 6% | 1% |
| Constipation | 6% | 1% |
| Anxiety | 5% | 1% |
| Diarrhea | 4% | 2% |
| Decreased Weight | 4% | 0% |
| Hyperhidrosis | 4% | 0% |
| Vomiting | 2% | 1% |
| Gastroenteritis | 2% | 1% |
| Paresthesia | 2% | 1% |
| Pruritis | 2% | 1% |
| Upper Abdominal Pain | 2% | 0% |
| Energy Increased | 2% | 0% |
| Urinary Tract Infection | 2% | 0% |
| Nightmare | 2% | 0% |
| Restlessness | 2% | 0% |
| Oropharyngeal Pain | 2% | 0% |

¹ Includes all preferred terms containing the word “insomnia.”

² Includes the preferred terms heart rate increased and tachycardia.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of VYVANSE. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: palpitations, cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, tics, bruxism, depression, dermatillomania, aggression, Stevens-Johnson Syndrome, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, and constipation.

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with VYVANSE

Table 5: Effect of Other Drugs on VYVANSE

| Concomitant Drug Name or Drug Class | Clinical Rationale | Clinical Recommendation |
|-------------------------------------|---|--|
| Acidifying and Alkalinizing Agents | Ascorbic acid and other agents that acidify urine increase urinary excretion and decrease the half-life of amphetamine. Sodium bicarbonate and other agents that alkalinize urine decrease urinary excretion and extend the half-life of amphetamine. | Adjust the dose accordingly [<i>see Dosage and Administration (2.6)</i>] |

Table 6: Effect of VYVANSE on Other Drugs

| Concomitant Drug Name or Drug Class | Clinical Rationale | Clinical Recommendation |
|--------------------------------------|---|---|
| Monoamine Oxidase Inhibitors (MAOIs) | Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure. | Do not administer VYVANSE concomitantly or within 14 days after discontinuing MAOI treatment [<i>see Contraindications (4)</i>] |

7.2 Drugs Having No Clinically Important Interactions with VYVANSE

From a pharmacokinetic perspective, no dose adjustment of VYVANSE is necessary when VYVANSE is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when VYVANSE is co-administered [*see Clinical Pharmacology (12.3)*].

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g. omeprazole, lansoprazole, clobazam), and CYP3A4 (e.g. midazolam, pimoziide, simvastatin) is necessary when VYVANSE is co-administered [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with VYVANSE in pregnant women. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. Long-term neurochemical and behavioral effects have been reported in animal developmental studies using clinically relevant doses of amphetamine (d- or d,l-). Animal reproduction studies performed with lisdexamfetamine dimesylate in rats and rabbits showed no effects on embryofetal morphological development and survival. VYVANSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Amphetamines, such as VYVANSE, cause vasoconstriction and thereby may decrease placental perfusion. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Human Data

Available data in women using amphetamines during pregnancy do not show a clear increased risk of major congenital malformations. Two case control studies of over a thousand patients in total exposed to amphetamines at different gestational ages did not show an increase in congenital abnormalities.

Animal Data

Lisdexamfetamine dimesylate had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 4 and 27 times, respectively, the maximum recommended human dose of 70 mg/day given to adolescents, on a mg/m^2 body surface area basis.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.3 Nursing Mothers

Amphetamines are excreted into human milk. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

ADHD

Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1)*]. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

BED

Safety and effectiveness in patients less than 18 years of age have not been established.

Growth Suppression

Growth should be monitored during treatment with stimulants, including VYVANSE, and children who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions (5.5)*, *Adverse Reactions (6.1)*].

Juvenile Animal Data

Studies conducted in juvenile rats and dogs at clinically relevant doses showed growth suppression that partially or fully reversed in dogs and female rats but not in male rats after a four-week drug-free recovery period.

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine dimesylate from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m² basis for a child. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four-week drug-free recovery period, bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine dimesylate for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human

daily dose on a mg/m² basis for a child). This effect partially or fully reversed during a four-week drug-free recovery period.

8.5 Geriatric Use

Clinical studies of VYVANSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience and pharmacokinetic data [see *Clinical Pharmacology (12.3)*] have not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

Due to reduced clearance in patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m²), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR < 15 mL/min/1.73 m²) patients is 30 mg/day [see *Clinical Pharmacology (12.3)*].

Lisdexamfetamine and d-amphetamine are not dialyzable.

8.7 Gender

No dosage adjustment of VYVANSE is necessary on the basis of gender [see *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

VYVANSE contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including VYVANSE, other amphetamines, and methylphenidate-containing products have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been seen. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [see *Overdosage (10)*].

To reduce the abuse of CNS stimulants, including VYVANSE, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for VYVANSE use.

Studies of VYVANSE in Drug Abusers

A randomized, double-blind, placebo-control, cross-over, abuse liability study in 38 patients with a history of drug abuse was conducted with single-doses of 50, 100, or 150 mg of VYVANSE, 40 mg of immediate-release d-amphetamine sulphate (a controlled II substance), and 200 mg of diethylpropion hydrochloride (a controlled IV substance). VYVANSE 100 mg produced significantly less "Drug Liking Effects" as measured by the Drug Rating Questionnaire-Subject score, compared to d-amphetamine 40 mg; and 150 mg of VYVANSE demonstrated similar "Drug-Liking Effects" compared to 40 mg of d-amphetamine and 200 mg of diethylpropion.

Intravenous administration of 50 mg lisdexamfetamine dimesylate to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking", "Euphoria", "Amphetamine Effects", and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) may occur during the chronic therapy of CNS stimulants including VYVANSE.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including VYVANSE. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

10 OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

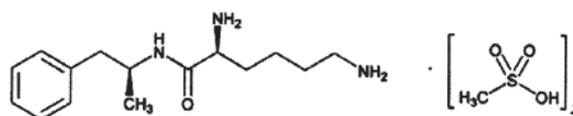
Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea,

vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Lisdexamfetamine and d-amphetamine are not dialyzable.

11 DESCRIPTION

VYVANSE (lisdexamfetamine dimesylate), a CNS stimulant, is a capsule for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$, which corresponds to a molecular weight of 455.60. The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). VYVANSE capsules contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate.

Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

12.3 Pharmacokinetics

Pharmacokinetic studies of dextroamphetamine after oral administration of lisdexamfetamine have been conducted in patients ages 6 to 12 years with ADHD and in healthy adult volunteers.

In 18 patients ages 6 to 12 years with ADHD, the T_{max} of dextroamphetamine was approximately 3.5 hours following single-dose oral administration of lisdexamfetamine dimesylate either 30 mg, 50 mg, or 70 mg after an 8-hour overnight fast. The T_{max} of lisdexamfetamine was approximately 1 hour. Linear pharmacokinetics of dextroamphetamine after single-dose oral administration of lisdexamfetamine dimesylate was established over the dose range of 30 mg to 70 mg in children ages 6 to 12 years and over a range of 50 mg to 250 mg in adults.

Dextroamphetamine pharmacokinetic parameters following administration of lisdexamfetamine dimesylate in adults exhibited low inter-subject (<25%) and intra-subject (<8%) variability. Safety and efficacy have not been studied above the maximum recommended dose of 70mg.

There is no accumulation of dextroamphetamine AUC at steady state in healthy adults and no accumulation of lisdexamfetamine after once-daily dosing for 7 consecutive days.

Neither food (a high fat meal or yogurt) nor orange juice affect the observed AUC and C_{max} of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of VYVANSE capsules. Food prolongs T_{max} by approximately 1 hour (from 3.8 hrs at fasted state to 4.7 hrs after a high fat meal or to 4.2 hrs with yogurt). After an 8-hour fast, the AUCs for dextroamphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

Weight/Dose normalized AUC and C_{max} were 22% and 12% lower, respectively, in adult females than in males on day 7 following a 70 mg/day dose of lisdexamfetamine dimesylate for 7 days. Weight/Dose normalized AUC and C_{max} values were the same in pediatric patients ages 6 to 12 years following single doses of 30-70 mg.

Metabolism and Excretion

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract. Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells. *In vitro* data demonstrated that red blood cells have a high capacity for metabolism of lisdexamfetamine; substantial hydrolysis occurred even at low hematocrit levels (33% of normal). Lisdexamfetamine is not metabolized by cytochrome P450 enzymes. Following the oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in studies of lisdexamfetamine dimesylate in volunteers.

Drug Interaction Studies

Figure 1: Effect of Other Drugs on VYVANSE:

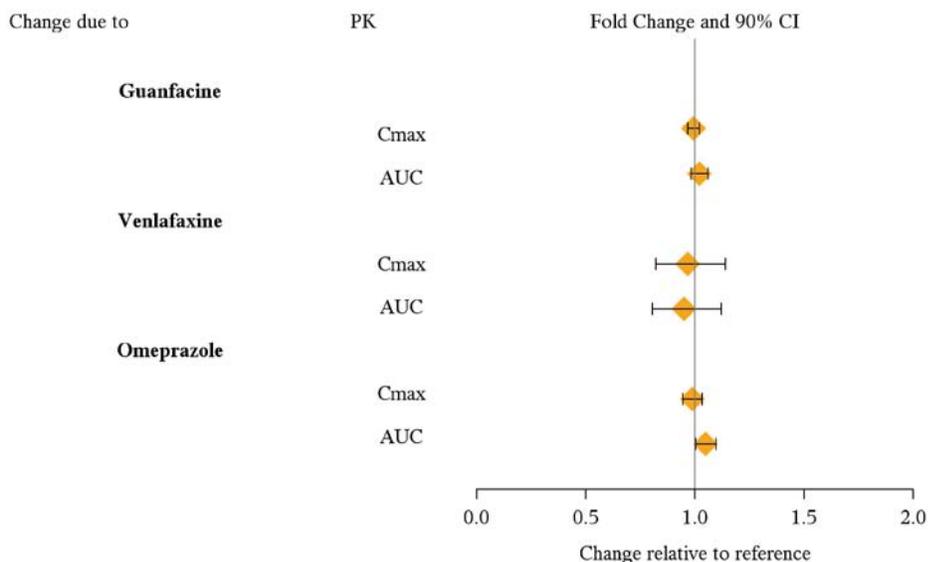
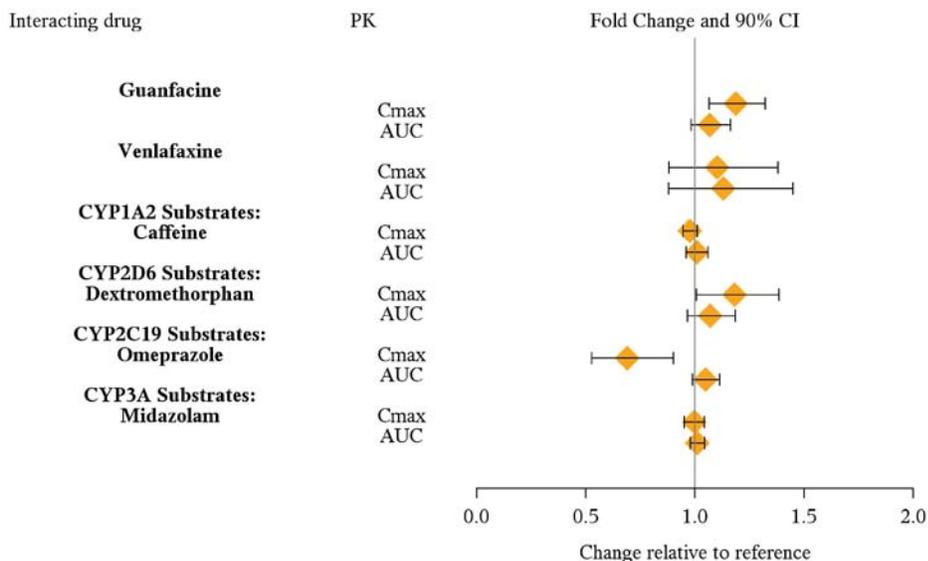


Figure 2: Effect of VYVANSE on Other Drugs:

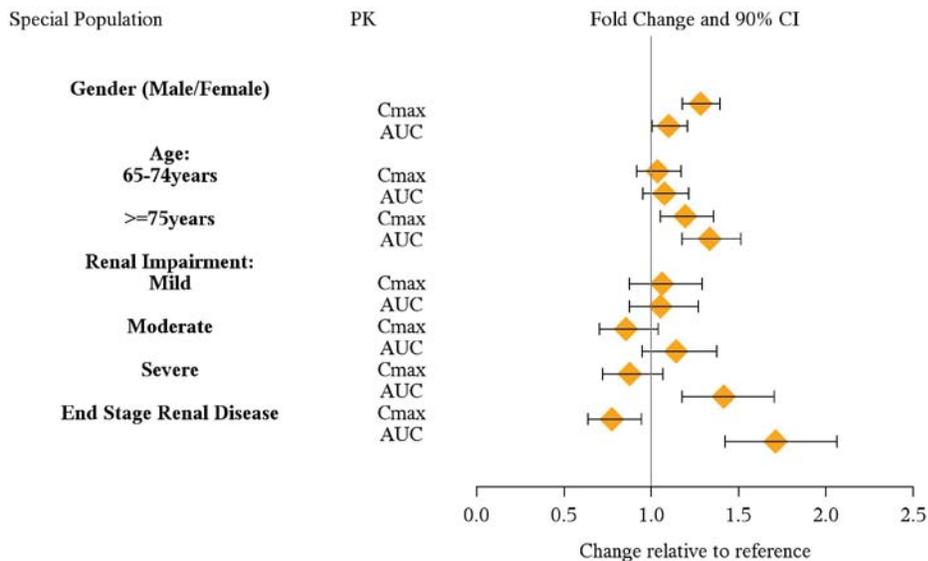


Studies in Specific Populations

Renal Impairment

In a pharmacokinetic study of lisdexamfetamine in subjects with normal and impaired renal function mean d-amphetamine clearance was reduced from 0.7 L/hr/kg in normal subjects to 0.4 L/hr/kg in subjects with severe renal impairment (GFR 15 to <30mL/min/1.73m²) and 0.3 L/hr/kg in ESRD patients. Dialysis did not significantly affect the clearance of d-amphetamine; the mean clearance of d-amphetamine was 0.3 L/hr/kg for both pre- and post- dialysis [see Use in Specific Populations (8.6)].

Figure 3: Specific Populations*:



*Figure 3 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of lisdexamfetamine dimesylate have not been performed. No evidence of carcinogenicity was found in studies in which d-, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats.

Mutagenesis

Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK⁺ mouse lymphoma assay *in vitro*.

Impairment of Fertility

Amphetamine (d- to l-enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

14 CLINICAL STUDIES

Efficacy of VYVANSE in the treatment of ADHD has been established in the following trials:

- Three short-term trials in children (6 to 12 years, Studies 1, 2, 3)
- One short-term trial in adolescents (13 to 17 years, Study 4)
- One short-term trial in children and adolescents (6 to 17 years, Study 5)
- Two short-term trials in adults (18 to 55 years, Studies 7, 8)
- Two randomized withdrawal trials in children and adolescents (6 to 17 years, Study 6), and adults (18 to 55 years, Study 9)

Efficacy of VYVANSE in the treatment of BED has been established in two 12-week trials in adults (18 to 55 years) with moderate to severe BED (Study 10 and 11).

14.1 Attention Deficit Hyperactivity Disorder (ADHD)

Patients Ages 6 to 12 Years Old with ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 1) was conducted in children ages 6 to 12 years (N=290) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of VYVANSE or placebo once daily in the morning for a total of four weeks of treatment. All patients receiving VYVANSE were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS), an 18-item questionnaire with a score range of 0-54 points that measures the core symptoms of ADHD which includes both hyperactive/impulsive and inattentive subscales. Endpoint was defined as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained. All VYVANSE dose groups were superior to placebo in the primary efficacy outcome. Mean effects at all doses were similar; however, the highest dose (70 mg/day) was numerically superior to both lower doses (Study 1 in Table 7). The effects were maintained throughout the day based on parent ratings (Conners' Parent Rating Scale) in the morning (approximately 10 am), afternoon (approximately 2 pm), and early evening (approximately 6 pm).

A double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 2) was conducted in children ages 6 to 12 years (N=52) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 3-week open-label dose optimization with Adderall XR[®], patients were randomly assigned to continue their

optimized dose of Adderall XR (10 mg, 20 mg, or 30 mg), VYVANSE (30 mg, 50 mg, or 70 mg), or placebo once daily in the morning for 1 week each treatment. Efficacy assessments were conducted at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose using the Swanson, Kotkin, Agler, M.Flynn, and Pelham Department scores (SKAMP-DS), a 4-item subscale of the SKAMP with scores ranging from 0 to 24 points that measures department problems leading to classroom disruptions. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-DS across the 8 assessments were observed between patients when they received VYVANSE compared to patients when they received placebo (Study 2 in Table 7). The drug effect reached statistical significance from hours 2 to 12 post-dose, but was not significant at 1 hour.

A second double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 3) was conducted in children ages 6 to 12 years (N=129) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose optimization with VYVANSE (30 mg, 50 mg, 70 mg), patients were randomly assigned to continue their optimized dose of VYVANSE or placebo once daily in the morning for 1 week each treatment. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-Department scores across all 7 assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0, 12.0, and 13.0 hours post-dose, were observed between patients when they received VYVANSE compared to patients when they received placebo (Study 3 in Table 7, Figure 4).

Patients Ages 13 to 17 Years Old with ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 4) was conducted in adolescents ages 13 to 17 years (N=314) who met DSM-IV criteria for ADHD. In this study, patients were randomized in a 1:1:1:1 ratio to a daily morning dose of VYVANSE (30 mg/day, 50 mg/day or 70 mg/day) or placebo for a total of four weeks of treatment. All patients receiving VYVANSE were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained. All VYVANSE dose groups were superior to placebo in the primary efficacy outcome (Study 4 in Table 7).

Patients Ages 6 to 17 Years Old: Short-Term Treatment in ADHD

A double-blind, randomized, placebo- and active-controlled parallel-group, dose-optimization study (Study 5) was conducted in children and adolescents ages 6 to 17 years (n=336) who met DSM-IV criteria for ADHD. In this eight-week study, patients were randomized to a daily morning dose of VYVANSE (30, 50 or 70mg/day), an active control, or placebo (1:1:1). The study consisted of a Screening and Washout Period (up to 42 days), a 7-week Double-blind Evaluation Period (consisting of a 4-week Dose-Optimization Period followed by a 3-week Dose-Maintenance Period), and a 1-week Washout and Follow-up Period. During the Dose Optimization Period, subjects were titrated until an optimal dose, based on tolerability and

investigator's judgment, was reached. VYVANSE showed significantly greater efficacy than placebo. The placebo-adjusted mean reduction from baseline in the ADHD-RS-IV total score was 18.6. Subjects on VYVANSE also showed greater improvement on the Clinical Global Impression-Improvement (CGI-I) rating scale compared to subjects on placebo (Study 5 in Table 7).

Patients Ages 6 to 17 Years Old: Maintenance Treatment in ADHD

Maintenance of Efficacy Study (Study 6) - A double-blind, placebo-controlled, randomized withdrawal study was conducted in children and adolescents ages 6 to 17 (N=276) who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in Study 5 and 40 subjects directly enrolled. Subjects were treated with open-label VYVANSE for at least 26 weeks prior to being assessed for entry into the randomized withdrawal period. Eligible patients had to demonstrate treatment response as defined by CGI-S <3 and Total Score on the ADHD-RS \leq 22. Patients that maintained treatment response for 2 weeks at the end of the open label treatment period were eligible to be randomized to ongoing treatment with the same dose of VYVANSE (N=78) or switched to placebo (N=79) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. A significantly lower proportion of treatment failures occurred among VYVANSE subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomized withdrawal period. The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS Total Score and CGI-S were observed. Treatment failure was defined as a \geq 50% increase (worsening) in the ADHD-RS Total Score and a \geq 2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase. Subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at their last on-treatment visit were classified as treatment failures (Study 6, Figure 5).

Adults: Short-Term Treatment in ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 7) was conducted in adults ages 18 to 55 (N=420) who met DSM-IV criteria for ADHD. In this study, patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of VYVANSE or placebo for a total of four weeks of treatment. All patients receiving VYVANSE were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained. All VYVANSE dose groups were superior to placebo in the primary efficacy outcome (Study 7 in Table 7).

The second study was a multi-center, randomized, double-blind, placebo-controlled, cross-over, modified analog classroom study (Study 8) of VYVANSE to simulate a workplace environment in 142 adults ages 18 to 55 who met DSM-IV-TR criteria for ADHD. There was a 4-week open-label, dose optimization phase with VYVANSE (30 mg/day, 50 mg/day, or 70 mg/day in the morning). Patients were then randomized to one of two treatment sequences: 1) VYVANSE (optimized dose) followed by placebo, each for one week, or 2) placebo followed by

VYVANSE, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. VYVANSE treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose (Study 8 in Table 7, Figure 6).

Adults: Maintenance Treatment in ADHD

A double-blind, placebo-controlled, randomized withdrawal design study (Study 9) was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV criteria for ADHD. At study entry, patients must have had documentation of treatment with VYVANSE for a minimum of 6 months and had to demonstrate treatment response as defined by Clinical Global Impression Severity (CGI-S) ≤ 3 and Total Score on the ADHD-RS < 22 . ADHD-RS Total Score is a measure of core symptoms of ADHD. The CGI-S score assesses the clinician’s impression of the patient’s current illness state and ranges from 1 (not at all ill) to 7 (extremely ill). Patients that maintained treatment response at week 3 of the open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of VYVANSE (N=56) or switched to placebo (N=60) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6-week double-blind phase. The efficacy endpoint was the proportion of patients with treatment failure during the double-blind phase. Treatment failure was defined as a $\geq 50\%$ increase (worsening) in the ADHD-RS Total Score and ≥ 2 -point increase in the CGI-S score compared to scores at entry into the double-blind phase. Maintenance of efficacy for patients treated with VYVANSE was demonstrated by the significantly lower proportion of patients with treatment failure (9%) compared to patients receiving placebo (75%) at endpoint during the double-blind phase (Study 9, Figure 7).

Table 7: Summary of Primary Efficacy Results from Short-term Studies of VYVANSE in Children, Adolescents, and Adults with ADHD

| Study Number (Age range) | Primary Endpoint | Treatment Group | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
|---------------------------|------------------|--------------------------------|--------------------------|-----------------------------------|---|
| Study 1 (6 - 12 years) | ADHD-RS-IV | VYVANSE (30 mg/day)* | 43.2 (6.7) | -21.8 (1.6) | -15.6 (-19.9, -11.2) |
| | | VYVANSE (50 mg/day)* | 43.3 (6.7) | -23.4 (1.6) | -17.2 (-21.5, -12.9) |
| | | VYVANSE (70 mg/day)* | 45.1(6.8) | -26.7 (1.5) | -20.5 (-24.8, -16.2) |
| | | Placebo | 42.4 (7.1) | -6.2 (1.6) | -- |
| Study 2 (6 - 12 years) | Average SKAMP-DS | VYVANSE (30, 50 or 70 mg/day)* | -- ^b | 0.8 (0.1) ^d | -0.9 (-1.1, -0.7) |
| | | Placebo | -- ^b | 1.7 (0.1) ^d | -- |
| Study 3 (6 - 12 years) | Average SKAMP-DS | VYVANSE (30, 50 or 70 mg/day)* | 0.9 (1.0) ^c | 0.7 (0.1) ^d | -0.7 (-0.9, -0.6) |
| | | Placebo | 0.7 (0.9) ^c | 1.4 (0.1) ^d | -- |

| | | | | | |
|-------------------------------|------------------|--------------------------------|---------------------------|--------------------------|----------------------|
| Study 4 (13 - 17 years) | ADHD-RS- IV | VYVANSE (30 mg/day)* | 38.3 (6.7) | -18.3 (1.2) | -5.5 (-9.0, -2.0) |
| | | VYVANSE (50 mg/day)* | 37.3 (6.3) | -21.1 (1.3) | -8.3 (-11.8, -4.8) |
| | | VYVANSE (70 mg/day)* | 37.0 (7.3) | -20.7 (1.3) | -7.9 (-11.4, -4.5) |
| | | Placebo | 38.5 (7.1) | -12.8 (1.2) | -- |
| Study 5 (6 - 17 years) | ADHD-RS- IV | VYVANSE (30, 50 or 70 mg/day)* | 40.7 (7.3) | -24.3 (1.2) | -18.6 (-21.5, -15.7) |
| | | Placebo | 41.0 (7.1) | -5.7 (1.1) | -- |
| Study 7 (18 - 55 years) | ADHD-RS- IV | VYVANSE (30 mg/day)* | 40.5 (6.2) | -16.2 (1.1) | -8.0 (-11.5, -4.6) |
| | | VYVANSE (50 mg/day)* | 40.8 (7.3) | -17.4 (1.0) | -9.2 (-12.6, -5.7) |
| | | VYVANSE (70 mg/day)* | 41.0 (6.0) | -18.6 (1.0) | -10.4 (-13.9, -6.9) |
| | | Placebo | 39.4 (6.4) | -8.2 (1.4) | -- |
| Study 8 (18 - 55 years) | Average PERMP | VYVANSE (30, 50 or 70 mg/day)* | 260.1 (86.2) ^c | 312.9 (8.6) ^d | 23.4 (15.6, 31.2) |
| | | Placebo | 261.4 (75.0) ^c | 289.5 (8.6) ^d | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

^a Difference (drug minus placebo) in least-squares mean change from baseline.

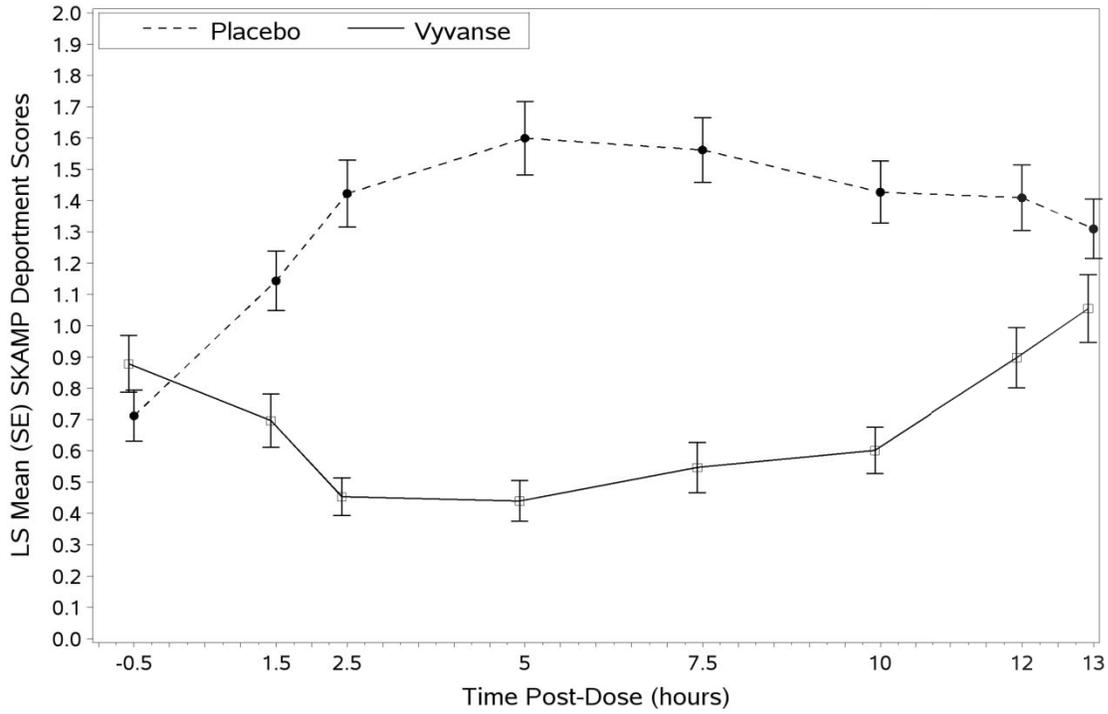
^b Pre-dose SKAMP-DS was not collected.

^c Pre-dose SKAMP-DS (Study 3) or PERMP (Study 8) total score, averaged over both periods.

^d LS Mean for SKAMP-DS (Study 2 and 3) or PERMP (Study 8) is post-dose average score over all sessions of the treatment day, rather than change from baseline.

* Doses statistically significantly superior to placebo.

Figure 4 LS Mean SKAMP Department Subscale Score by Treatment and Time-point for Children Ages 6 to 12 with ADHD after 1 Week of Double Blind Treatment (Study 3)



Higher score on the SKAMP-Department scale indicates more severe symptoms

Figure 5 Kaplan-Meier Estimation of Proportion of Patients with Treatment Failure for Children and Adolescent Ages 6-17 (Study 6)

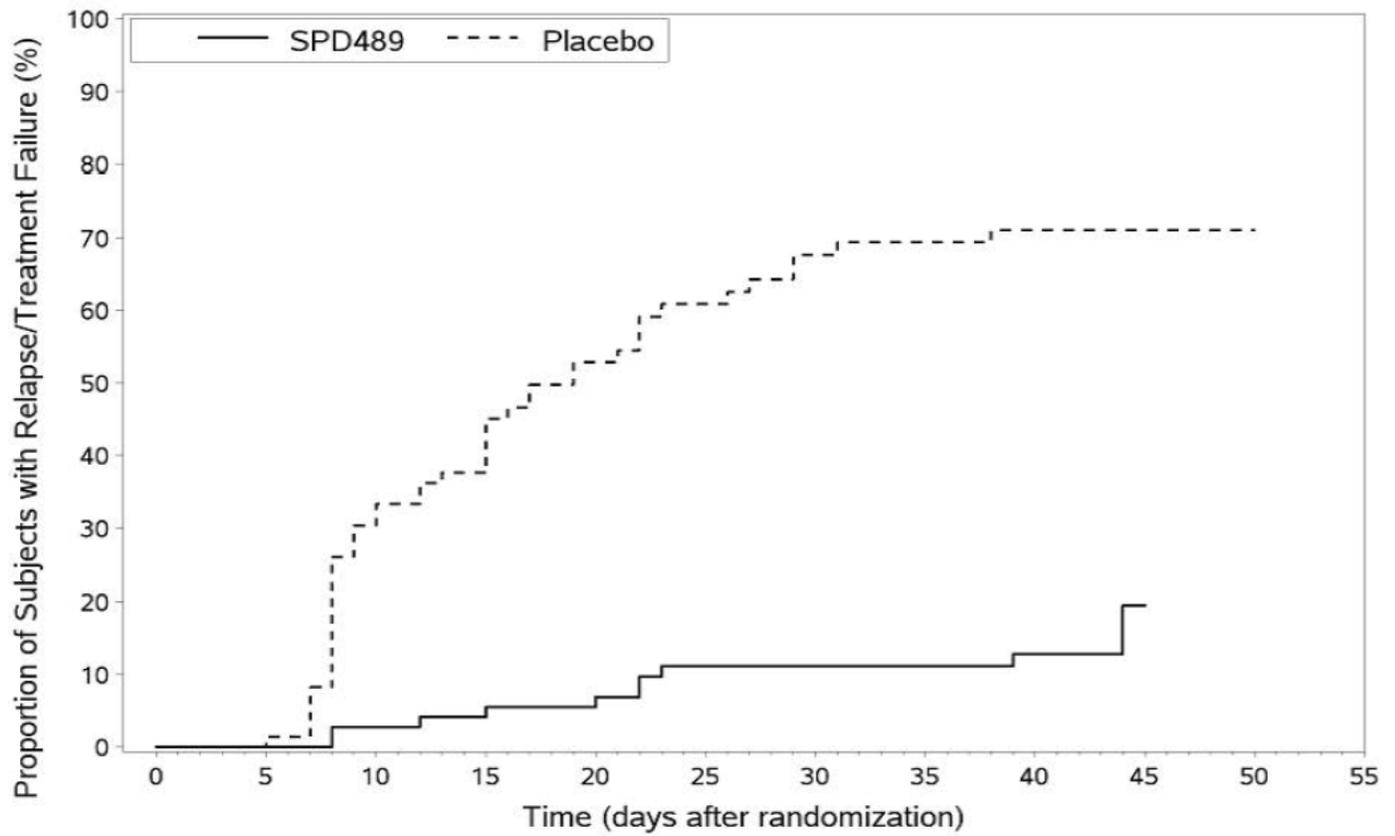
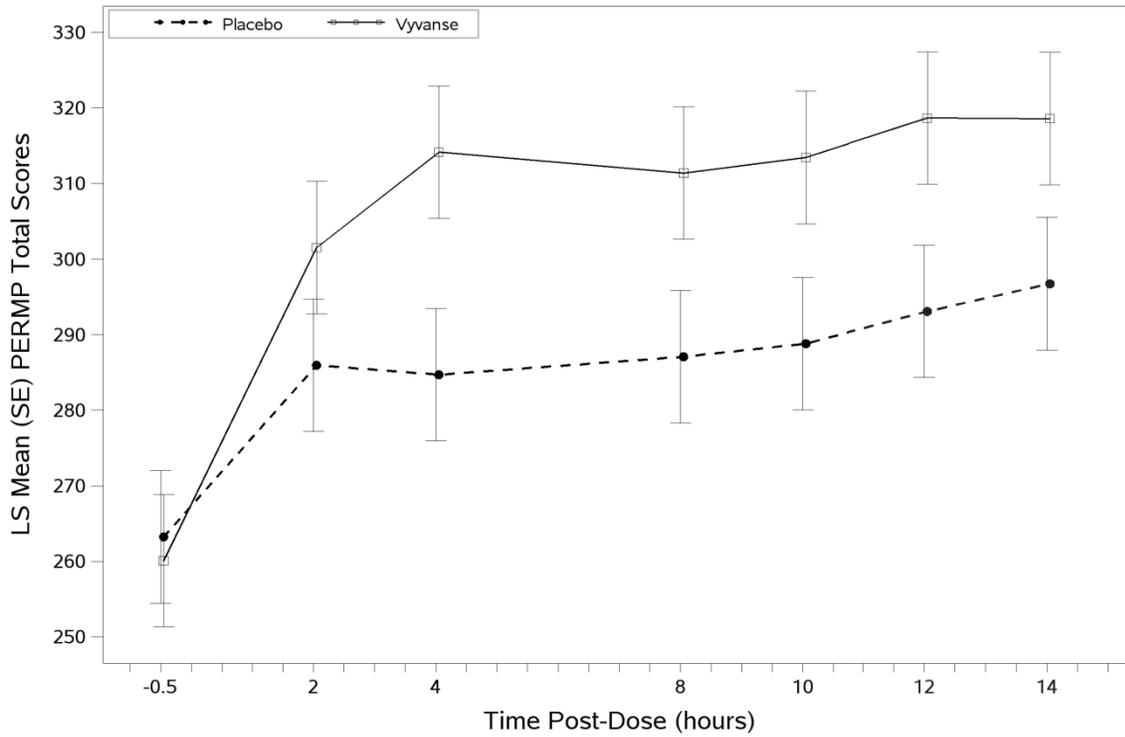
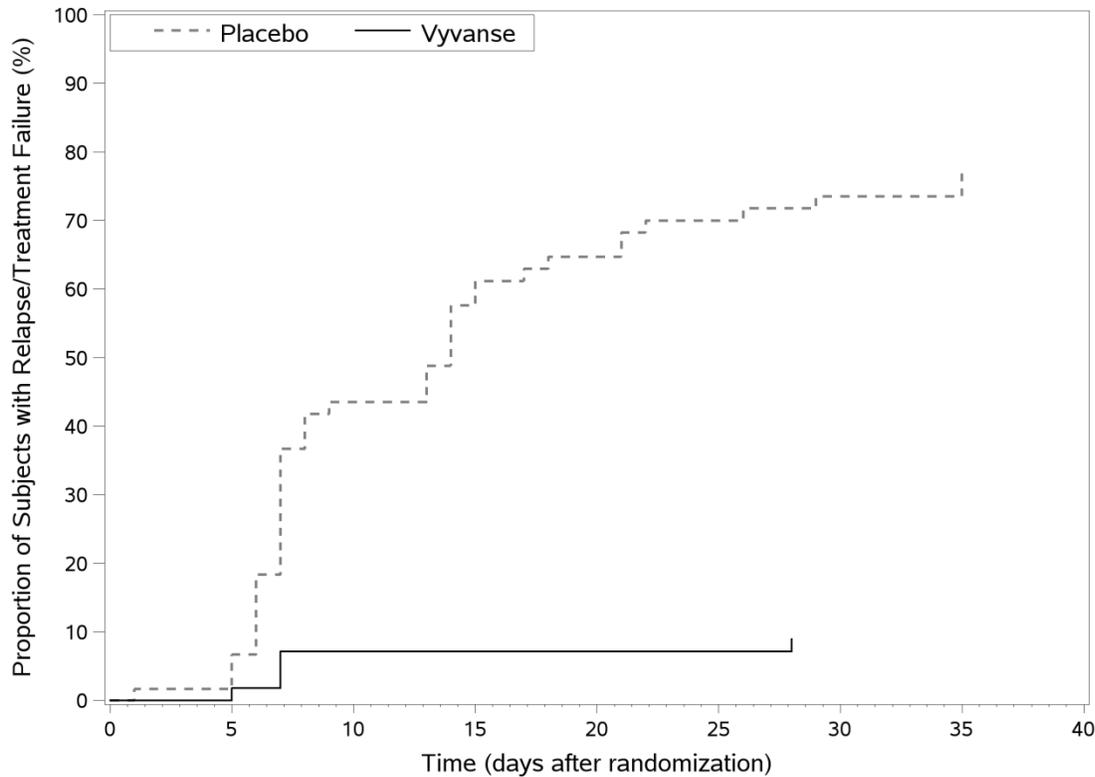


Figure 6 LS Mean (SE) PERMP Total Score by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double Blind Treatment (Study 8)



Higher score on the PERMP scale indicates less severe symptoms.

Figure 7 Kaplan-Meier Estimation of Time to Treatment Failure in Adults with ADHD (Study 9)



14.2 Binge Eating Disorder (BED)

A phase 2 study evaluated the efficacy of VYVANSE 30, 50 and 70 mg/day compared to placebo in reducing the number of binge days/week in adults with at least moderate to severe BED. This randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration study consisted of an 11-week double-blind treatment period (3 weeks of forced-dose titration followed by 8 weeks of dose maintenance). VYVANSE 30 mg/day was not statistically different from placebo on the primary endpoint. The 50 and 70 mg/day doses were statistically superior to placebo on the primary endpoint.

The efficacy of VYVANSE in the treatment of BED was demonstrated in two 12-week randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose-optimization studies in adults aged 18-55 years (Study 10: N=374, Study 11: N=350) with moderate to severe BED. A diagnosis of BED was confirmed using DSM-IV criteria for BED. Severity of BED was determined based on having at least 3 binge days per week for 2 weeks prior to the baseline visit and on having a Clinical Global Impression Severity (CGI-S) score of ≥ 4 at the baseline visit. For both studies, a binge day was defined as a day with at least 1 binge episode, as determined from the subject's daily binge diary.

Both 12-week studies consisted of a 4-week dose-optimization period and an 8-week dose-maintenance period. During dose-optimization, subjects assigned to VYVANSE began treatment at the titration dose of 30 mg/day and, after 1 week of treatment, were subsequently titrated to 50mg/day. Additional increases to 70 mg/day were made as tolerated and clinically indicated. Following the dose-optimization period, subjects continued on their optimized dose for the duration of the dose-maintenance period.

The primary efficacy outcome for the two studies was defined as the change from baseline at Week 12 in the number of binge days per week. Baseline is defined as the weekly average of the number of binge days per week for the 14 days prior to the baseline visit. Subjects from both studies on VYVANSE had a statistically significantly greater reduction from baseline in mean number of binge days per week at Week 12. In addition, subjects on VYVANSE showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subjects rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score.

Table 8: Summary of Primary Efficacy Results in BED

| Study Number | Treatment Group | Primary Efficacy Measure: Binge Days per Week at Week 12 | | |
|--------------|----------------------------|--|-----------------------------------|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
| Study 10 | VYVANSE (50 or 70 mg/day)* | 4.79 (1.27) | -3.87 (0.12) | -1.35 (-1.70, -1.01) |
| | Placebo | 4.60 (1.21) | -2.51 (0.13) | -- |
| Study 11 | VYVANSE (50 or 70 mg/day)* | 4.66 (1.27) | -3.92 (0.14) | -1.66 (-2.04, -1.28) |
| | Placebo | 4.82 (1.42) | -2.26 (0.14) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

^a Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

Examination of population subgroups based on age (there were no patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness in the treatment of BED.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VYVANSE capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg), bottles of 100, NDC 59417-101-10

VYVANSE capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417-102-10

VYVANSE capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417-103-10

VYVANSE capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10

VYVANSE capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417-105-10

VYVANSE capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10

VYVANSE capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 100, NDC 59417-107-10

16.2 Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP.

Store at room temperature, 20°C to 25° C (68°F to 77° F). Excursions permitted between 15°C and 30° C (59 to 86° F) [*see USP Controlled Room Temperature*].

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired VYVANSE by a medicine take-back program.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients that VYVANSE is a controlled substance and it can be abused and lead to dependence and not to give VYVANSE to anyone else [*see Drug Abuse and Dependence (9.1, 9.2, and 9.3)*]. Advise patients to store VYVANSE in a safe place, preferably locked, to prevent abuse. Advise patients to dispose of remaining, unused, or expired VYVANSE by a medicine take-back program.

Serious Cardiovascular Risks

Advise patients that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with VYVANSE use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [*see Warnings and Precautions (5.2)*].

Hypertension and Tachycardia

Instruct patients that VYVANSE can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects.

Psychiatric Risks

Advise patients that VYVANSE at recommended doses may cause psychotic or manic symptoms even in patients without prior history of psychotic symptoms or mania [see *Warnings and Precautions* (5.4)].

Suppression of Growth

Advise patients that VYVANSE may cause slowing of growth including weight loss [see *Warnings and Precautions* (5.5)].

Impairment in Ability to Operate Machinery or Vehicles

Advise patients that VYVANSE may impair their ability to engage in potentially dangerous activities such as operating machinery or vehicles. Instruct patients to find out how VYVANSE will affect them before engaging in potentially dangerous activities [see *Adverse Reactions* (6.1, 6.2)].

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]

Instruct patients beginning treatment with VYVANSE about the risk of peripheral vasculopathy, including Raynaud's Phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes. **Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking VYVANSE.** Further clinical evaluation (e.g. rheumatology referral) may be appropriate for certain patients [see *Warnings and Precautions* (5.6)].

Manufactured for: Shire US Inc., Wayne, PA 19087

Made in USA

For more information call 1-800-828-2088

VYVANSE® is a trademark of Shire LLC

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US Pat No. 7,105,486 and US Pat No. 7,223,735

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

SUMMARY REVIEW

MEMORANDUMDEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 30 Jan 2015

FROM: Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products, HFD-130

TO: File NDA 21977 S-037

SUBJECT: Summary memo and approval decision for lisdexamfetamine for the treatment of Binge Eating Disorder

Background

Lisdexamfetamine is a pro-drug stimulant approved in 2007 for the treatment of ADHD. It is approved to treat pediatric and adult patients. This supplement provides data from adult trials to treat Binge Eating Disorder (BED). There are no medications currently approved to treat BED.

BED diagnostic criteria (DSM-5) include:

- A. Recurrent episodes of binge eating which are characterized by both eating an amount of food in a discrete period of time that is larger than what most people would eat in a similar timeframe and a sense of lack of control over eating during the episodes.
- B. Binge eating episodes are associated with at least three of the following:
 - Eating much more rapidly than normal
 - Eating until feeling uncomfortably full
 - Eating large amounts of food when not feeling physically hungry
 - Eating alone because of embarrassment by how much is eaten
 - Feelings of disgust, depression, or guilt after an episode
- C. Marked Distress over binge eating
- D. Binge eating occurs, on average, at least once a week for 3 months
- E. Binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia or anorexia nervosa.

Severity of BED is characterized by number of episodes per week:

- Mild: 1-3 episodes per week
- Moderate: 4-7 episodes per week
- Severe: 8-13 episodes per week
- Extreme: 14 or more episodes per week.

The sponsor conducted one Phase 2 (proof-of-concept and dose-finding) and two Phase 3 efficacy and safety trials enrolling patients with moderate to severe BED. This application was granted a priority review secondary to being the first drug for consideration to treat BED.

Clinical Summary and Statistics

Dr. Gregory Dubitsky has reviewed the clinical development program data and has recommended approval, and I agree with him. Dr. Thomas Birkner conducted the biometrics review and he too concluded that the efficacy endpoints have been met.

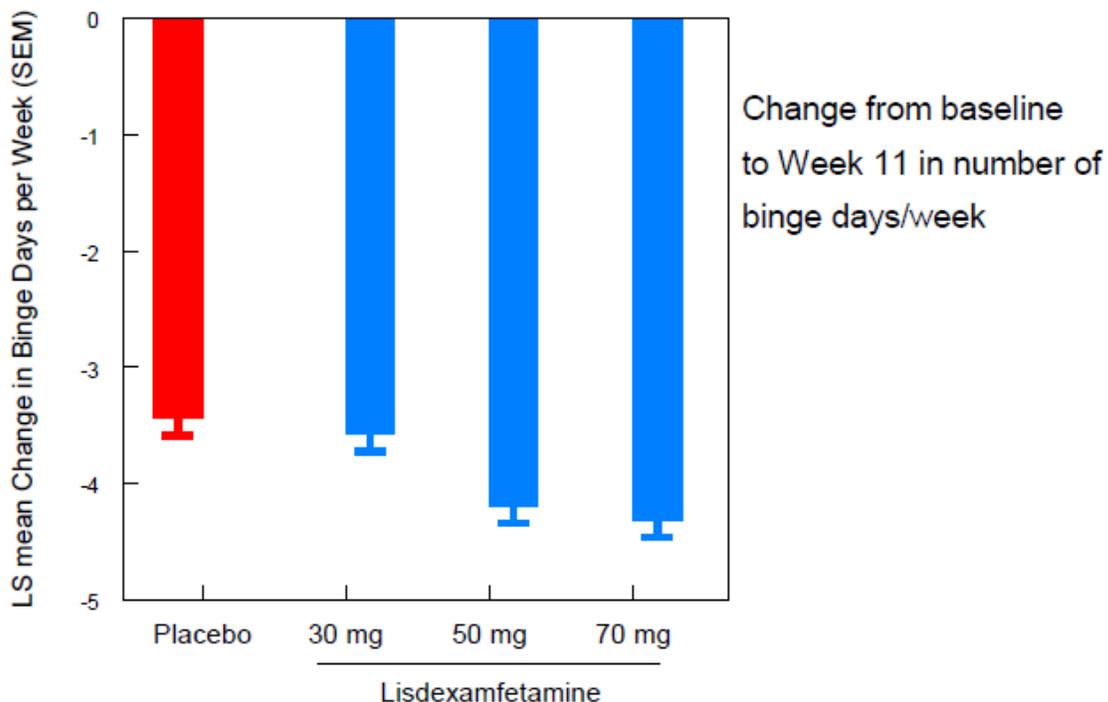
One Phase 2 and two pivotal 12-week studies were conducted in adults with moderate to severe BED. The fixed-dose Phase 2 study was used to define the appropriate dose range for Phase 3 (see below). Both Phase 3 studies supported efficacy, and neither identified any new safety concerns for this drug that is already approved for use in the adult population. Doses in the pivotal trials were 50 mg or 70 mg, the higher end of the approved range for ADHD (30 mg – 70 mg). Each study randomized approximately 400 patients to drug or placebo. The primary efficacy endpoint was reduction in the number of binge days per week and was based on a daily diary maintained by the patient. In addition, statistical superiority was demonstrated on the following 5 secondary efficacy endpoints in both trials: 1) CGI-Improvement score; 2) proportion of subjects with cessation of all binge eating for the last 4 weeks of the trial; 3) percent reduction in body weight; 4) change in the Y-BOC_BE total score and; 5) change in fasting serum triglycerides.

As noted in the reviews, the primary and secondary endpoints were all positive for both trials.

Dose Response

The Sponsor conducted a Phase 2 trial to evaluate three doses (30 mg, 50 mg, and 70 mg) vs. placebo in adults with BED. Lisdexamfetamine at doses of 50 mg and 70 mg per day were statistically significantly better at reducing BED symptoms compared to placebo; the 30 mg dose was not effective compared to placebo. Secondary to these data, 50 mg and 70 mg dosed flexibly were explored in Phase 3. The results from the dose-finding study are presented below.

Exploration of Dose Response in Phase 2 (Study 208)



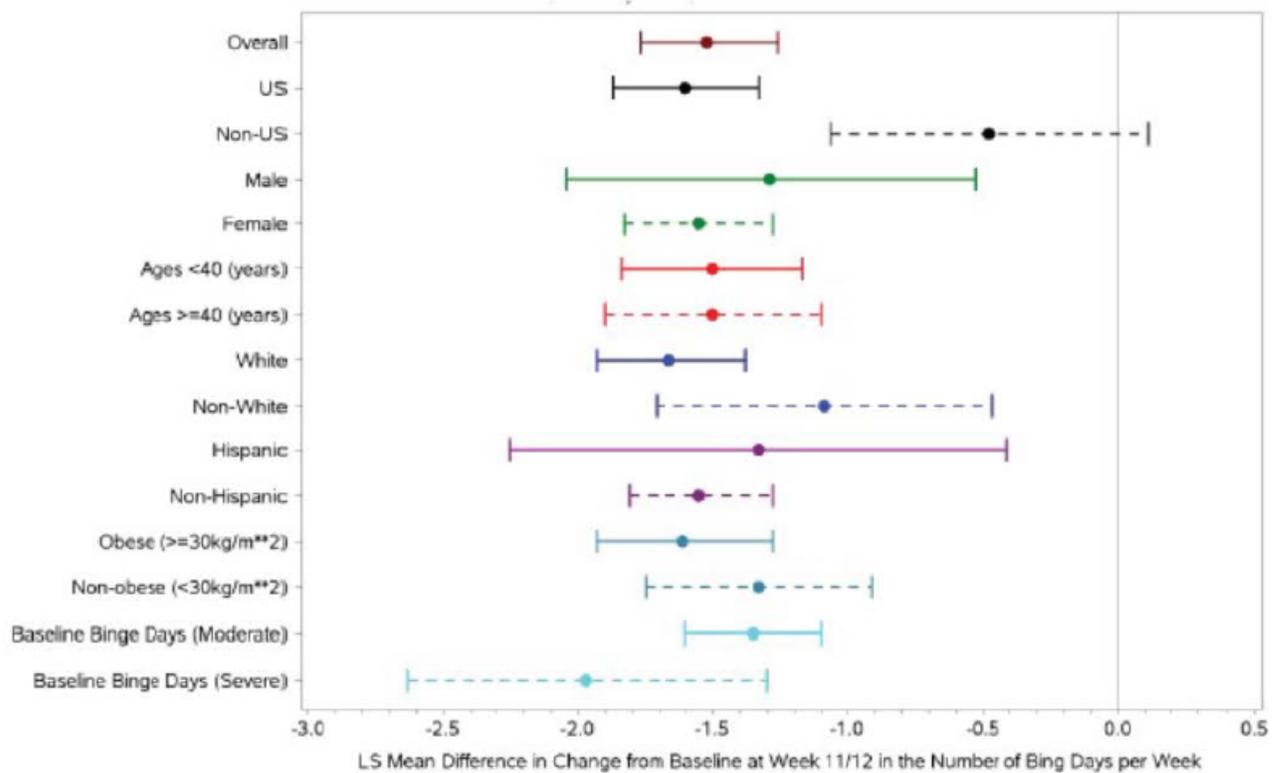
Phase 3--Study 1 (SPD489-343) and Study 2 (SPD489-344)

The two Phase 3 studies were identically designed as randomized, double-blind placebo-controlled, parallel group, flexible dose (50 mg or 70 mg) trials to assess the efficacy and safety of lisdexamfetamine in adults (18-65) with moderate to severe Binge Eating Disorder. The treatment duration was 12 weeks and approximately 400 patients were randomized per trial.

Patients were started on 30 mg/day, increased to 50 mg/day after a week, and subsequently increased (second or third week) to 70 mg/day if tolerated or as clinically indicated to achieve an optimal dose.

Patient demographics were consistent with the population suffering from BED, including approximately 70% who were obese, and approximately 20% with morbid obesity. Subgroup analyses demonstrated that the primary endpoint was positive regardless of subgroup (see below).

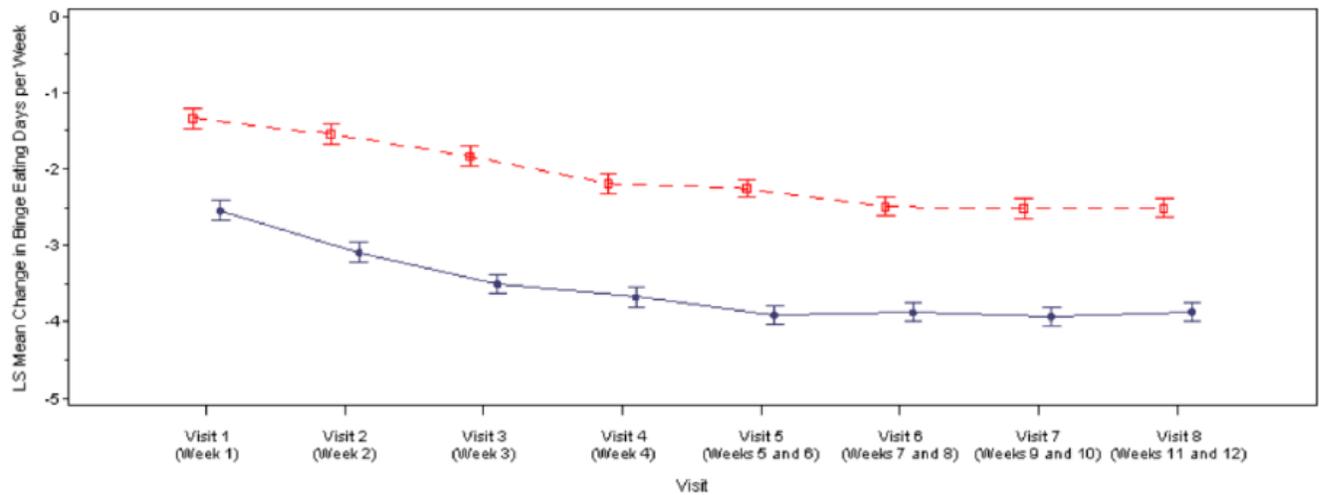
LS Mean Difference (95% CI) in the Change from Baseline to Endpoint in Number of Binge Days per Week by Subgroup for Trials 343 and 344 Combined



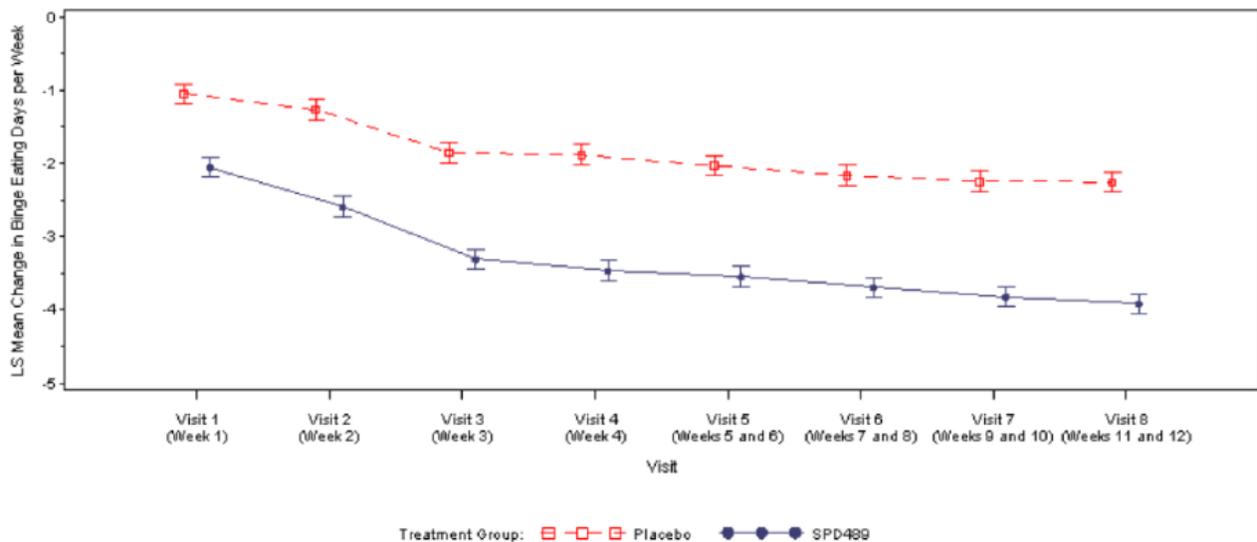
Primary Efficacy Results

Both studies were positive for the primary endpoint and the by-visit data are presented below.

LS Mean Change from Baseline in Number of Binge Days per Week (Study 343)



LS Mean Change from Baseline in Number of Binge Days per Week (Study 344)



The review team believes that there is clear evidence of a positive drug effect in reducing number of binge days per week, and I agree with them. The most clinically impressive secondary endpoint, in my view, was Percent of Patients with a 4-week cessation of binge eating. These were patients who had zero events of binge eating for at least 4 weeks. The results by study are presented below.

Secondary Endpoint: Percentage of Patients with a 4-week Cessation of Binge Eating

| Study # | 343 | | 344 | |
|---------------------------|----------------------|------------------|----------------------|------------------|
| | Placebo | LDX | Placebo | LDX |
| Percent Cessation | 14.1 (26/184) | 40.0 (76/190) | 13.1 (23/176) | 36.2 (63/174) |
| Diff. (95% CI) | 25.9 (17.3, 34.5) | | 23.1 (14.4, 31.8) | |

(Source: 343 Study Report p. 113, 344 Study Report p. 115, and Reviewer's analysis; Results replicated by reviewer)

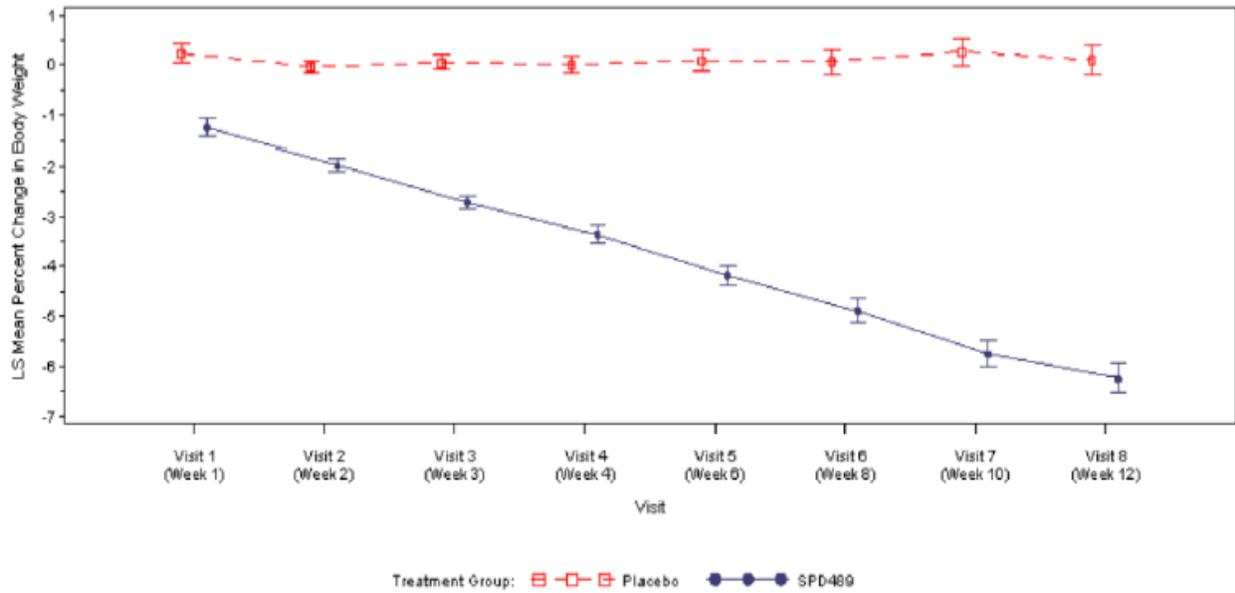
Another secondary endpoint that was meaningful, in my view, was Percent Change in Body Weight. Patients on drug had significant decreases in weight compared to placebo. This matters clinically because 70%-80% of BED patients are overweight.

Secondary Endpoint: Percent Change in Body Weight

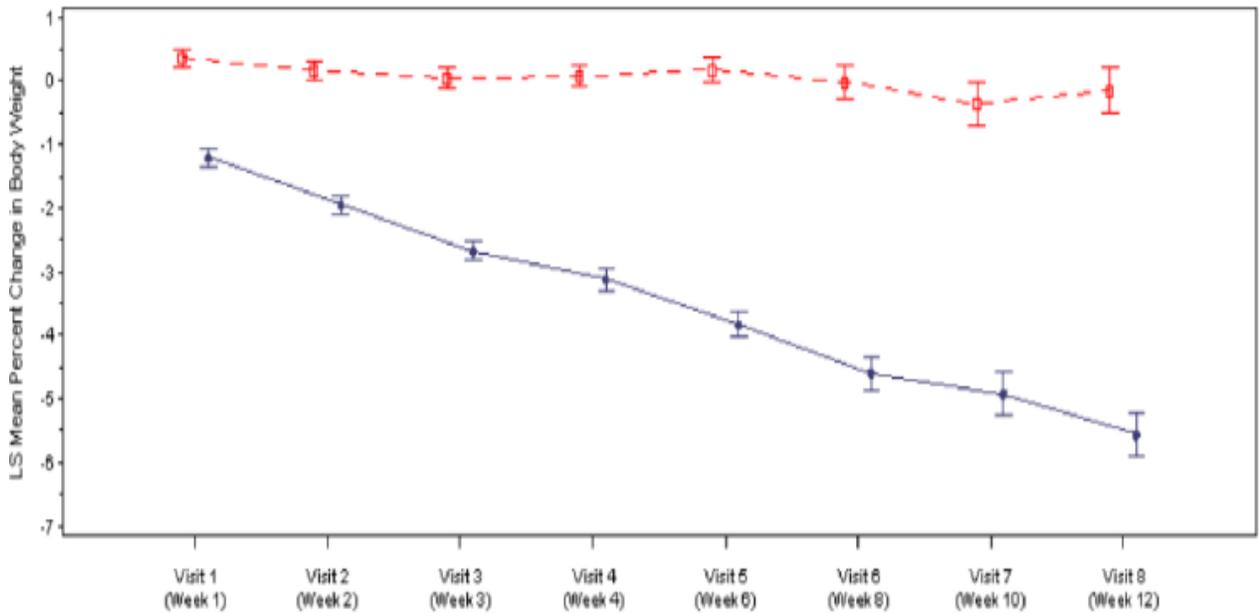
| Study # | 343 | | 344 | |
|---|-------------------------|----------------|-------------------------|----------------|
| | Placebo (N=184) | LDX (N=190) | Placebo (N=176) | LDX (N=174) |
| Baseline Mean | | | | |
| lbs | 204.8 | 207.1 | 205.3 | 208.9 |
| kg | 92.9 | 94.0 | 93.1 | 94.8 |
| LS Mean Percent Change from Baseline | 0.11 | -6.25 | -0.15 | -5.57 |
| LS Mean Percent Diff.* (95% CI) | -6.35 (-7.17, -5.54) | | -5.41 (-6.39, -4.44) | |

Body Weight Change over time:

LS Mean Percent Change from Baseline in Body Weight by Visit (343)



LS Mean Percent Change from Baseline in Body Weight by Visit (344)



Safety Issues of Interest

Weight Loss

In the BED trials, a much larger proportion of patients on lisdexamfetamine experienced substantial weight loss (greater than or equal to 10% loss from baseline) compared to placebo (20% vs. less than 1%). This might be expected for an effective drug used to treat BED where most patients are overweight at baseline.

Weight loss is a known adverse reaction for this drug; it has been in the labeling under the Adverse Reactions section of labeling since the approval for ADHD. While clearly adverse in an ADHD population (one of the main reasons patients have to stop taking the drug), weight loss could be viewed as an efficacy signal in BED (most patients are overweight and the result of reduced binge days should be weight loss). This conflict (adverse reaction or efficacy endpoint) was the subject of a great deal of discussion within OND because, although the drug causes weight loss, it has not been evaluated to the regulatory standard of a weight loss drug (longer trials, cardiovascular (CV) outcomes study, etc.), and there have been past instances of adverse CV outcomes in patients taking sympathomimetic drugs for weight loss. As a result, the team agreed that the primary efficacy endpoint is most important information for clinicians, and for patients with BED (reducing binge eating days), and so the emphasis in labeling should be on the psychiatric aspects of the disorder; the team also agreed that the drug should be explicitly labeled as not indicated for weight loss/treatment of obesity. This resulted in a Limitation of Use Statement in labeling which was accepted by the sponsor.

Cardiovascular Risk

We consulted the Division of Cardiovascular and Renal Products to assess the known (and labeled) persistently increased blood pressure and heart rate findings for this drug and to comment on cardiovascular risk. Dr. Targum completed the consult and found no cardiovascular safety signals in the BED population. Although, the sample size was relatively small for detecting fairly rare events and it is difficult to assess risk when the drug increases some risks (small increases in heart rate and blood pressure) and decreases other risks (obesity and triglycerides). The drug is and always has been labeled with a cardiovascular warning for patients with structural heart defects, cardiac abnormalities, cardiomyopathy, arrhythmia, or coronary artery disease. The labeling also states in Warnings and Precautions that blood pressure should be monitored during use.

Chemistry Manufacturing and Controls (CMC)

There were no CMC data submitted as part of this application. CMC recommended an approval action.

Nonclinical Pharmacology/Toxicology

No new studies were submitted as part of this application.

Office of Clinical Pharmacology (OCP)

No new clinical pharmacology/bio-pharmaceutical issues were identified during the review.

Labeling

Labeling was updated to include information from the BED program. We included a Limitation of Use statement in the Indications and Usage section of labeling to address the fact that this drug has

not been evaluated and is not recommended for weight loss or to treat obesity, and the sponsor agreed. (b) (4)

Postmarketing Requirements/Commitments

The sponsor has agreed to conduct a maintenance study in patients with BED (ongoing).

Pediatrics

The sponsor requested a full waiver to study pediatric patients due to low prevalence of BED in the population and the Division in consultation with PeRC granted the waiver.

Conclusions and Recommendations

Sufficient information has been submitted to conclude that lisdexamfetamine is safe and effective in treating Binge Eating Disorder.

The labeling and the Medication Guide have been negotiated to current Division standards. Labeling includes a Limitation of Use statement for weight loss/treatment of obesity.

The sponsor has agreed to labeling and to conduct a maintenance study post-marketing; this application should be approved by the PDUFA date.

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/s/

MITCHELL V Mathis
01/30/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 21977/S-037

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Thomas Birkner
Tiffany Farchione
Mitchell Mathis
Susannah O'Donnell
Robert Temple
Ellis Unger
Sharon Williams
Peiling Yang
Jing Zhang
Hao Zhu

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

DATE: January 23, 2015

FROM: Jing Zhang, MD. PhD.
Medical Team Leader, Division of Psychiatry Products
HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 021977/S37

**Proprietary/
Established name:** Vyvanse/Lisdexamfetamine Dimesylate

**Dosage forms/
Strength:** Oral capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

Indication: Moderate to Severe Binge Eating Disorder

Recommendation: Approval

1. Introduction and Background

Vyvanse, also referred as lisdexamfetamine dimesylate or SPD489, is a CNS stimulant. Vyvanse (30, 50, and 70mg) was first approved in the US for treatment of attention deficit/hyperactivity disorder (ADHD) in children (6-12 years) in February 2007. Intermediate dose strengths of 20, 40, and 60mg were approved for use in December 2007.

Vyvanse is a pro-drug of d-amphetamine and is converted to therapeutically active d-amphetamine after being taken orally. Shire submitted this supplemental NDA (sNDA) to seek an indication for Vyvanse in the treatment of moderate to severe binge eating disorder (BED) in adults. The BED development program was conducted under IND 110,503, which was submitted to FDA on March 4, 2011.

BED is a serious mental illness affected about 3% (life time prevalence) adult population and there is no medication available at present. During the BED development program, the Diagnostic and Statistical Manual of Mental Disorders was revised from the previous edition (DSM-IV) to the version 5 (DSM-5). DSM-IV contained Research Criteria for

BED intended primarily for research purposes. DSM-5 incorporated criteria for BED as a formal clinical disorder. The only significant difference between the DSM-IV and DSM-5 criteria for BED is that the minimum average frequency of binge eating required for diagnosis is once weekly for the prior 3 month period (DSM-5) instead of at least 2 days per week over the previous 6 months (DSM-IV).

The mechanism of action in BED is unknown. It is hypothesized that dopaminergic and noradrenergic hypo-function may play a role in BED since both dopamine and norepinephrine are thought to be important in regulating eating behavior and reward.

An End-of-Phase 2 meeting was held on July 30, 2012. In the meeting, the sponsor presented the positive results from study SPC489-208, a phase 2, placebo controlled, fixed dose study, and discussed their phase 3 development plan including two 12-week, placebo-controlled, dose-optimization trials; one open-label, 12 month extension trial and a randomized withdrawal trial. FDA accepted the use of binge days as the primary endpoint, (b) (4)

Pre-NDA comments were forward to the sponsor on March 4, 2014. The agency requested safety and efficacy analyses both with and without data from the three discontinued study sites.

This sNDA was submitted on Aug. 1, 2014 and was granted a priority review.

2. Chemistry, Manufacturing and Controls (CMC)

The supplement does not provide for any changes to the drug product, manufacturing process, or specifications and there are no CMC-related labeling changes. A claim for categorical exclusion is included and CMC team recommends approval of this application from a CMC perspective.

3. Nonclinical Pharmacology/Toxicology

Vyvanse is an approved drug. No nonclinical pharmacology and toxicology issues were identified during review.

4. Clinical Pharmacology/Bio-pharmaceutics

No clinical pharmacology/bio-pharmaceutic issues were identified during review.

5. Clinical/Statistical

Gregory Dubitsky, MD., is the medical reviewer and Thomas Birkner, PhD., is the statistical reviewer for this submission. Please refer to their reviews for details.

The sponsor conducted 2 identical phase 3 efficacy and safety trials (SPD489-343, -343). Both trials demonstrated superiority of SPD489 in doses of 50 and 70 mg/day over placebo in the treatment of BED as measured by a statistically significant reduction in the number

of binge days per week, based on a daily diary maintained by the subjects. In addition, statistical superiority favoring SPD489 was also shown on 5 key secondary efficacy variables: Clinical Global Impression-Improvement (CGI-I) score, proportion of subjects with cessation of all binge eating for the last 4 weeks of trial participation, percentage reduction in body weight, the Y-BOC-BE total score, and fasting serum triglyceride levels.

5.1 Efficacy

5.1.1 Clinical studies essential to regulatory decision (design, analytic features, and results)

Study Design

Study SPD-489-343 (study 343) and SPD-489-344 (study 344) were 12 weeks, randomized, double-blind, placebo-controlled, optimal dosed (50 mg/d or 70 mg/d), parallel group trials of the safety and efficacy of SPD489 in adults (ages 18-55) with moderate to severe BED. The studies included a 2 to 4 week screening period, a 12-week double-blind treatment period (4 weeks of dose optimization and 8 weeks of maintenance treatment at the optimized dose) and a one-week follow-up period. The randomization ratio was 1:1 (SPD-489: placebo).

Both studies are multi-center studies conducted simultaneously from Nov. 2012 to Sept. 2013 in the US and in Europe. Study 343 was conducted at 50 sites in the US, Germany, Sweden, and Spain. Study 344 was conducted at 41 sites in the US and two sites in Germany.

The key inclusion criteria were: DSM-IV-TR diagnosis of BED; BED of at least moderate severity (at least 3 binge eating days per week for the 14 days prior to baseline as documented in a binge diary, with a binge day defined as a day in which at least one binge eating episode occurs); CGI-severity score ≥ 4 at screening and baseline, and BMI ≥ 18 but ≤ 45 at screening and baseline. The studies excluded subjects who had current diagnosis of bulimia nervosa or anorexia nervosa.

Subjects randomized to SPD489 started treatment with 30 mg/day. The doses were increased to 50 mg/day, or subsequently increased to 70 mg/day on weekly basis as tolerated and clinically indicated to achieve an optimal dose. No dose changes were permitted after the Week 3 visit. If intolerance or unacceptable efficacy occurred during maintenance treatment, treatment could be discontinued, but no dose change was allowed.

Binge eating information was collected daily by the subject in a paper diary, which was distributed at each visit and collected at the next visit. This diary captured the number of binges per day, total hours spent bingeing each day, type of binge (mealtime versus non-mealtime), and a description of the binge (amounts and types of food). At each visit, the investigator reviewed the completed diary with the patient and confirmed whether each recorded eating episode was a binge. The number of confirmed binges each day was then recorded in the case report form.

The primary efficacy endpoint was the change from baseline to Week 12 in the number of binge days per week during Weeks 11 and 12. At baseline, this number was calculated as the weekly average from the 14 days preceding baseline. At final visit, this number was computed as the number of binge days multiplied by 7 then divided by the number of days in the period. The analysis was performed using MMRM (Mixed-effects Model for Repeated Measures) over the Full Analysis Set (FAS), defined as all subjects who had taken at least one dose of study drug and had one post-baseline primary efficacy assessment.

There were 5 key secondary efficacy variables: CGI-Improvement score at Week 12; CGI-Improvement score at Week 12 or End of Treatment dichotomized as the percentage improved; proportion of subjects with a 4-week cessation of binge eating (no binges) for the 28 day period prior to Week 12 or End of Treatment for dropouts; percentage change from baseline to Week 12 in body weight; change from baseline to Week 12 in the Y-BOCS-BE total score; and change from baseline to Week 12 or End of Treatment in fasting triglycerides. Analysis of the key secondary variables was conducted over the FAS. Multiplicity was addressed by hierarchical testing, with each variable tested at a two-sided 0.05 level of significance in the order shown above. The CGI-I and proportion with cessation of binge eating were compared between treatment groups using a Chi-Square test. Percentage change in body weight and change in Y-BOCS-BE were compared using MMRM. Triglycerides were compared between groups using an ANCOVA model.

Efficacy Results

In study 343, 383 subjects were randomized and the completion rate was 82.2% (82.3 % in SPD489 and 82.2% in placebo). The most common reason for discontinuation was withdrawal by subject (6.3% and 7.3% in SPD489 and placebo, respectively). Discontinuation due to adverse events was slightly higher in SPD489 treatment group (6.3% vs. 2.6%). In study 344, 390 subjects were randomized and 75.4% of them (SPD489 or placebo) completed the study. The most common reason for discontinuation was lost to follow up (7.7% and 9.2% in SPD489 and placebo, respectively).

Baseline demographic features were very similar in both studies and were comparable between the SPD489 and placebo treatment groups in both studies. The mean age was 38 years in both studies (range 19 to 55 years) with little more than half subjects under the age of 40 (53% and 54% in study 343 and 344, respectively). Majority of patients were female (87% and 85% in study 343 and 344, respectively) and most were of the White (78% and 73% in study 343 and 344, respectively). Mean body weight was 94 kg in both studies (range 49-149 kg and 50-176 kg in study 343 and 344, respectively) and mean BMI was 33 kg/m² (range of 19-45) in study 343 and 34 kg/m² (range of 20-45) in study 344. About two thirds (67% and 69% in study 343 and 344, respectively) were obese (BMI ≥30 kg/m²); and 18% and 19% (study 343 and 344, respectively) were morbidly obese (BMI ≥40 kg/m²).

There were 3 sites, 1 in study 343 and 2 in study 344, were excluded by the sponsor from the efficacy analyses. Shire notified FDA about the exclusion of these sites at the IND stage. Site 66 (21 subjects) was close because of concerns about signs of investigational drug tampering during the conduct of another trial ((b) (4) (b) (4)). Site 15 (11 subjects) was removed for

reason unrelated to the study, and Site 79 (12 subjects) was excluded because Good Clinical Practice (GCP) infractions, failure to follow study procedures, improper entry of subject data, and inadequate oversight. Dr. Birkner, our statistical reviewer for this sNDA, indicated in his review that the exclusion of this site from the primary and key secondary efficacy analyses has no substantial effect on the efficacy results.

The optimized dose and mean dose of SPD489 were very similar in both studies. The optimized dose was 50 mg/d for 30% (study 343) and 29% (study 344) of SPD489 subjects and 70 mg/d for 61% (study 343) and 62% (study 344) of the subjects. The remaining 9% of the SPD489 subjects in both studies failed to achieve an optimized dose and were discontinued from the trial. During the period for dose optimization, the mean dose was 50 mg/d in study 343 and 51 mg/d in study 344, and, during the dose maintenance phase, the mean dose was 63 mg/d in study 343 and 64 mg/d in study 344.

Primary Endpoint

The primary efficacy variable was the change from Baseline at Week 12 in the Number of Binge Days per week. The efficacy results of the primary endpoint (FAS) for study 343 and 344 were summarized in the following table.

The change from Baseline at Week 12 in the Number of Binge Days per week—FAS, Study 343 and 344

| Study # | 343 | | 344 | |
|-------------------------------------|-------------------------|----------------|-------------------------|----------------|
| | Placebo (N=184) | LDX (N=190) | Placebo (N=176) | LDX (N=174) |
| Baseline Mean | 4.60 | 4.79 | 4.82 | 4.66 |
| LS Mean Change from Baseline | -2.51 | -3.87 | -2.26 | -3.92 |
| LS Mean Diff.* (95% CI) | -1.35 (-1.70, -1.01) | | -1.66 (-2.04, -1.28) | |

Source: Dr. Birkner’s review

In study 343, the LS mean changes from baseline were – 2.51 in placebo and -3.87 in SPD489 at Week 12. The LS mean difference between SPD489 and placebo was -1.35 (95% CI: -1.70, -1.01), p<0.001.

In study 344, the LS mean changes from baseline were – 2.26 in placebo and -3.92 in SPD489 at Week 12. The LS mean difference between SPD489 and placebo was -1.66 (95% CI: -2.04, -1.28), $p < 0.001$.

It is noticeable in both studies that most of the mean decrease in Binge Days occurs early (up to Week 3 and 4), and the Binge Days remains almost same after Week 3 and 4.

The results from sensitive analyses (permutation, based completed set or Missing Not At Random assumption) conducted by the sponsor were consistent with the primary analysis.

Key Secondary End Points

The testing of the five key secondary efficacy measures in Studies 343 and 344 was conducted following a fixed sequence to control the overall type 1 error. Statistically significant treatment advantage was demonstrated in SPD489 treatment in all 5 key secondary endpoints in both study 343 and 344.

1. Dichotomized CGI-I

The first key secondary endpoint was the percentage improved at week in CGI-I scale. At week 12 there were roughly twice as many SPD489 patients in the improved category compared to placebo patients. The differences between treatment arms (35% in study 343 and 43% in study 344) were statistically significant ($p < 0.001$).

2. Four Week Binge Eating Cessation

The second key secondary endpoint is 4-week binge eating cessation, defined as no binge episodes for 28 consecutive days prior to the last study visit (week 12 or early termination visit). In study 343, the percentage of subjects with 4-week cessation was 14.1% (study 343) and 13.1% (study 344) in placebo and 40% (study 343) and 36.2 % (study 344) in SPD489. The estimated differences of 25.9 % (study 343) and 23.1 % (study 344) are highly statistically significant ($p < 0.001$).

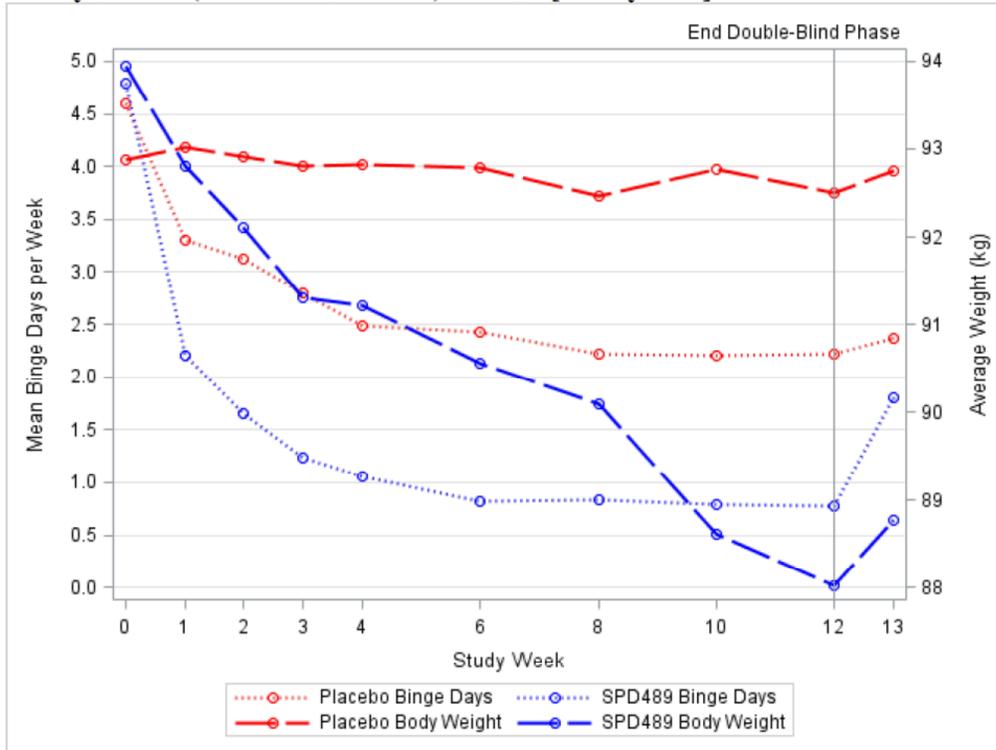
3. Body Weight

The change from baseline to week 12 in body weight was the third key secondary endpoint. For placebo treatment, there was no weight change (LS % Δ from baseline: 0.11 in study 343, and -0.15 in study 344) observed at the Week 12. However, a significant weight loss was seen in the SPD489 treatment at the Week 12. The LS mean percent changes from baseline were -6.25 in study 343 and -5.57 in study 344 in SPD489 subjects. The differences between treatment arms were highly statistically significant ($p < 0.001$) for both Study 343 and Study 344.

It is noteworthy that there is a disconnection between the weight loss and the reduction of binge days in both studies. Dr. Birkner explored the relationship of change in binge days and the change in body weight. He found that in placebo groups, the average binge days were reduced by ~ 2.5 days at Week 12. But it was not associated with any weight loss,

whereas the reduction in binge days for SPD489 patients appears to be well correlated with weight loss in the first 3 weeks of treatment. The weight loss in the SPD489 group continues until the end of the study even though the average number of binge days stabilizes (see following figure).

Average Binge Days Per Week and Body Weight by Treatment Group and Study Week (Observed Values)—FAS, Study 343



Source: Dr. Birkner’s review

4. Y-BOCS-BE Total Score

The LS mean changes in Y-BOCS-BE Total Score from baseline were 4th key secondary endpoint. In study 343, the LS mean changes from baseline were -8.3 in placebo and -15.7 in SPD489. In study 344, the LS mean change from baseline was -7.4 in placebo and -15.4 in SPD489. The differences between treatment arms (-7.4 and -7.9 in study 343 and 344, respectively) were statistically significant (p < 0.001).

5. Triglycerides

Fasting triglycerides were assessed only at baseline and at week 12 or the early termination visit. In study 343, the LS mean changes from baseline to Week 12 were 10.8 mg/dl in placebo and -6.8 mg/dl in SPD489. In study 344, the LS mean changes from baseline to Week 12 were 5.5 mg/dl in placebo and -11.8 mg/dl in SPD489. The differences between two treatment arms (-17.6 and -17.3 mg/dL in study 343 and 344, respectively) were statistically significant with very small p-values (p < 0.001).

Our statistical reviewer, Thomas Birkner, PhD., conducted his own analyses on the all primary and key secondary endpoints based on the data submitted by the sponsor. The efficacy results from his analyses were consistent with that from the sponsor's analyses.

Subgroup Analysis

Subgroup analysis of the primary efficacy measure was conducted by the sponsor based on the following characteristics for the FAS from the pool of study 343 and 344: age, sex, race, ethnicity, region, BMI, and baseline binge eating severity.

The mean changes in the number of binges per week were greater for the SPD489-treated subjects than for the placebo group, regardless of subgroup. However, the 95% CIs for non-US subjects (Studies 343 and 344), males (Study 343), and non-whites (Study 343) were relatively wide (potentially because of a relatively small sample size) and crossed zero, which indicates similarity between treatment groups. Because the randomization was not stratified based on subgroup, the number of subjects within a subgroup was not consistently balanced. Therefore, a definitive conclusion regarding efficacy results based on subgroup cannot be drawn.

5.1.2 Discussion of primary reviewers' comments and conclusions

Both clinical reviewer, Gregory Dubitsky, MD., and statistical reviewer, Thomas Birkner, PhD, concluded in their review that Trials SPD489-343 and SPD489-344 adequately demonstrate the superiority of SPD489 50 and 70 mg/day over placebo in the treatment of moderate to severe BED in adults for up to 12 weeks. The positive results from pre-specified key secondary endpoints provided additional supportive evidence. I agree with their conclusion.

5.1.3 Dose identification/selection and limitations

The sponsor conducted a Phase 2 trial (SPD489-208) to evaluate the efficacy of 3 doses of SPD489 (30, 50, and 70 mg/day) versus placebo in the treatment of adults with moderate to severe BED. This was a multicenter, randomized, double-blind, placebo-controlled, forced-dose titration study in which eligible subjects were randomized in a 1:1:1:1 ratio to one of the 3 doses of SPD489 or placebo. Subjects randomized to the 2 higher doses of drug were titrated up at a rate of 20 mg/day/week with no allowance for dose changes. After the 3-week dose forced-dose titration, subjects continued on their assigned dose for an additional 8 weeks for total treatment duration of 11 weeks.

A total of 271 subjects were randomized and 213 completed the trial. The primary efficacy endpoint was the change from baseline to Week 11 in the log-transformed number of binge days/week, analyzed using MMRM. SPD489 in doses of 50 and 70 mg/day were highly statistically significantly superior to placebo on the primary efficacy endpoint. There was no substantial difference between the 50 and 70 mg/day doses. The 30 mg/day dose was

not effective compared to placebo. The results of this trial were used to determine the dose levels for the two Phase 3 efficacy trials.

Dr. Birkner did exploratory analysis by optimized dose (50 mg vs. 70 mg) in study 344. About 29% and 62% of SPD489 patients reached optimal doses at 50 mg/d and 70 mg/d, respectively. There is no treatment differences identified between these two groups based on the efficacy result from the primary endpoint. However, it is notable that patients who were on 50 mg-dose are on average 10 kg lighter compared to patients who were on 70 mg/d as the optimal dose (86.7 kg vs. 97.7 kg).

5.1.4 Pediatric use/PREA waivers/deferrals

The sponsor requested a full waiver for pediatric studies on Oct. 16, 2013 because the low prevalence of BED in pediatric population and pediatric studies would be impossible or highly impractical. The request was discussed with PeRC on Oct. 22, 2014 and a full waiver was granted.

5.2 Safety

5.2.1 General safety considerations

Dr. Gregory Dubitsky is the medical reviewer who conducted the safety review for this sNDA. Please refer to his review for this sNDA for details. The safety evaluation of SPD489 in the treatment of moderate to severe BED were mainly based on pooled safety data from 2 phase 3 randomized, double-blind, placebo-controlled trials, SPD489-343 and SPD489-344. In addition, safety data from a phase 2 dose finding study, SPD489-208, and the 12-month open-label extension study SPD489-345, were also used to examine deaths, serious adverse events and new or unexpected safety signals.

SPD 489 has been approved for marketing for ADHD since Feb. 2007. The safety profile of SPD489 has been well characterized. Compared with the ADHD programs, the BED program studied a population carrying a slightly higher cardiovascular risk —adults, and most of them are overweight. In general, the safety profile of SPD489 in BED program remained no change. There were no new safety signals identified. Increased blood pressure and heart rate compared to placebo were observed in these studies and the blood pressure increase with SPD489 treatment remained during the whole study period and was not correlated with weight loss.

Total Exposure

A total of 833 subjects across all 4 phase 2/3 trials were exposed to at least 1 dose of SPD489. The target dose of SPD489 for the treatment of BED is 50 or 70 mg/day. As of June 30, 2014, and across all 4 clinical trials, 768 subjects received a daily dose of 50 or 70mg for some duration of time, 488 received these doses for 180 days or longer and 224 received these doses for 361 days or longer.

5.2.2 Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Deaths

There was one death reported in study SPD489-208. Subject 208-036-0006 was a 29 year old Asian male in the 70mg dose group who died about 1 month after in the trial. The post-mortem examination revealed methamphetamine and amphetamine levels consistent with a methamphetamine overdose.

Serious Adverse Events (SAEs)

In the placebo-controlled trials, there were 6 patients in SPD489 treatment and 4 patients in placebo treatment reported 10 non-fatal serious adverse events. Syncope was reported in 3 patients (2 on SPD489 and 1 on placebo) and cholecystitis occurred in 1 SPD489 patient. The rest SAEs only occurred in 1 patient and seemed less likely to be drug related.

In the open-label extension trial (SPD489-345), 15 patients reported 16 SAEs. Four patients reported 4 cholecystitis or cholelithiasis. The rest SAEs were reported only in 1 patient and seemed less likely to be drug related.

Special Interests of SAEs:

Cholecystitis/Cholelithiasis

In the Phase 2/3 placebo-controlled trials, there was one report of cholecystitis and another of cholelithiasis on drug and none on placebo. In the 12-month open label study, there were 4 reports of cholecystitis and two of cholelithiasis. The overall rate of gallstone-related adverse events in the safety database was 1.0% (8/833). Most of the 8 cases from these clinical trials were classified as serious. Characteristics of the patients who experienced these events are all female and obese (BMI >30 kg/m²). Seven out of 8 had lost substantial weight prior to the event.

The Division of Metabolism and Endocrinology Products (DMEP) was consulted for their opinion on a potential causal link between SPD489 treatment and gallstone-related adverse events. A consultative review was completed on November 12, 2014, by Julie Golden, M.D. In summary, Dr. Golden made the following points:

- the studied population (female and obese) is at risk for gallstones.
- weight loss can increase the risk of these events and, thus, it is plausible that SPD489, via its effects on food intake and weight, may increase the risk of cholelithiasis in this population already at risk for these events.
- it is unknown whether these patients had cholelithiasis prior to SPD489 treatment because of lack of baseline evaluations.
- the degree of lipid alterations associated with SPD489 is consistent with its effect on weight and an independent effect on lipid metabolism seems less likely.
- independent effects on gallbladder motility are unknown.

- labeling of DMEP products associated with gallstone-related events in clinical trials (e.g., obesity drugs and fibrates) describe the risk under Warnings and Precautions because of the existence of a plausible causal link, the potential for serious complications, and early recognition might mitigate serious morbidity.

In Dr. Dubitsky's review, he thought that there is insufficient evidence at this time to support a clear causal relationship between these events and SPD489 treatment. I agree with him and no labeling change in the section of Warning and Precaution regarding these events is recommended.

Adverse Events Leading to Discontinuation

Treatment-emergent adverse events led to dropout in 5.1% of SPD489-treated subjects and 2.4% of placebo subjects in the pool of studies 343 and 344. Specific events that led to discontinuation reported in at least 2 SPD489-treated subjects are irritability, syncope, heart rate increased/tachycardia, and insomnia/initial insomnia.

Treatment-Emergent Adverse Events

In the pooled safety data from two phase 3 studies, the most commonly observed TEAEs with SPD489 ($\geq 5\%$ in SPD489 treated patients and at least twice the rate of placebo) were dry mouth, insomnia, decreased appetite, heart rate increased, constipation, feeling jittery, and anxiety.

The profile of common adverse events of SPD 489 in the pooled safety data from study 343 and 344 is similar to that obtained from other indications of SPD489 except the rate of decreased appetite. There were much fewer reports for decreased appetite in SPD489 treated patients in BED program (8% in SPD489 and 2% in placebo) compared with that in other indications (27-39% in SPD489 and 2-4% in placebo). A possible explanation for this discrepancy is that BED patients did not think reduced appetite an AE and did not reported, or the investigators did not consider reduced appetite as an AE.

Clinical Laboratory Evaluations

In general, no clinically significant effects of SPD489 were noted on any chemistry or hematology laboratory parameters during the clinical development program.

Vital Signs, Weight, and ECG Findings

Blood Pressure Changes

Mean increases in SBP and DBP were seen in SPD489-treated patients compared to decreases in the placebo group: at Week 12, the mean change from baseline in SBP was -2.5 mmHg for placebo and +0.8 mmHg for SPD489; the mean change from baseline in DBP was -1.4 mmHg for placebo and +1.4 mmHg for SPD489. On average, mean increases in pulse rate were seen in both treatment arms but were substantially greater in the SPD489 group. For example, at Week 12, the mean change from baseline in pulse rate was +1.8 bpm for placebo and +5.4 bpm for SPD489.

Changes in blood pressure and pulse rate relative to placebo tended to remain stable over time throughout these trials. There was no correlation between the rate of change in sblood

pressure and rate of change in body weight in either the SPD489-treated patients or the placebo group in the safety pool of trials SPD489-343 and SPD489-344 (blood pressure remained increase even though patients lost weight).

Weight Loss

A much larger proportion of patients in the SPD489 arm experienced substantial weight loss ($\geq 10\%$ baseline body weight) compared to the placebo arm (20% vs. $< 1\%$).

Body weight changes from baseline at Week 12 were -12.8 lbs in the SPD489 group versus +0.1 lbs in the placebo group. Weight decrease tended to occur gradually during the course of these short-term trials and was not correlated with reduction of binge episodes. In the long-term, open-label trial (SPD489-345), mean body weight decreased over time achieving a maximum decrease at week 28 (16.8 lbs on average) for those in the trial, with increases in mean body weight thereafter.

ECG

Mean changes in PR, QRS, QT, QTcB, and QTcF intervals suggested no tendency for SPD489 to cause prolongation of these parameters.

Suicidality Assessment

The emergence of suicidal ideation and behavior was assessed at each visit using the Columbia-Suicide Severity Rating Scale (C-SSRS). There were few positive responses and the rate of positive responses was not substantially higher for the SPD489 arm compared to placebo.

Adverse Events of Special Interest

Cardiovascular Risk

The Division of Cardiovascular and Renal products (DCaRP) was consulted for assessing the cardiovascular risk of SPD489 in patients with BED in view of the persistently increased blood pressure and heart rate observed in the BED trials and given that BED patients are generally obese (often morbidly obese) and will likely take the drug for long term.

Shari L. Targum, M.D., Clinical Team Leader and cardiologist in DCaRP, did the consult review (see her review on January 8, 2015). Her examination of safety data from the BED trials in this supplement revealed no cardiovascular safety signal although the low rates of events provided only limited reassurance and made it difficult to quantify the level of cardiovascular risk. She mentioned that use of blood pressure curves, such as those based on the Framingham study, to estimate cardiovascular risk may not be appropriate in this case. For those with modest risk, the benefits of Vyvanse in BED may outweigh the potential cardiovascular risk. Given that “serious cardiovascular reactions” and “blood pressure and heart rate increase” have been labeled in the Warning and Precaution section of the label, Dr. Targum recommended that the risks can be addressed to some extent through blood pressure monitoring and, if needed, antihypertensive treatment; limiting the duration of treatment, and avoiding use in patients at particularly high baseline risk. These

measures could be recommended in labeling and possibly other risk communication mechanisms.

Dr. Targum also recommended (after the review had been filed) that we describe the study population (a relatively low risk population other than overweight because of exclusion criteria) in the product label to inform the reader that “the real world” or high risk patients were not studied in BED program. We included the following language “Patients with cardiovascular risk factors other than obesity and smoking were excluded” in section 6.1 of the product label.

6 Labeling Recommendations

Significant weight loss had been observed in the BED program, and measuring the weight loss is one of key secondary endpoints. A serious concern of potential promotion of SPD489 by the sponsor for weight loss indication was raised during the review cycle. The FDA has a different standard for approval of a weight loss drug. To gain a weight loss indication, it is usually required by FDA to conduct long-term efficacy studies and it may require a cardiovascular outcome study for drugs that have cardiovascular risk. This sNDA submission only included two 12-week placebo-controlled studies and patients who have cardiovascular risk other than overweight were excluded from the studies. (b) (4)

Vyvanse has been approved for marketing since 2007 and it is a widely used drug. We have plenty post-marketing safety data for stimulants as a class. Increase of blood pressure and heart rate are well known adverse events for stimulants and “serious cardiovascular reactions” and “blood pressure and heart rate increase” have been labelled in the Warning and Precaution section of the product label. Considering BED is a serious psychiatric condition, the division recommended the following labeling changes to address this safety concern:

1. Add “Limitation of Use” in the label to prevent off label use of Vyvanse for weight loss indication. The Limitation of Use includes the following statement “VYVANSE is not indicated for weight loss. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.” (b) (4)
2. (b) (4)
3. (b) (4)

7 The Office of Scientific Investigation (OSI) Audits

The Office of Scientific Investigations (OSI) inspected 2 clinical sites that participated in the pivotal trials that support this supplement: Alexander E. Horwitz, M.D., (SPD489-343/site 83, 24 subjects) and H. Mikel Thomas, M.D. (SPD489-344/Site 32, 25 subjects). John Lee, MD is the OSI medical reviewer, in his Clinical Inspection Summary, he stated that there were no significant Good Clinical Practice violations at either site and both were given a preliminary classification of NAI (No Action Indicated).

8 Conclusions and Recommendations

8.1 Recommended regulatory action

After considering the conclusions and recommendations from all review teams, I recommend that the division take an approval action on this sNDA. I agree that study SPD489-343 and SPD489-344 adequately demonstrate the superiority of SPD489 50 and 70 mg/day over placebo in the treatment of moderate to severe BED in adults for up to 12 weeks. The positive results from pre-specified key secondary endpoints provided additional supportive evidence. The safety findings from this sNDA did not prevent the approval of this sNDA.

8.2 Safety concerns to be followed post-marketing

The cardiovascular risk of SPD489 needs to be followed during post-marketing period. There are no specific studies required at this time.

8.3 Risk Minimization Action Plan

Currently, I do not recommend any specific risk minimization actions.

8.4 Postmarketing studies required

A maintenance study with a randomize withdrawal design is ongoing. We have no additional post-marketing studies required.

The sponsor requested a full waiver for pediatric studies on Oct. 16, 2013 because the low prevalence of BED in pediatric population. The request was discussed with PeRC on Oct. 22, 2014 and a full waiver was granted. No pediatric studies are required at this time.

8.5 Comments to be conveyed to the applicant in the regulatory action letter

I do not have any comments to be conveyed to the applicant in the regulatory action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JING ZHANG
01/23/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type sNDA
Application Number 21-977 S-037
Priority or Standard Priority

Submission Date August 1, 2014
Received Date August 1, 2014
PDUFA Goal Date February 1, 2015
Division/Office DPP/ODE 1

Reviewer Name Gregory M. Dubitsky, MD
Review Completion Date January 9, 2015

Established Name Lisdexamfetamine(SPD489)
Trade Name Vyvanse
Therapeutic Class Stimulant Prodrug
Applicant Shire

Formulation Capsules
Dosing Regimen 50 to 70 mg once daily
Indication Binge Eating Disorder (BED)
Intended Population Adults with moderate to severe BED

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1 RECOMMENDATIONS/RISK-BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

It is recommended that this supplement be approved after agreement on labeling.

1.2 Risk-Benefit Assessment

Benefits from the alleviation of distress and impairment experienced by patients with moderate to severe Binge Eating Disorder (BED) are judged to outweigh the risks of treatment, in particular persistent increases in heart rate and blood pressure.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None are recommended at this time.

1.4 Recommendations for Postmarketing Requirements and Commitments

The sponsor must conduct an adequate and well-controlled trial of maintenance efficacy in BED. Such a trial (b) (4) is currently underway.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Vyvanse, also known as lisdexamfetamine or SPD489, is a prodrug of the stimulant d-amphetamine. Vyvanse was approved in 2007 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients age 6 years and older.

This supplement is intended to support the approval of Vyvanse for the treatment of moderate to severe BED in adults. According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), the criteria for BED are as follows (Criteria A through E must be met to establish the diagnosis).¹

A. Recurrent episodes of binge eating which are characterized by both eating an amount of food in a discrete period of time that is larger than what most people

¹ American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

would eat in a similar timeframe and a sense of lack of control over eating during the episodes.

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

- eating much more rapidly than normal.
- eating until feeling uncomfortably full.
- eating large amounts of food when not feeling physically hungry.
- eating alone because of embarrassment by how much is eaten.
- feelings of disgust, depression, or guilt after an episode.

C. Marked distress over binge eating.

D. Binge eating occurs, on average, at least once a week for 3 months.

E. Binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.

BED severity is based on the number of episodes per week:

Mild: 1-3 episodes per week.

Moderate: 4-7 episodes per week.

Severe: 8-13 episodes per week.

Extreme: 14 or more episodes per week.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved treatments in the U.S. for BED.

2.3 Availability of Proposed Active Ingredient in the United States

Vyvanse contains no active ingredients. Dextroamphetamine is available in many products marketed in the U.S.

2.4 Important Issues With Consideration to Related Drugs

The active moiety produced *in vivo* after ingestion of Vyvanse is the sympathomimetic amine, d-amphetamine. Amphetamines are known to cause several adverse effects, importantly elevations in heart and blood pressure, decreased appetite and weight loss, abuse, tolerance, physical dependence, insomnia, peripheral vasculopathy, and, in pediatric patients, suppression of growth.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting was held on February 9, 2011. This meeting included a discussion of the following topics:

- inclusion and exclusion criteria for trial SPD489-208, a proof-of-concept (POC) study of three fixed doses of SPD489 (30, 50, and 70 mg/day) in BED.
- acceptability of the proposed primary efficacy variable in this trial, i.e., the number of binge days per week.
- collection of data on caloric intake, which was not felt by the Agency to be necessary.
- the high likelihood that an application for BED would be taken to the Psychopharmacological Drugs Advisory Committee (PDAC).

The Vyvanse BED development program was conducted under IND 110,503, which was submitted on March 4, 2011.

An End-of-Phase 2 meeting was held on July 30, 2012. The following were among the topics discussed:

- primary efficacy results from trial SPD489-208.
- proposed short-term, placebo-controlled, dose-optimization trials (SPD489-343 and SPD489-344) using doses of 50 and 70 mg/day.
- proposed open-label, 12-month extension trial (SPD489-345) and estimated exposure in this trial at initial submission and at the Four-Month Safety Update in a planned sNDA.
- proposed randomized withdrawal trial ((b) (4)).
- relative merits of using binge episodes versus binge days as the standard for measuring efficacy. The Agency accepted the use of binge days as the standard measure in part because it can be difficult to determine precisely when one binge episode begins and the next begins.
- sponsor's assertion, based on a survey of expert clinicians, that a mean reduction of ≥ 0.5 binge days per week is clinically meaningful.
- clarification of planned assessments of changes in weight and triglycerides was requested by the Agency.
- the sponsor was informed that labeling language would be a matter for review after the sNDA was submitted.

(b) (4)

- recommendation that subjects in the randomized withdrawal trial be (b) (4)

(b) (4)

- PREA requirements. The Agency stated that a partial waiver of requirements for pediatric trials from birth to 12 years was likely to be acceptable because of

the low prevalence of BED in this age range. Also, a deferral for ages 13 to 17 years was also likely acceptable. However, the sponsor was informed that they must submit data to support a partial waiver request.

Pre-sNDA comments were forwarded to the sponsor on March 4, 2014. These comments conveyed information that included the following items:

- Agency request for safety and efficacy analyses both with and without data from three discontinued sites.
- Agency opinion that patient exposure and safety data appear to be sufficient to support filing of an sNDA.
- Agency advice on the sponsor's requesting priority review status.
- the possibility of an Advisory Committee meeting during the sNDA review.

2.6 Other Relevant Background Information

The sponsor requested and was granted priority review status for this supplement because there are no other drugs approved for the BED indication.

During the BED development program, the Diagnostic and Statistical Manual of Mental Disorders was revised from the previous edition (DSM-IV) to the current version (DSM-5). DSM-IV contained Research Criteria for BED intended primarily for research purposes. After extensive research into the clinical utility and validity of BED, DSM-5 incorporated criteria for BED as a formal clinical disorder. The only significant difference between the DSM-IV and DSM-5 criteria for BED is that the minimum average frequency of binge eating required for diagnosis is once weekly for the prior 3 month period (DSM-5) instead of at least 2 days per week over the previous 6 months (DSM-IV).

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

I audited case report forms (CRF's) to evaluate the consistency of adverse event information across the CRF, narrative summary, and the individual trial adverse event tabulations (ae.xpt) for a sample of the following 6 patients:

| Study | Center | Patient |
|--------------|---------------|----------------|
| SPD489-208 | 008 | 0007 |
| SPD489-343 | 052 | 3014 |
| SPD489-343 | 062 | 3004 |
| SPD489-344 | 079 | 4014 |
| SPD489-344 | 090 | 4010 |
| SPD489-345 | 072 | 3002 |

The adverse event information was found to be consistent across the above three documents for these patients.

In addition, I audited a 10% sample of reported adverse events from the ISS dataset adae.xpt to compare the reported (verbatim) term (AETERM) with the coded (or preferred) term (ISSPT). I identified no deficiencies in adverse event coding from this audit. However, during the course of my review of the safety data, I noticed a few instances where multiple coded terms could represent very similar adverse events (e.g., insomnia and initial insomnia, heart rate increased and tachycardia). For purposes of this review, all preferred terms reflective of insomnia as well as those indicating increases in heart rate were combined.

3.2 Compliance with Good Clinical Practices

Trials SPD489-208, SPD489-343, SPD489-344, and SPD489-345 were conducted in accordance with Good Clinical Practices.

The Office of Scientific Investigations (OSI) inspected 2 clinical sites that participated in the pivotal trials that support this supplement:

- SPD489-343/Site 83 (24 subjects), PI: Alexander E. Horwitz, M.D., Oregon Center for Clinical Investigations, Salem, Oregon.
- SPD489-344/Site 32 (25 subjects), PI: H. Mikel Thomas, M.D., Clinical Trials Technology, Prairie Village, Kansas.

According to the Clinical Inspection Summary dated October 24, 2014, there were no significant Good Clinical Practice violations at either site and both were given a preliminary classification of NAI (No Action Indicated).

3.3 Financial Disclosure Template

Application Number: 21-977

Submission Date(s): Aug 1, 2014

Applicant: Shire

Product: Vyvanse

Reviewer: Greg Dubitsky

Date of Review: January 8, 2015

Covered Clinical Study (Number): SPD489-343

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: <u>51</u> | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

Covered Clinical Study (Number): SPD489-344

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: <u>46</u> | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.² Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

² See [web address].

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

There were no disclosable financial interests or arrangements among the principal investigators for trials SPD489-343 and SPD489-344.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

No significant CMC issues are noted.

4.3 Nonclinical Pharmacology/Toxicology

No significant nonclinical issues are noted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action in BED is unknown. It is hypothesized that dopaminergic and noradrenergic hypofunction may play a role in BED since both dopamine and norepinephrine are thought to be important in regulating eating behavior and reward. BED may represent a “reward deficiency syndrome” in which deficient dopaminergic signaling promotes binge eating in an attempt to restore dopamine functioning to normal levels. It is speculated that SPD489 may alleviate binge eating by stabilizing the reward deficit via prolonged blockade of dopamine reuptake.

4.4.2 Pharmacodynamics

Shire commissioned [REDACTED] ^{(b) (4)} to build a population PK/PD model to describe d-amphetamine concentrations after administration of lisdexamfetamine and to model the relationship between these concentrations and systolic and diastolic ambulatory blood pressure. Data for this endeavor was derived from trial SPD489-116, a two-period, double-blind crossover study in healthy older adult subjects who received a single dose of SPD489 50mg or placebo. There were 48 subjects enrolled across 3 age ranges (55-64, 65-74, and 75 and older) with approximately 8 subjects of each gender within each age range. Blood samples were obtained for PK assessments pre-dose and at multiple time points from 0.5 to 72 hours post-dose. Ambulatory blood pressure monitoring was conducted from 24 hours before dosing to 48 hours post-dose using an Ambulo 2400 24-hour ambulatory blood pressure

monitoring system. Based on this model, the sponsor reports that both systolic and diastolic blood pressure increased as a function of dose, with increases slightly higher for subjects with lower body weight. Blood pressure increases were predicted to be small when the SPD489 dose was increased from 50mg to 70mg: <1.1 mmHg diastolic and <1.5mmHg systolic. The largest changes occurred at times of maximal d-amphetamine plasma levels.

4.4.3 Pharmacokinetics

Shire requested that (b) (4) develop a population PK model for d-amphetamine based on data from 4 adult studies (N=110 males and 55 females) as well as data from a single pediatric study (N=14, ages 6-11 years) for comparison to the adult model. Single and multiple doses in the adult trials ranged from 30mg to 250mg. PK parameters determined from the model were similar to those reported in clinical studies and the literature, according to the sponsor. Subject weight appeared to be the main factor influencing d-amphetamine PK although the impact was only marginal (a deviation >50% was required to produce a meaningful change in PK). Subjects older than age 50 had an age-related decline in clearance. The pediatric model was consistent with the adult model.

4.5 Office of New Drugs (OND)

The need for a cardiovascular outcome trial in view of the drug-related changes in blood pressure and heart rate and the likelihood that many patients might use Vyvanse treatment for weight loss was discussed at a December 12, 2014, internal CDER Regulatory Briefing and a subsequent December 19, 2014, internal meeting of senior staff from the CDER OND, including representation from the Division of Metabolism and Endocrinology Products (DMEP). Although 12-month cardiovascular outcome trials are currently a standard requirement in the DMEP for weight loss drugs, which also tend to chronically elevate blood pressure and heart rate, it was decided that such a trial is not necessary in this case because Vyvanse will be indicated for moderate to severe binge eating

(b) (4)
recruitment of a sufficient number of BED patients for an adequately powered cardiovascular outcome study would likely be impossible. However, there was a strong feeling that labeling must clearly indicate that Vyvanse is not to be used for weight loss.

4.6 Division of Cardiovascular and Renal Products (DCaRP)

DCaRP was consulted to address the following. 1) Evaluate the magnitude of cardiovascular risk of Vyvanse® in patients with BED in view of the persistently increased blood pressure and heart rate observed in the BED trials and given that BED patients are generally obese (often morbidly obese) and will likely take Vyvanse®, if approved for BED, for several months to years. 2) Recommend any

further pre-approval work-up or Postmarketing Requirements (PMRs) that should be requested to more fully characterize the risk/benefit ratio of Vyvanse® in this population from a cardiovascular standpoint.

Shari L. Targum, M.D., Clinical Team Leader and cardiologist in DCaRP, provided a consultative memorandum dated January 8, 2015. Her examination of safety data from the BED trials in this supplement revealed no cardiovascular safety signal although the low rates of events provided only limited reassurance and made it difficult to quantify the level of cardiovascular risk. Use of blood pressure curves, such as those based on the Framingham study, to estimate cardiovascular risk may not be appropriate because of the multiplicity of effects produced by Vyvanse in this population (e.g., increases in heart rate and blood pressure as well as reductions in lipids and weight). For those with modest risk, the benefits of Vyvanse in BED may tilt the risk:benefit ratio in favor of using the drug. Dr. Targum recommended that the risks be addressed to some extent through blood pressure monitoring and, if needed, antihypertensive treatment; limiting the duration of treatment, and avoiding use in patients at particularly high baseline risk. These measures could be recommended in labeling and possibly other risk communication mechanisms.

4.7 Division of Metabolism and Endocrinology Products (DMEP)

DMEP was formally consulted to evaluate the case of cholecystitis and cholelithiasis reported in the BED trials. Their response is discussed in section 7.3.2 of this review.

In addition, DMEP provided feedback regarding the potential use of Vyvanse for weight loss during a December 12, 2014, Regulatory Briefing and a December 19, 2014, follow-up meeting with senior staff of the Office of New Drugs, as discussed above.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

The clinical trials that comprise this supplement are summarized in the table below.

| Table 1: Clinical Trials in BED | |
|--|---|
| Phase/Trial | Description |
| Phase 2 | |
| SPD489-208 | 11-week, randomized, double-blind, placebo-controlled, parallel group trial of 3 fixed doses (30, 50, and 70 mg/day). N= 271 randomized. |
| Phase 3 | |
| SPD489-343 | 12-week, randomized, double-blind, placebo-controlled, parallel group trial using flexible dosing of 50 or 70 mg/day. N= 383 randomized. |
| SPD489-344 | 12-week, randomized, double-blind, placebo-controlled, parallel group trial using flexible dosing of 50 or 70 mg/day. N= 390 randomized. |
| SPD489-345 | Ongoing, 52-week, open-label, uncontrolled extension trial using flexible dosing of 50 or 70 mg/day. N= 604 enrolled as of June 30, 2014. |

5.2 Review Strategy

The efficacy review focused on each of the two placebo-controlled Phase 3 trials (SPD489-343 and SPD489-344). The safety review entailed an examination of serious adverse events, premature discontinuations secondary to adverse events, and other important adverse experiences from all four Phase 2/3 trials, including those events described in the Four-Month Safety Update Report (submitted November 21, 2014 with a cutoff date of June 30, 2014). Analyses which provided supportive safety information (including common adverse events, laboratory testing, vital signs, and ECGs) were based on the pool of the two placebo-controlled Phase 3 trials. Evaluation of dose-response for both efficacy and safety measures relied on the findings from the fixed dose trial (SPD489-208).

5.3 Discussion of Individual Studies/Clinical Trials

The review of efficacy was based on the individual study reports for trials SPD489-343 and SPD489-344.

6 REVIEW OF EFFICACY

Efficacy Summary

The sponsor conducted two Phase 3 efficacy trials to definitively demonstrate the efficacy of SPD489 in the treatment of moderate to severe BED in adults. These trials (SPD489-343 and SPD489-344) adequately demonstrated the superiority of

SPD489 in doses of 50 and 70 mg/day over placebo in the treatment of BED as measured by a statistically significant reduction in the number of binge days per week, based on a daily diary maintained by the subject. In addition, statistical superiority favoring SPD489 was shown on 5 key secondary efficacy variables: CGI-Improvement score, proportion of subjects with cessation of all binge eating for the last 4 weeks of trial participation, percentage reduction in body weight, the Y-BOC-BE total score, and fasting serum triglyceride levels.

6.1 Studies Pertinent to Binge Eating Disorder

6.1.1 Rationale for Selection of Studies for Review

Two Phase 3 pivotal efficacy trials were selected for review: SPD489-343 and SPD489-344. Both trials used a randomized, double-blind, placebo-controlled, parallel group design. In addition, a Phase 2 proof-of-concept trial was conducted by the sponsor to determine effective doses for the Phase 3 trials: SPD489-208. The latter trial will be discussed in the context of dose response.

6.1.2 Study Summaries

Study 1 (SPD489-343)

Methods/Study Design/Analysis Plan

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel group trial of the safety and efficacy of SPD489 in adults (ages 18-55) with moderate to severe Binge Eating Disorder (BED). The treatment duration was 12 weeks. A total of 383 subjects were enrolled from 50 sites, 44 of which were in the U.S. and 6 in Europe (Sweden, Germany, and Spain). Relevant inclusion and exclusion criteria were as follows:

Inclusion

- DSM-IV-TR diagnosis of BED.
- BED diagnosis confirmed with the eating disorder module of the SCID-I (Structured Clinical Interview for DSM) and EDE-Q (Eating Disorder Examination-Questionnaire).
- binge eating occurred, on average, at least 2 days a week for 6 months.
- BED of at least moderate severity (at least 3 binge eating days per week for the 14 days prior to baseline as documented in a binge diary, with a binge day defined as a day in which at least one binge eating episode occurs).
- CGI-severity score ≥ 4 at screening and baseline.
- BMI ≥ 18 but ≤ 45 at screening and baseline.

Exclusion

- current diagnosis of bulimia nervosa or anorexia nervosa.
- receiving psychotherapy or weight loss intervention for BED that started within 3 months of screening. Treatments that began earlier could continue only if the

subject agreed to not make any changes in the frequency or nature of the intervention.

- use of psychostimulants to facilitate fasting or dieting within 6 months of screening.
- lifetime history of psychosis, mania, hypomania, dementia, or ADHD.
- MADRS total score >18 at screening.
- considered to be a suicide risk by the investigator.
- symptomatic cardiovascular disease, advanced atherosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, a clinically significant ECG abnormality at baseline, or a family history of either sudden cardiac death or ventricular arrhythmia.
- abnormal thyroid function.
- started treatment with a lipid-lowering agent within 3 months of screening. Use of such an agent at a stable dose for longer than 3 months was permitted.
- substance abuse or dependence (except nicotine) within the past 6 months.
- bariatric surgery, lap bands, duodenal stents, or other procedures for weight loss.

This trial was conducted in 3 phases:

- 2 to 4 week screening period.
- 12-week double-blind treatment period (4 weeks of dose optimization and 8 weeks of maintenance treatment at the optimized dose).
- one-week follow-up period.

Subjects randomized to SPD489 started treatment with 30 mg/day following all baseline assessments. At the end of the first week, the dose was increased to 50 mg/day with a subsequent increase to 70 mg/day after the second or third week as tolerated and clinically indicated to achieve an optimal dose (either 50 or 70 mg/day). No dose changes were permitted after the Week 3 visit. The optimized dose was maintained for the remainder of the 12-week treatment phase. If intolerance or unacceptable efficacy occurred during maintenance treatment, treatment could be discontinued but no dose change was allowed.

Binge eating information was collected daily by the subject and recorded in a paper diary, which was distributed at each visit and collected at the next visit. This diary captured the number of binges per day, total hours spent bingeing each day, type of binge (mealtime versus non-mealtime), and a description of the binge (amounts and types of food). At each visit, the investigator reviewed the completed diary with the patient and confirmed whether each recorded eating episode was a binge. The number of confirmed binges each day was then recorded in the CRF.

Other relevant efficacy assessments during the treatment phase were as follows:

- CGI at baseline and at Weeks 1, 2, 3, 4, 6, 8, 10, and 12.

- Y-BOCS-BE (Yale-Brown Obsessive Compulsive Scale modified for Binge Eating) was rated at baseline and at Weeks 4, 8, and 12. This is a clinician-rated 10-item scale, with each item rated from 0 (no symptoms) to 4 (extreme symptoms). The scale asks questions regarding the amount of time spent on obsessions, the amount of impairment or distress experienced, and resistance and control over obsessional thoughts as well as similar questions pertaining to compulsions. Total scores of 8 to 15 are interpreted as mild symptomatology, 16 to 23 as moderate, 24 to 31 as severe, and 32 to 40 as extreme.
- clinical laboratory tests (including serum triglycerides, total cholesterol, and HbA1c) were performed after a 12 hour fast during screening and at Week 12.

The primary efficacy endpoint was the change from baseline to Week 12 in the number of binge days per week during Weeks 11 and 12. At baseline, this number was calculated as the weekly average from the 14 days preceding baseline. At final visit, this number was computed as the number of binge days multiplied by 7 then divided by the number of days in the period. The analysis was performed using MMRM (Mixed-effects Model for Repeated Measures) over the Full Analysis Set (FAS), defined as all subjects who had taken at least one dose of study drug and had one post-baseline primary efficacy assessment.

Key secondary efficacy variables were the following:

- CGI-Improvement score at Week 12 or End of Treatment dichotomized as the percentage improved (i.e., very much improved and much improved) versus the percentage not improved (other ratings).
- proportion of subjects with a 4-week cessation of binge eating (no binges) for the 28 day period prior to Week 12 or End of Treatment for dropouts.
- percentage change from baseline to Week 12 in body weight.
- change from baseline to Week 12 in the Y-BOCS-BE total score.
- change from baseline to Week 12 or End of Treatment in fasting triglycerides.³

Analysis of the key secondary variables was conducted over the FAS. Multiplicity was addressed by hierarchical testing, with each variable tested at a two-sided 0.05 level of significance in the order shown above. The CGI-I and proportion with cessation of binge eating were compared between treatment groups using a Chi-Square test. Percentage change in body weight and change in Y-BOCS-BE were compared using MMRM. Triglycerides were compared between groups using an ANCOVA model.

Results

Demographics

Baseline demographic features were comparable between the SPD489 and placebo treatment groups. Overall, the mean age was 38 years (range 19 to 55

³ The March 28, 2013, Statistical Analysis Plan added “End of Treatment” as a time point of interest for analysis of triglyceride data.

years) with 53% of subjects under the age of 40. Most (87%) of subjects were female and most (78%) were of the White race. Mean body weight was 94 kg (range 49-149 kg) and mean BMI was 33 kg/m² (range of 19-45). About two-thirds (67%) were obese (BMI ≥30 kg/m²); a small minority (10%) were underweight or normal weight (BMI <25 kg/m²) but 18% were morbidly obese (BMI ≥40 kg/m²).

Baseline Characteristics

The SPD489 and placebo groups were similar in terms of the age at BED diagnosis (median 37 years) and other baseline illness characteristics. For the groups combined, the median binge days per week was 4.50 and the median binge episodes per week was 5.50. The median Y-BOCS-BE total score was 21.00. About half (49%) of subjects were moderately ill as rated by the CGI-Severity score, with 43% markedly ill, 7% severely ill, and <1% among the most extremely ill.

Patient Disposition

A total of 642 subjects were screened for this trial, of which 383 were randomized to treatment. Subject disposition is shown in the table below. The FAS was comprised of 374 subjects (190 randomized to SPD489 and 184 to placebo). Nine randomized subjects were excluded from the FAS because they received no study drug (N=4) or they had binge eating diary information only at baseline (N=5); none of these 9 subjects completed the trial.

Concomitant Medication Use

I examined the listing of concomitant medications used during this trial and found none that would likely bias the efficacy findings, in my judgment.⁴

Important Protocol Violations

No protocol violations that were likely to affect the efficacy findings of this trial were identified.

On November 10, 2014, Shire notified the Agency that site 066 (N=21 patients enrolled) was being closed because of concerns about signs of investigational drug tampering during the conduct of another trial ((b) (4) - (b) (4)). On November 12, 2014, the biometrics reviewer, Dr. Birkner, indicated by email to me that the exclusion of this site from the primary and key secondary efficacy analyses has no substantial effect on the efficacy results.

⁴ Based on Table 1.3.2 of the Clinical Study Report.

Table 2: Subject Disposition (Trial SPD489-343)

| | Placebo n (%) | SPD489 n (%) | Total n (%) |
|-------------------------------------|------------------|-----------------|----------------|
| Screened Set | | | 642 |
| Randomized Set | 191 | 192 | 383 |
| Safety Analysis Set ^{a, b} | 187 (97.9) | 192 (100) | 379 (99.0) |
| Full Analysis Set ^c | 184 (96.3) | 190 (99.0) | 374 (97.7) |
| Completed Follow-up Visit | 162 (84.8) | 172 (89.6) | 334 (87.2) |
| Completed Study | 157 (82.2) | 158 (82.3) | 315 (82.2) |
| Completer Set ^d | 157 (82.2) | 158 (82.3) | 315 (82.2) |
| Did Not Complete Study | 34 (17.8) | 34 (17.7) | 68 (17.8) |
| Primary Reason for Discontinuation | | | |
| Withdrawal by Subject | 14 (7.3) | 12 (6.3) | 26 (6.8) |
| Adverse Event | 5 (2.6) | 12 (6.3) | 17 (4.4) |
| Lost to Follow-up | 8 (4.2) | 3 (1.6) | 11 (2.9) |
| Protocol Violation | 4 (2.1) | 2 (1.0) | 6 (1.6) |
| Lack of Efficacy | 1 (0.5) | 0 | 1 (0.3) |
| Other Reasons | 2 (1.0) | 5 (2.6) | 7 (1.8) |

^a The Safety Analysis Set includes all randomized subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

^b Four placebo subjects were excluded from the Safety Analysis Set. Of these 4 subjects, 2 were lost to follow-up prior to receiving investigational product (055-3002 and 803-3008) and 2 were withdrawn due to a protocol violation (mis-randomization) prior to receiving investigational product (064-3004 and 072-3006).

^c The Full Analysis Set includes all subjects in the Randomized Set who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment.

^d The Completer Set includes all subjects in the Full Analysis Set who completed the Visit 8 (Week 12) assessments.

Note: All proportions are based on the Randomized Set.

Note: Primary reasons for withdrawal are presented by decreasing frequency based on the SPD489 group.

Dosing

The optimized dose of SPD489 was 50 mg/day for 30% of subjects and 70mg for 61% of subjects. The remaining 9% of the SPD489 group failed to achieve an optimized dose and were discontinued from the trial. During the period for dose optimization, the mean dose was 50 mg/day and, during the dose maintenance phase, the mean dose was 63 mg/day.

Efficacy Results

Results for the primary endpoint (mean change from baseline in the number of binge days per week during Weeks 11 and 12) are displayed in the table below. The difference between SPD489 and placebo was highly statistically significant ($p < 0.001$).

Table 3: Mean Change in the Number of Binge Days/Week (Trial SPD489-343)

| Visit | Placebo (N=184) | | SPD489 (N=190) | |
|-------------------------------------|-----------------|----------------------|----------------|----------------------|
| | Observed Value | Change from Baseline | Observed Value | Change from Baseline |
| Baseline^a | | | | |
| n | 184 | | 190 | |
| Mean (SEM) | 4.60 (0.089) | | 4.79 (0.092) | |
| SD | 1.210 | | 1.271 | |
| Median | 4.50 | | 4.50 | |
| Min, Max | 2.5, 7.0 | | 2.5, 7.0 | |
| Visit 8 (Weeks 11 and 12) | | | | |
| n | 160 | 160 | 158 | 158 |
| Mean (SEM) | 2.22 (0.154) | -2.39 (0.163) | 0.78 (0.102) | -4.00 (0.124) |
| SD | 1.942 | 2.064 | 1.277 | 1.554 |
| Median | 2.00 | -2.38 | 0.00 | -4.00 |
| Min, Max | 0.0, 7.0 | -7.0, 2.5 | 0.0, 7.0 | -7.0, 0.5 |
| <i>Based on MMRM:^b</i> | | | | |
| LS Mean (SEM) | | -2.51 (0.125) | | -3.87 (0.124) |
| Difference in LS Mean | | | | -1.35 |
| 95% CI of the Difference in LS Mean | | | | -1.70, -1.01 |
| Effect size | | | | 0.83 |
| p-value | | | | <0.001 |

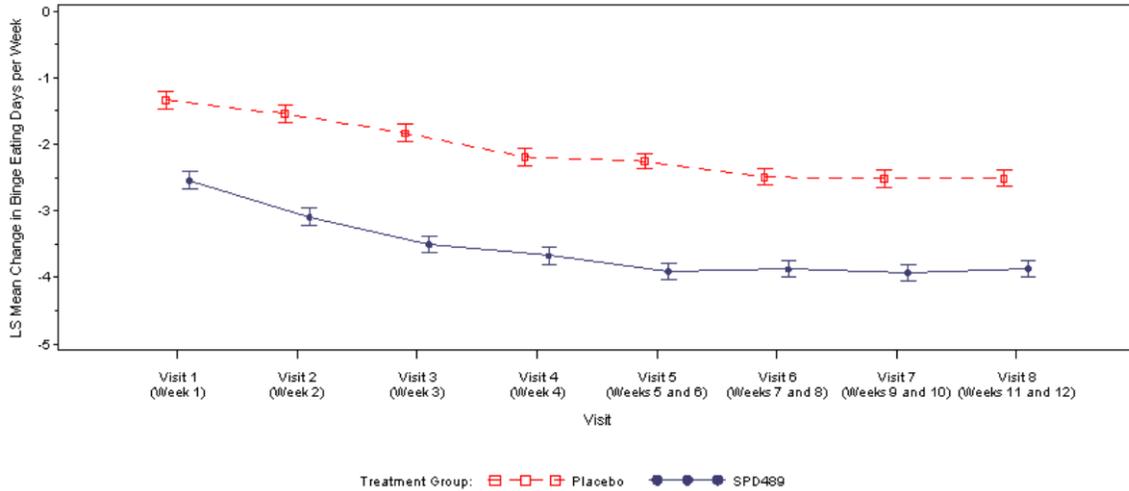
^a Baseline is the weekly average of the number of binge days per week for the 14 days prior to the Baseline Visit (Visit 0).

^b The LS mean (SEM), the difference in LS mean, the 95% confidence interval of the difference in LS mean, and the p-value were derived from a MMRM over all post-baseline visits during the Double-blind Treatment Phase, with change from baseline 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. The difference in LS means is calculated as SPD489 (-) Placebo. The model-based effect size was defined as the difference in LS means at Visit 8 (Weeks 11 and 12) divided by the estimated standard deviation of the change from baseline at Visit 8 (Weeks 11 and 12).

CI=confidence interval; LS=least squares; MMRM=mixed-effects model for repeated measures; SD=standard deviation; SEM=standard error of the mean

The least-squares mean change from baseline in the number of binge days per week over time is shown in the following figure.

Figure 1: LS Mean (SEM) Change from Baseline in the Number of Binge Days/Week Over Time (SPD489-343)



Results on the five key secondary endpoints are summarized in the table below.

| Table 4: Summary of Key Secondary Efficacy Results at Week 12⁵ (Trial SPD489-343) | | | | | |
|---|----------------|-------------|---------------|-------------|----------------|
| | Placebo | | SPD489 | | p-value |
| | N | Mean | N | Mean | |
| Key Secondary Endpoints | | | | | |
| % CGI-I Improved | 184 | 47% | 190 | 82% | <0.001 |
| % 4-Wk Binge Cessation | 184 | 14% | 190 | 40% | <0.001 |
| % Change in Body Weight | 160 | +0.11% | 159 | -6.25% | <0.001 |
| Change in Y-BOCS-BE Total | 161 | -8.28 | 160 | -15.68 | <0.001 |
| Change in Fasting Triglycerides (mmol/L) | 170 | +0.122 | 181 | -0.077 | <0.001 |

SPD489 was statistically superior to placebo at Week 12 on all five key secondary efficacy variables. The changes in serum fasting triglycerides in metric units were +11 mg/dl for placebo and -7 mg/dl for SPD489, or a placebo-adjusted reduction of -18 mg/dl for SPD489.

Conclusions

Trial SPD489-343 demonstrated the superiority of SPD489 over placebo on the primary efficacy measure (number of binge days per week) and on the 5 prespecified key secondary efficacy variables.

⁵ Values for body weight and Y-BOCS-BE are LS means.

Study 2 (SPD489-344)

Methods/Study Design/Analysis Plan

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel group trial of the safety and efficacy of SPD489 in adults (ages 18-55) with moderate to severe Binge Eating Disorder (BED). The treatment duration was 12 weeks. A total of 390 subjects were enrolled from 44 sites, 41 of which were in the U.S. and 3 in Germany.

The inclusion/exclusion criteria, study design, and dosing regimen were the same as for trial SPD489-343.

Also as in that trial, binge eating information was collected daily by the subject and recorded in diary, which captured the number of binges per day, total hours spent bingeing each day, type of binge (mealtime versus non-mealtime), and a description of the binge (amounts and types of food). At each visit, the investigator reviewed the completed diary and confirmed whether each recorded eating episode was a binge, which was recorded in the CRF. Other relevant assessments (CGI, Y-BOCS-BE, and clinical laboratory tests) were performed as in trial SPD489-343.

The primary and key secondary efficacy measures and analyses of these measures are much the same as for trial SPD489-343. However, one difference is that the primary analysis dataset (FAS) for this trial excludes data from two sites that were closed during the conduct of this trial:

- Site 015 enrolled 11 subjects and was closed by the sponsor “for reasons unrelated to the study,” according to the sponsor. This site is reported to be (b) (7)(A) the scope and purpose of which is apparently not known by the sponsor, who excluded this site to be prudent.⁶ A revised Statistical Analysis Plan (SAP) to exclude this site was submitted to the Agency on August 20, 2013, and was reviewed by the biometrics team on October 1, 2013. On October 30, 2013, the sponsor was informed by email that the exclusion of this site would be a matter for review during the NDA examination.
- Site 079 enrolled 12 subjects and was closed by the sponsor for reasons to include, but not limited to, multiple Good Clinical Practice (GCP) infractions related to data documentation, failure to follow critical study procedures described in the protocol, improper entry of subject data, and inadequate oversight by the investigator. A amended Statistical Analysis Plan (SAP) to exclude this site from the efficacy analysis was submitted to the Agency on September 27, 2013. This amendment was reviewed by the biometrics team on November 19, 2013, and the sponsor was informed by email on that date that the exclusion of this site would be a matter for review after NDA submission.

⁶ According to Section 2.2 of the Summary of Clinical Efficacy.

The decision to exclude these sites was made prior to locking the dataset and unblinding. Ad hoc analyses which included these two sites are provided in Section 14.3 of the Clinical Study Report. The results of these analyses are consistent with those that excluded these sites. In view of the above, I have no objection from a clinical standpoint to excluding these two sites from the FAS.

It should be noted that a third site in this trial (Site 032) was also closed by the sponsor after a for-cause audit revealed evidence of tampering with the study drug product from a trial under a (b) (4) (b) (4). The tampering included broken or reattached seals, broken or punctured capsules, chipped capsules, and residue on the capsules. The cause of the tampering could not be ascertained. At the time of site closure, trial SPD489-344 had been completed; this site enrolled 25 subjects into that trial. This investigator had also participated in trial SPD489-208, which had also been completed that time. Trial SPD489-345 was ongoing and closed, with the last patient visit at this site on March 5, 2014. Because there was no evidence of misconduct in the Shire BED trials, this site was not excluded from the FAS databases for those trials.⁷ Inclusion of this site in the analyses of the BED trials seems reasonable based on the presence of significant findings in only the (b) (4). Nonetheless, this site was chosen for routine inspection by the Office of Scientific Investigations.

Results

Demographics

Baseline demographic features were roughly comparable between the SPD489 and placebo treatment groups. Overall, the mean age was 38 years (range 18 to 56 years) with 54% of subjects under the age of 40. Most (85%) of subjects were female and most (73%) were of the White race. Mean body weight was 94 kg (range 50-176 kg) and mean BMI was 34 kg/m² (range of 20-45). About two-thirds (69%) were obese (BMI ≥30 kg/m²), with 19% very obese (BMI ≥40 kg/m²); 9% were underweight or normal weight (BMI <25 kg/m²).

Baseline Characteristics

The SPD489 and placebo groups were similar in terms of the age at BED diagnosis (median 37 years) and other baseline illness characteristics. For the groups combined, the median binge days per week was 4.75 and the median binge episodes per week was 6.52. The median Y-BOCS-BE total score was 21.00. Over on-half (56%) of subjects were moderately ill as rated by the CGI-Severity score, with 34% markedly ill, 9% severely ill, and 1.6% among the most extremely ill.

⁷ This information was provided by the sponsor at the request Dr. John Lee of the CDER Office of Scientific Investigations (submissions dated September 15, 2014 (Serial #0139) and September 18, 2014 (Serial #0141)).

Patient Disposition

A total of 700 subjects were screened for this trial, of which 390 were eventually randomized to treatment. Most of the excluded subjects were eliminated because they met one or more exclusionary criteria.

Subject disposition is shown in the table below. The FAS was comprised of 350 subjects (174 randomized to SPD489 and 176 to placebo). As noted above, the FAS excludes subjects from sites 015 and 079.

Concomitant Medication Use

I examined concomitant medication use during this trial. None was judged likely to bias the efficacy results.⁸

Important Protocol Violations

In my judgment, there were no protocol violations that would likely influence the efficacy results of this trial. Nevertheless, the sponsor excluded Sites 015 and 079 from the FAS.

Dosing

The optimized dose of SPD489 was 50 mg/day for 29% of subjects and 70mg for 62% of subjects. The remaining 9% of the SPD489 group failed to achieve an optimized dose and were discontinued from the trial. During the period for dose optimization, the mean dose was 51 mg/day and, during the dose maintenance phase, the mean dose was 64 mg/day. Thus, actual dosing in this trial was very similar to dosing in SPD489-343.

⁸ Information is contained in Table 1.3.2 of the Clinical Study Report.

Table 5: Subject Disposition (Trial SPD489-344)

| | Placebo n (%) | SPD489 n (%) | Total n (%) |
|--|------------------|-----------------|----------------|
| Screened Set | | | 700 |
| Randomized Set | 195 | 195 | 390 |
| Safety Analysis Set ^{a, b, c} | 185 (94.9) | 181 (92.8) | 366 (93.8) |
| Sensitivity Safety Analysis Set ^d | 178 (91.3) | 177 (90.8) | 355 (91.0) |
| Full Analysis Set ^{e, f} | 176 (90.3) | 174 (89.2) | 350 (89.7) |
| Completed Follow-up Visit | 153 (78.5) | 160 (82.1) | 313 (80.3) |
| Completed Study | 147 (75.4) | 147 (75.4) | 294 (75.4) |
| Completer Set ^{g, h} | 142 (72.8) | 145 (74.4) | 287 (73.6) |
| Did Not Complete Study | 48 (24.6) | 48 (24.6) | 96 (24.6) |
| Primary Reason for Discontinuation | | | |
| Lost to Follow-up | 18 (9.2) | 15 (7.7) | 33 (8.5) |
| Withdrawal by Subject | 7 (3.6) | 13 (6.7) | 20 (5.1) |
| Adverse Event | 5 (2.6) | 7 (3.6) | 12 (3.1) |
| Protocol Violation | 4 (2.1) | 2 (1.0) | 6 (1.5) |
| Lack of Efficacy | 1 (0.5) | 0 | 1 (0.3) |
| Other Reasons ⁱ | 13 (6.7) | 11 (5.6) | 24 (6.2) |

^a The Safety Analysis Set includes all randomized subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

^b All subjects enrolled at Site 015 (11 subjects) were excluded from the Safety Analysis Set.

^c In addition to the 11 subjects from Site 015 who were excluded from the Safety Analysis Set, 12 subjects had not been treated and 1 subject (SPD489) had been treated but did not have any safety follow-up assessments.

^d The Sensitivity Safety Analysis Set includes all subjects in the Safety Analysis Set, with the exception of 11 subjects from Site 079 (the twelfth subject from Site 079 had already been excluded from the Safety Analysis Set).

^e The Full Analysis Set includes all subjects in the Randomized Set who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment.

^f All subjects enrolled at Sites 015 (11 subjects) and 079 (12 subjects) were excluded from the Full Analysis Set.

^g The Completer Set includes all subjects in the Full Analysis Set who completed the Visit 8 (Week 12) assessments.

^h Seven subjects (2 from Site 015 and 5 from Site 079) completed the study. However, because these subjects were excluded from the Full Analysis Set, they were also excluded from the Completer Set.

ⁱ Other primary reasons for withdrawal include discontinuation due to sponsor request, which was reported for 8 subjects enrolled at Site 015 (SPD489, 5 subjects and placebo, 3 subjects).

Note: All proportions are based on the Randomized Set.

Note: Primary reasons for withdrawal are presented by decreasing frequency based on the SPD489 group.

Efficacy Results

Results for the primary endpoint (mean change from baseline in the number of binge days per week during Weeks 11 and 12) are displayed in the table below. The difference between SPD489 and placebo was highly statistically significant ($p < 0.001$).

**Table 6: Mean Change in the Number of Binge Days/Week
(Trial SPD489-344)**

| Visit | Placebo (N=176) | | SPD489 (N=174) | |
|-------------------------------------|--------------------|----------------------|-------------------|----------------------|
| | Observed Value | Change from Baseline | Observed Value | Change from Baseline |
| Baseline^a | | | | |
| n | 176 | | 174 | |
| Mean (SEM) | 4.82 (0.107) | | 4.66 (0.097) | |
| SD | 1.422 | | 1.273 | |
| Median | 4.50 | | 4.50 | |
| Min, Max | 2.0, 7.0 | | 2.0, 7.0 | |
| Visit 8 (Weeks 11 and 12) | | | | |
| n | 142 | 142 | 146 | 146 |
| Mean (SEM) | 2.57 (0.191) | -2.30 (0.186) | 0.77 (0.101) | -3.86 (0.129) |
| SD | 2.271 | 2.212 | 1.218 | 1.559 |
| Median | 2.17 | -2.00 | 0 | -4.00 |
| Min, Max | 0.0, 7.0 | -7.0, 3.0 | 0.0, 7.0 | -7.0, 0.5 |
| <i>Based on MMRM:^b</i> | | | | |
| LS Mean (SEM) | | -2.26 (0.137) | | -3.92 (0.135) |
| Difference in LS Mean | | | | -1.66 |
| 95% CI of the Difference in LS Mean | | | | -2.04, -1.28 |
| Effect size | | | | 0.97 |
| p-value | | | | <0.001 |

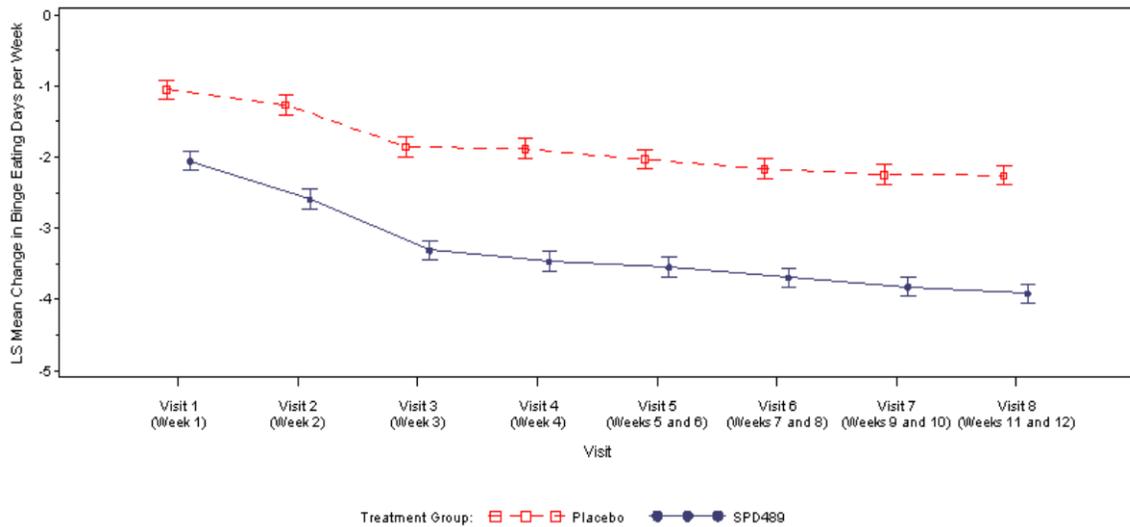
^a Baseline is the weekly average of the number of binge days per week for the 14 days prior to the Baseline Visit (Visit 0).

^b The LS mean (SEM), the difference in LS mean, the 95% CI of the difference in LS mean, and the p-value were derived from a MMRM over all post-baseline visits during the Double-blind Treatment Phase, with change from baseline 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. The difference in LS means is calculated as SPD489 (-) Placebo. The model-based effect size was defined as the difference in LS means at Visit 8 (Weeks 11 and 12) divided by the estimated standard deviation of the change from baseline at Visit 8 (Weeks 11 and 12).

CI=confidence interval; LS=least squares; MMRM=mixed-effects model for repeated measures; SD=standard deviation; SEM=standard error of the mean

The least-squares mean change from baseline in the number of binge days per week over time is shown in the following figure.

Figure 2: LS Mean (SEM) Change from Baseline in the Number of Binge Days/Week Over Time (SPD489-344)



Results on the five key secondary endpoints are summarized in the following table.

| Table 7: Summary of Key Secondary Efficacy Results at Week 12⁹ (Trial SPD489-344) | | | | | |
|---|----------------|-------------|---------------|-------------|----------------|
| | Placebo | | SPD489 | | p-value |
| | N | Mean | N | Mean | |
| Key Secondary Endpoints | | | | | |
| % CGI-I Improved | 176 | 43% | 174 | 86% | <0.001 |
| % 4-Wk Binge Cessation | 176 | 13% | 174 | 36% | <0.001 |
| % Change in Body Weight | 143 | -0.15% | 146 | -5.57% | <0.001 |
| Change in Y-BOCS-BE Total | 145 | -7.42 | 151 | -15.36 | <0.001 |
| Change in Fasting Triglycerides (mmol/L) | 153 | +0.062 | 156 | -0.133 | 0.002 |

SPD489 was statistically superior to placebo at Week 12 on all five key secondary efficacy variables. The changes in serum fasting triglycerides in metric units were +5 mg/dl for placebo and -12 mg/dl for SPD489, or a placebo-adjusted reduction of -17 mg/dl for SPD489.

Ad hoc efficacy analyses to include Sites 015 and 079 were performed by the sponsor and produced results consistent with those based on the FAS, which excluded those two sites. The ad hoc analysis results are summarized below.

⁹ Values for body weight and Y-BOCS-BE are LS means.

| Table 8: Summary of Ad Hoc Efficacy Findings (Trial SPD489-344) (Including Sites 015 and 079)¹⁰ | | | | | |
|---|----------------|-------------|---------------|-------------|----------------|
| | Placebo | | SPD489 | | p-value |
| | N | Mean | N | Mean | |
| Primary Endpoint | | | | | |
| Change from Baseline in Binge Days/Week to Weeks 11/12 | 144 | -2.20 | 146 | -3.88 | <0.001 |
| Key Secondary Endpoints | | | | | |
| % CGI-I Improved | 181 | 42% | 179 | 86% | <0.001 |
| % 4-Wk Binge Cessation | 181 | 13% | 179 | 36% | <0.001 |
| % Change in Body Weight | 145 | -0.06% | 146 | -5.47% | <0.001 |
| Change in Y-BOCS-BE Total | 147 | -7.24 | 152 | -15.24 | <0.001 |
| Change in Fasting Triglycerides (mmol/L) | 158 | +0.066 | 161 | -0.123 | 0.002 |

Conclusions

Trial SPD489-344 demonstrated the superiority of SPD489 over placebo on the primary efficacy measure (number of binge days per week) and on the 5 prespecified key secondary efficacy endpoints.

6.1.3 Crosscutting Issues

Subgroup Analyses

Analysis of the primary efficacy measure (mean change from baseline to Weeks 11 and 12 in the number of binge days/week) was conducted by subgroup based on the following characteristics for the FAS from the pool of the 2 Phase 3 trials SPD489-343 and SPD489-344: age, sex, race, ethnicity, region, BMI, and baseline binge eating severity. The results are depicted in the table below.

| Table 9: Mean Change in the Number of Binges/Week by Subgroup (SPD489-343 and SPD489-344) | | |
|--|----------------|---------------|
| Subgroup/Variable | Placebo | SPD489 |
| AGE CATEGORY | | |
| <40 years | | |
| N | 156 | 164 |
| LS Mean Change | -2.30 | -3.80 |
| Difference in LS Mean Change ¹¹ | --- | -1.50 |
| 95% CI of Difference | --- | -1.84, -1.17 |
| ≥40 years | | |
| N | 146 | 140 |
| LS Mean Change | -2.49 | -3.99 |
| Difference in LS Mean Change | --- | -1.50 |

¹⁰ Values for number of binge days, body weight, and Y-BOCS-BE are LS means.

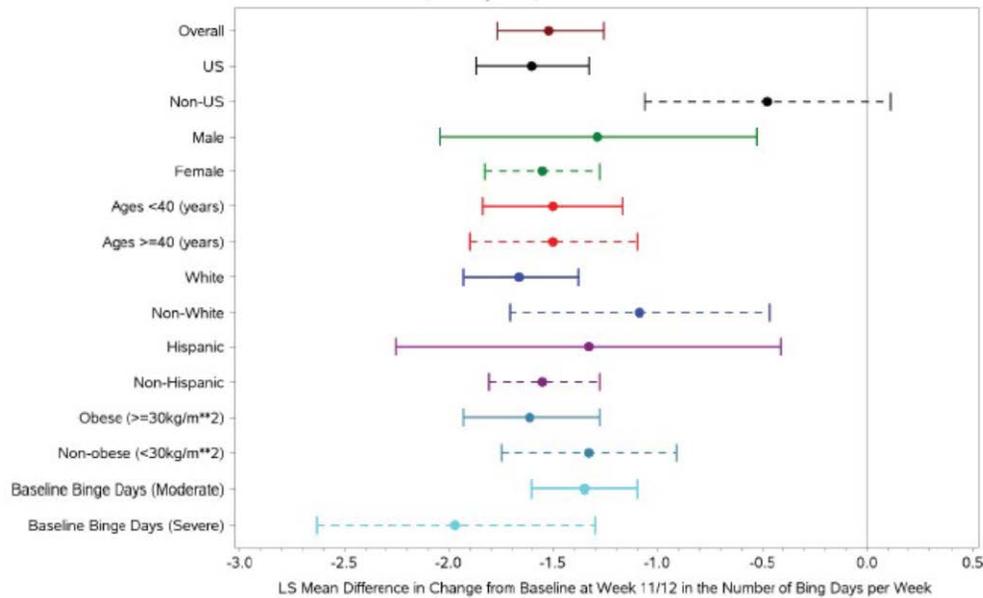
¹¹ The difference was calculated as SPD489 minus placebo, i.e., negative numbers reflect superiority of drug over placebo.

| Table 9: Mean Change in the Number of Binges/Week by Subgroup (SPD489-343 and SPD489-344) | | |
|--|----------------|---------------|
| Subgroup/Variable | Placebo | SPD489 |
| 95% CI of Difference | --- | -1.90, -1.10 |
| SEX | | |
| Male | | |
| N | 40 | 38 |
| LS Mean Change | -2.31 | -3.59 |
| Difference in LS Mean Change | --- | -1.29 |
| 95% CI of Difference | --- | -2.04, -0.53 |
| Female | | |
| N | 262 | 266 |
| LS Mean Change | -2.39 | -3.94 |
| Difference in LS Mean Change | --- | -1.55 |
| 95% CI of Difference | --- | -1.83, -1.28 |
| RACE CATEGORY | | |
| White | | |
| N | 227 | 235 |
| LS Mean Change | -2.28 | -3.94 |
| Difference in LS Mean Change | --- | -1.66 |
| 95% CI of Difference | --- | -1.93, -1.38 |
| Non-White | | |
| N | 75 | 69 |
| LS Mean Change | -2.69 | -3.78 |
| Difference in LS Mean Change | --- | -1.09 |
| 95% CI of Difference | --- | -1.71, -0.47 |
| ETHNICITY | | |
| Hispanic | | |
| N | 33 | 39 |
| LS Mean Change | -2.30 | -3.63 |
| Difference in LS Mean Change | --- | -1.33 |
| 95% CI of Difference | --- | -2.25, -0.41 |
| Non-Hispanic | | |
| N | 269 | 265 |
| LS Mean Change | -2.38 | -3.93 |
| Difference in LS Mean Change | --- | -1.55 |
| 95% CI of Difference | --- | -1.81, -1.28 |
| REGION | | |
| US | | |
| N | 278 | 278 |
| LS Mean Change | -2.33 | -3.92 |
| Difference in LS Mean Change | --- | -1.6 |
| 95% CI of Difference | --- | -1.87, -1.33 |
| Non-US | | |

| Table 9: Mean Change in the Number of Binges/Week by Subgroup (SPD489-343 and SPD489-344) | | |
|--|----------------|---------------|
| Subgroup/Variable | Placebo | SPD489 |
| N | 24 | 26 |
| LS Mean Change | -3.19 | -3.67 |
| Difference in LS Mean Change | --- | -0.48 |
| 95% CI of Difference | --- | -1.06, +0.11 |
| BMI CATEGORY | | |
| Obese (≥ 30 kg/m²) | | |
| N | 208 | 206 |
| LS Mean Change | -2.43 | -4.03 |
| Difference in LS Mean Change | --- | -1.61 |
| 95% CI of Difference | --- | -1.93, -1.28 |
| Non-Obese (<30 kg/m²) | | |
| N | 94 | 98 |
| LS Mean Change | -2.26 | -3.59 |
| Difference in LS Mean Change | --- | -1.33 |
| 95% CI of Difference | --- | -1.75, -0.91 |
| BASELINE SEVERITY | | |
| Moderate (≤ 7 episodes/week) | | |
| N | 226 | 223 |
| LS Mean Change | -2.20 | -3.56 |
| Difference in LS Mean Change | --- | -1.35 |
| 95% CI of Difference | --- | -1.60, -1.10 |
| Severe (>7 episodes/week) | | |
| N | 76 | 81 |
| LS Mean Change | -2.88 | -4.85 |
| Difference in LS Mean Change | --- | -1.97 |
| 95% CI of Difference | --- | -2.63, -1.30 |

The subgroup analysis results are summarized graphically in the figure below.

Figure 3: LS Mean Difference (95% CI) in the Change from Baseline to Weeks 11 and 12 in the Number of Binge Days/Week by Subgroup for SPD489-343 and SPD489-344 Combined



Note: A 95% CI that falls left of 0 indicates a greater mean improvement for SPD489 subjects compared to placebo subjects. A 95% CI that crosses zero indicates similarity between treatment groups.
 CI=confidence interval; LS=least squares; US=United States

The mean changes in the number of binges per week were greater for the SPD489-treated subjects than for the placebo group, regardless of subgroup. Furthermore, the confidence intervals for the intergroup differences excluded the null and favored drug except for the non-US subgroup in the region analysis, where the upper limit of the confidence interval slightly exceeded zero. The point estimate of the difference in the non-US subgroup was considerably smaller than that for US subgroup: -0.5 versus -1.6. However, given the relatively small N's in the non-US subgroup (24 on placebo and 26 on drug or about 10% of the total sample), this finding is difficult to definitively interpret.

Dose Response

The sponsor conducted a Phase 2 trial (SPD489-208) to evaluate the efficacy of 3 doses of SPD489 (30, 50, and 70 mg/day) versus placebo in the treatment of adults with moderate to severe BED. This was a multicenter, randomized, double-blind, placebo-controlled, forced-dose titration study in which eligible subjects were randomized in a 1:1:1:1 ratio to one of the 3 doses of SPD489 or placebo. Subjects randomized to the 2 higher doses of drug were titrated up at a rate of 20 mg/day/week with no allowance for dose changes. After the 3-week

dose forced-dose titration, subjects continued on their assigned dose for an additional 8 weeks for a total treatment duration of 11 weeks.

A total of 271 subjects were randomized and 213 completed the trial. Subjects were roughly comparable at baseline across the 4 treatment groups in terms of demographics and illness severity. The FAS encompassed 266 subjects.

The primary efficacy endpoint was the change from baseline to Week 11 in the log-transformed number of binge days/week, analyzed using MMRM. The efficacy findings are summarized in the following table.

Table 10: Change from Baseline in the Log-Transformed Number of Binge Days/Week (Trial SPD489-208)

| Visit Endpoint Type Mean Change From Baseline | Placebo (N=65) | SPD489 30mg (N=68) | SPD489 50mg (N=67) | SPD489 70mg (N=66) |
|---|-------------------|--------------------------|--------------------------|--------------------------|
| Visit 1 (Week 1) | | | | |
| LS Mean (SE) | -0.34 (0.071) | -0.68 (0.070) | -0.76 (0.070) | -0.75 (0.071) |
| 95% Confidence Interval | (-0.48, -0.20) | (-0.82, -0.55) | (-0.90, -0.62) | (-0.89, -0.61) |
| Comparison vs. Placebo ^a | | | | |
| Difference in LS Means (SE) | | -0.341 (0.1000) | -0.415 (0.1005) | -0.409 (0.1007) |
| 95% Confidence Interval | | (-0.538, -0.144) | (-0.613, -0.217) | (-0.607, -0.211) |
| Visit 3 (Week 3) | | | | |
| LS Mean (SE) | -0.69 (0.077) | -0.91 (0.076) | -1.09 (0.076) | -1.24 (0.076) |
| 95% Confidence Interval | (-0.84, -0.53) | (-1.06, -0.76) | (-1.24, -0.94) | (-1.39, -1.09) |
| Comparison vs. Placebo ^a | | | | |
| Difference in LS Means (SE) | | -0.220 (0.1085) | -0.404 (0.1084) | -0.551 (0.1086) |
| 95% Confidence Interval | | (-0.434, -0.006) | (-0.618, -0.191) | (-0.765, -0.337) |
| Visit 8 (Week 11) | | | | |
| LS Mean (SE) | -1.17 (0.068) | -1.26 (0.066) | -1.50 (0.065) | -1.58 (0.066) |
| 95% Confidence Interval | (-1.30, -1.04) | (-1.39, -1.13) | (-1.63, -1.37) | (-1.71, -1.45) |
| Comparison vs. Placebo ^a | | | | |
| Difference in LS Means (SE) | | -0.090 (0.0950) | -0.328 (0.0944) | -0.409 (0.0946) |
| 95% Confidence Interval | | (-0.277, 0.098) | (-0.514, -0.142) | (-0.595, -0.223) |
| p-value | | 0.3470 | 0.0006 | <0.0001 |

^a Negative estimates indicate numeric superiority of the active treatment group.

Note: Statistics are from a mixed-effects model for repeated measures (MMRM) that includes fixed factors for treatment and visit, the interaction of treatment and visit, a covariate of log (baseline number of binge days per week +1) and the interaction of the baseline covariate and visit. The response variable is the change from baseline in log (number of binge days per week +1).

LS=least square

SPD489 in doses of 50 and 70 mg/day were highly statistically significantly superior to placebo on the primary efficacy endpoint. There was no substantial difference between the 50 and 70 mg/day doses. The 30 mg/day dose was not effective compared to placebo. The results of this trial were used to determine the dose levels for the two Phase 3 efficacy trials.

Key Secondary Variables

Both Phase 3 placebo-controlled trials examined the same 5 prespecified key secondary efficacy variables:

- CGI-Improvement score at Week 12 or End of Treatment dichotomized as the percentage improved (including very much improved and much improved) versus the percentage not improved (other ratings).
- proportion of subjects with a 4-week cessation of binge eating (no binges) for the 28 day period prior to Week 12 or End of Treatment.
- percentage change from baseline at Week 12 in body weight.
- change from baseline at Week 12 in the Y-BOCS-BE total score.
- change from baseline at Week 12 or End of Treatment in fasting triglycerides.

In my opinion, these 5 variables are acceptable as measures of both binge eating behavior (global improvement, cessation of binge eating, and obsessions and compulsions surrounding binge eating) as well as health-related measures possibly correlated with binge eating (body weight and triglyceride levels).

SPD489 demonstrated superiority over placebo on all 5 variables in both trials

(b) (4)

Effect Size

The mean changes in the raw number of binge days/week by treatment group for the 2 Phase 3 trials is shown below.

| Trial | Placebo | | SPD489 | | Δ of Δ at Wk 11/12 |
|------------|----------|------------|----------|------------|--------------------|
| | Baseline | Δ Wk 11/12 | Baseline | Δ Wk 11/12 | |
| SPD489-343 | 4.60 | -2.39 | 4.79 | -4.00 | -1.61 |
| SPD489-344 | 4.82 | -2.30 | 4.66 | -3.86 | -1.56 |

For both trials, SPD489 reduced the number of binge days/week by about 1.6 days compared to placebo from a baseline of almost 5 binge days/week. There are no effect size values with other agents for comparison because no drugs have been approved for the treatment of BED to date. It is noteworthy that a much greater percentage of subjects treated with SPD489 (versus placebo) experienced total cessation of binge eating for the last 28 days of trial participation: 40% versus 14% in SPD489-343 and 36% versus 13% in SPD489-344. From a clinical standpoint, these effects are non-negligible.

Long-Term Efficacy

(b) (4) is a randomized withdrawal study intended to evaluate long-term efficacy and is currently ongoing.

(b) (4)

Pediatric Development

The sponsor submitted a initial Pediatric Study Plan (iPSP) on October 16, 2013, which conveyed the sponsor's intent to request a full waiver of PREA requirements (ages 0 to 17 years) for SPD489 in the treatment of BED.

On October 22, 2014, the PREA Subcommittee of the PeRC met and agreed with the Division that a full waiver could be granted because pediatric studies would be impossible or highly impractical because there are too few pediatric patients with BED.

6.1.4 Efficacy Conclusions Regarding BED

Trials SPD489-343 and SPD489-344 adequately demonstrate the superiority of SPD489 50 and 70 mg/day over placebo in the treatment of moderate to severe BED in adults for up to 12 weeks.

7 REVIEW OF SAFETY

Safety Summary

As of June 30, 2014, there was one death in four Phase 2/3 BED trials. A 29 year old male in the 70mg dose group of study SPD489-208 died of an apparent methamphetamine overdose, which seems unlikely to be a direct effect of prescribed SPD489 treatment. Other noteworthy serious adverse events were syncope and cholecystitis. For both events, a causal role for SPD489 is questionable.

Common, possibly drug-related adverse events in the Phase 3 placebo-controlled trials are: dry mouth, insomnia, decreased appetite, heart rate increased, constipation, feeling jittery, and anxiety. Dropout rates because of these events was very low (<1%).

SPD489 increased blood pressure and heart rate compared to placebo. Placebo-adjusted changes from baseline to end of double-blind treatment in the Phase 3 placebo-controlled trials were +3.3 mmHg systolic BP, +2.8 mmHg diastolic BP, and +3.6 bpm in pulse rate. These changes persisted during the 12-week trials but were not clearly associated with major adverse cardiovascular events.

In sum, there are no safety findings that would preclude approval of this supplement or require major changes to the safety sections of Vyvanse labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pool of the two Phase 3 randomized, double-blind, placebo-controlled trials (SPD489-343 and SPD489-344) form the primary safety database for this review. In addition, adverse events at the more serious end of the spectrum (deaths, non-fatal serious adverse events, and adverse events that led to premature

termination of subjects) were also examined from the Phase 2 dose-finding trial SPD489-208 and the 12-month open-label extension study SPD489-345. At the time of the original supplement submission, the latter trial was ongoing. This review incorporates limited safety data from the Four-Month Safety Update Report from that trial, which was submitted on November 21, 2014, and had a cutoff date of June 30, 2014. Studies SPD489-208, SPD489-343, and SPD489-344 were completed and had Clinical Study Reports before the original submission of this supplement .

7.1.2 Categorization of Adverse Events

Reported adverse events from all studies were coded by the sponsor to Preferred Terms using MedDRA Version 15.1.

Adverse events were also categorized as serious or non-serious. According to the study protocols, serious adverse events (SAEs) were defined by one of the following criteria:

- results in death.
- life-threatening (at actual risk of death at the time of the event).
- requires inpatient hospitalization or prolongation of hospitalization.
- results in persistent or significant disability or incapacity.
- congenital abnormality or birth defect.
- an important medical event, that is, an event not meeting any of the above criteria but which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Studies SPD489-343 and SPD489-344 were essentially identical in design and, thus, were pooled for purposes of estimating adverse event incidence and other standard safety analyses.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The planned duration of each of the four Phase 2/3 studies is as follows:

- placebo-controlled study SPD489-208 = 11 weeks.
- placebo-controlled study SPD489-343 = 12 weeks.
- placebo-controlled study SPD489-344 = 12 weeks.
- open-label study SPD489-345 = 52 weeks.

Across all four Phase 2/3 trials, 833 subjects comprised the Safety Analysis Set and received some dose of SPD489. Among these subjects, 51% (427/833) were under age 40 and 49% (406/833) were age 40 or older. Most subjects were female (86% or 718/833). Only 12% (99/833) were of Hispanic or Latino ethnicity. The most common race of subjects was White (76%) followed by Black or African American (18%). Subjects who were obese (defined as a BMI ≥ 30 kg/m²) comprised 71% (588/833) of the sample and morbidly obese subjects (defined as a BMI ≥ 40 kg/m²) comprised 20% (165/833) of the sample. The vast majority of subjects (95% or 793/833) participated at U.S. sites.

The target dose of SPD489 for the treatment of BED is 50 or 70 mg/day. As of June 30, 2014, and across all 4 clinical trials, 768 subjects received a daily dose of 50 or 70mg for some duration of time, 488 received these doses for 180 days or longer, and 224 received these doses for 361 days or longer.¹²

The extent of SPD489 exposure in the BED trials is deemed to be adequate to evaluate safety.

7.2.2 Explorations for Dose Response

Safety findings by dose were explored in the Phase 2 trial SPD489-208 in which subjects were randomized to treatment with SPD489 30, 50, or 70 mg/day or placebo.

¹² From information provided in the Four-Month Safety Update Report.

7.2.4 Routine Clinical Testing

Important safety assessments conducted during the four Phase 2/3 studies are summarized in the Table below.

Table 12: Safety Assessments in Phase 2/3 Studies

| Safety Assessment | Study | | | |
|--|---|---|---|---|
| | SPD489-208 | SPD489-343 | SPD489-344 | SPD489-345 |
| Adverse events | Screening, BL, weekly thru Wk 3, biweekly thru Wk 11, telephone F-U | Screening, BL, weekly thru Wk 4, biweekly thru Wk 12, F-U visit | Screening, BL, weekly thru Wk 4, biweekly thru Wk 12, F-U visit | BL ^a , Weekly thru Wk 4, every 4 wks thru Wk 52, F-U visit |
| Vital signs (blood pressure, pulse rate, respiration rate, and temperature) ^b | Screening, BL, weekly through Wk 3; biweekly through Wk 11 | Screening, BL, weekly thru Wk 4, biweekly thru Wk 12, F-U visit | Screening, BL, weekly thru Wk 4, biweekly thru Wk 12, F-U visit | BL ^c , Weekly thru Wk 4, every 4 wks thru Wk 52, F-U visit |
| Clinical laboratory tests | Screening, BL, Wk 11 | Screening ^d , Wk 12 ^d | Screening ^d , Wk 12 ^d | BL ^c , Wks 12, 24 & 52 ^d |
| 12-lead ECG ^e | Screening, BL, Wks 5 & 11 | Screening, BL, Wks 4 & 12 | Screening, BL, Wks 4 & 12 | BL ^c , Weekly thru Wk 4, Wks 20, 36 & 52, F-U visit |
| Physical examination | Screening, BL, Wk 11 | Screening, Wk12 | Screening, Wk12 | BL ^c , Wk 52 |
| Height | Screening | Screening | Screening | BL ^c |
| Weight (and BMI derived from weight and height) | Screening, BL, weekly thru Wk 3, biweekly through Wk 11 | Screening, BL, weekly thru Wk 4, biweekly thru Week 12, F-U visit | Screening, BL, weekly thru Wk 4, biweekly thru Week 12, F-U visit | BL ^c , Weekly thru Wk 4, every 4 wks thru Wk 52, F-U visit |

^a For subjects who enrolled ≥ 30 days from completing an antecedent study, assessment was also collected at the Screening visit.

^b In SPD489-208, blood pressure and pulse were single measurements. In SPD489-343 and -344, blood pressure and pulse measurement was automated; 3 measurements were obtained for each parameter and the average of the 3 measurements was reported

^c For subjects who enrolled directly or within 30 days of completing an antecedent study, assessment was completed as part of the antecedent study. For subjects who enrolled ≥ 30 days from completing an antecedent study, assessment was also collected at the Screening visit.

^d Fasting laboratory tests.

^e Baseline ECG included 3 recordings; subsequent ECGs included 1 recording.

In addition, the Amphetamine Cessation Symptom Assessment (ACSA) was performed in studies SPD489-343 and SPD489-344 at baseline and daily starting at week 12 and continuing through the safety follow-up visit. The Columbia-Suicide Severity Rating Scale (C-SSRS) was done at screening, baseline, and at regular intervals during study drug treatment in all four Phase 2/3 trials as well as at the safety follow-up visit in the three Phase 3 trials.

These clinical assessments are adequate to assess the safety of SPD489 in the treatment of adults with BED in these trials.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Other important adverse experiences observed with amphetamine products include drug abuse and withdrawal/rebound, serious cardiovascular events (sudden death, stroke, and myocardial infarction), increased heart rate, and increased blood pressure. Evaluations for these events in the Phase 2/3 trials were felt to be adequate.

7.3 Major Safety Results

7.3.1 Deaths

As of June 30, 2014, there was one death in one of the above BED trials. Subject 208-036-0006 was a 29 year old Asian male in the 70mg dose group of study SPD489-208 who, after about one month in the trial, was transported to the hospital and pronounced dead. The post-mortem examination revealed methamphetamine and amphetamine levels consistent with a methamphetamine overdose. Although the subject denied drug abuse at screening, information received after his death indicated that he had a prior history of methamphetamine and gamma-hydroxybutyrate abuse and had been participating in a drug rehabilitation program, where he was thought to have been “clean” for approximately 6 months. This death seems unlikely to be a direct effect of prescribed SPD489 treatment. However, the possibility that SPD489 precipitated a relapse of stimulant abuse, which then led to death, cannot be ruled out.

7.3.2 Nonfatal Serious Adverse Events

Non-fatal SAEs that occurred as of June 30, 2014, during one of the four Phase 2/3 trials, including those during the safety follow-up period, are listed in the table below.

| Table 13: Non-Fatal Treatment-Emergent SAEs (Phase 2/3 Trials) | | | | | | |
|--|-----|-----|---------------------------------------|---------------|-----------|------------------|
| Subject Number | Age | Sex | SAE | Onset Dose mg | Onset Day | Action on Dose |
| Placebo-Controlled Trials | | | | | | |
| Treatment = SPD489 | | | | | | |
| 208-012-0023 | 49 | F | Acute pancreatitis | 30 | 58 | D/C |
| 208-033-0037 | 42 | F | Appendicitis | 30 | 56 | None |
| 343-033-3037 | 54 | F | Syncope | 50 | 67 | D/C |
| 343-066-3013 | 44 | M | Syncope | 30 | 6 | D/C |
| 343-095-3001 | 32 | F | Cholecystitis | 70 | 82 | D/C |
| 344-090-4010 | 21 | F | Vertebral fractures (in car accident) | 70 | 40 | D/C |
| Treatment = Placebo | | | | | | |
| 343-088-3012 | 47 | F | Conversion disorder | 0 | 62 | D/C |
| 343-095-3005 | 31 | F | Anaphylaxis | 0 | 15 | D/C |
| 344-079-4020 | 42 | M | Agitation | 0 | 29 | None |
| | | | Anxiety | 0 | 29 | D/C |
| 344-092-4003 | 45 | F | Syncope | 0 | 70 | None |
| | | | Fibula fracture | 0 | 70 | D/C |
| Open-Label Extension Trial (SPD489-345) | | | | | | |
| Enrolled from SPD489-208 | | | | | | |
| 208-005-0005 | 56 | F | Medication error | 50 | 281 | None |
| | | | Supraventricular tachycardia | 50 | 281 | D/C |
| 208-010-0009 | 44 | F | Pneumonia | 70 | 241 | None |
| Enrolled from SPD489-343 or SPD489-344 Prior TX = Placebo | | | | | | |
| 344-010-4008 | 55 | F | Diverticulitis with bowel perforation | 50 | 17 | D/C |
| 343-066-3016 | 42 | F | Acute cholecystitis | 70 | 172 | D/C |
| 344-027-4004 | 48 | F | Increased LFTs | 70 | 196 | None |
| 343-074-3008 | 43 | F | Anxiety | 50 | 182 | None |
| 344-102-4007 | 49 | F | Cholecystitis | 70 | 121 | None |
| 344-205-4006 | 42 | M | Tinnitus | 50 | 51 | D/C |
| 343-064-3001 | 53 | F | Adjustment D/O | 70 | 322 | None |
| 343-001-3010 | 54 | F | Hip fracture | 70 | 247 | D/C |
| Enrolled from SPD489-343 or SPD489-344 Prior TX = SPD489 | | | | | | |
| 344-007-4009 | 33 | F | Spontaneous abortion | 50 | 230 | D/C |
| 344-012-4020 | 36 | F | Asthma | 70 | 130 | None |
| 343-052-3006 | 24 | F | Acute cholecystitis | 30 | 2 | None |
| 344-060-4001 | 43 | F | Viral gastroenteritis | 70 | 202 | Drug Interrupted |
| 344-027-4003 | 54 | F | Cholelithiasis | 50 | 254 | None |

A few of these events merit some discussion.

Cholecystitis/Cholelithiasis

In the three Phase 2/3 placebo-controlled trials (11-12 weeks in duration), there was one report of cholecystitis and another of cholelithiasis on drug and none on placebo, yielding reporting rates of 0.4% (2/569) and 0% (0/435), respectively.

In the 12-month study, there were 4 reports of cholecystitis and two of cholelithiasis, all on drug, for a reporting rate of 1.0% (6/599).

The overall rate of gallstone-related adverse events in the safety database was 1.0% (8/833).¹³

The medical history tabulation files (MH.xpt) for trials SPD489-343 and SPD489-344 were examined using the search terms “gall” and “chole” after eliminating terms related to cholesterol to estimate the lifetime prevalence of gallstone-related disease in this population. The proportion of enrolled patients who had a medical history of such conditions was 8% (62/772), indicating that these conditions are common in the BED population.

Most of the 8 cases from these clinical trials were classified as serious. Characteristics of the patients who experienced these events are as follows:

- all were female.
- all were obese (BMI >30 kg/m²); 4/7 were very obese (BMI >40 kg/m²).
- ages 24 to 54 years; 6 were older than 42 years.
- time to event was 58 to 309 days.
- 4/7 were taking a dose of 70mg, 2 were taking 50mg, and 2 were taking 30mg.
- 7/8 had lost substantial weight prior to the event.
- none had a documented history of gallbladder disease.

The Division of Metabolism and Endocrinology Products (DMEP) was consulted for their opinion on a potential causal link between SPD489 treatment and gallstone-related adverse events and labeling of this concern if a link is plausible. A consultative review was completed on November 12, 2014, by Julie Golden, M.D. In summary, Dr. Golden made the following points:

- the studied population (female and obese) is at risk for gallstones.
- weight loss can increase the risk of these events and, thus, it is plausible that lisdexamfetamine, via its effects on food intake and weight, may increase the risk of cholelithiasis in this population already at risk for these events.
- it is unknown whether these patients had cholelithiasis prior to lisdexamfetamine treatment because of lack of baseline evaluations.
- the degree of lipid alterations associated with lisdexamfetamine is consistent with its effect on weight and an independent effect on lipid metabolism seems less likely.
- independent effects on gallbladder motility are unknown.
- labeling of DMEP products associated with gallstone-related events in clinical trials (e.g., obesity drugs and fibrates) describe the risk under Warnings and

¹³ From trial 208: Patient #208-012-0023, from trial 343: Patient #343-095-3001, and from trial 345: Patient #208-032-0012, Patient #343-052-3006, Patient #343-066-3016, Patient #344-027-4004, Patient #344-102-4007, and Patient #344-027-4003.

Precautions because of the existence of a plausible causal link, the potential for serious complications, and early recognition might mitigate serious morbidity.

In my judgment, there is insufficient evidence at this time to support a clear causal relationship between these events and SPD489 treatment.

Syncope

There were 3 serious reports of syncope, all in the Phase 3 placebo-controlled trials. Two occurred on drug and one on placebo, yielding rates of 0.5% (2/373) and 0.3% (1/372), respectively. In each case, there were 2 episodes of loss of consciousness, either on the same day or one day apart. Of the two SPD489 cases, one was a 54 yo female who took a 50 mg/day dose for 2 months and the other was a 44 yo male who had taken a 30 mg/day dose for 5 days prior to the events. There were no obvious etiologies for syncope identified in any of the cases although the latter patient had a history of narcolepsy, raising the possibility that the syncopal episodes were actually sleep attacks. No other reports of syncope, fainting, or loss of consciousness were identified in these 2 trials or in study SPD489-208.

Elevated LFTs

Subject #344-027-4004 was a 48 year old obese female who underwent a sleeve gastrectomy during participation in trial SPD489-345. She experienced an increased in liver enzymes post-op: ALT and AST were about 4x ULN with a normal bilirubin. The increase was attributed to the surgery and the enzymes normalized one week later.

7.3.3 Dropouts and/or Discontinuations

Treatment-emergent adverse events led to dropout in 5.1% (19/373) of SPD489-treated subjects and 2.4% (9/372) of placebo subjects in the pool of studies SPD489-343 and SPD489-344. Specific events that led to discontinuation in at least 2 SPD489-treated subjects from this study pool are shown in the table below. Events that led to dropout in only one SPD489-treated subject in this study pool were: abdominal pain, anxiety, cholecystitis, dyspnea, lumbar vertebrae fracture (related to a motor vehicle accident), GGT increased, headache, jittery feeling, optic atrophy (suspected pallor of the optic disc), pneumonia, and rash.

| Table 14: Reporting Rates of Dropout Due To Adverse Events in ≥2 SPD489-Treated Subjects (Studies SPD489-343 and SPD489-344) | | |
|---|------------------------|-----------------------|
| Adverse Event Preferred Term | Placebo (N=372) | SPD489 (N=373) |
| Irritability | 0.0% | 0.5% |
| Syncope | 0.0% | 0.5% |
| Heart rate increased/Tachycardia | 0.0% | 0.5% |
| Insomnia/Initial insomnia | 0.0% | 0.5% |

The listings of adverse events that led to discontinuation of study drug in trials SPD489-208 and SPD489-345 were examined for any experiences that might indicate a new, significant safety risk associated with SPD489 treatment. Only one case was identified:

- Subject #344-205-4016 was a 43 year old White female who completed participation in trial SPD489-344 on placebo and commenced treatment in study SPD489-345. On day 44 of the latter study at a dose of 70 mg/day, she experienced postural dizziness without loss of consciousness, which was coded to the Preferred Term “circulatory collapse.”¹⁴ She presented at the emergency room where she was found to have elevated blood pressure (200/100) and moderate tachycardia. An ECG was reportedly normal. There was no treatment, no admission, and she was released from the emergency room. The postural dizziness resolved 3 days later while she continued to take SPD489. SPD489 was stopped the day after resolution and the hypertension and tachycardia resolved the day after stopping drug. She had no history of cardiovascular disease, ECG abnormality, or medication that might explain these events. Given the time course of the postural dizziness (onset after 44 days of treatment and resolution while continuing drug), it seems unlikely that SPD489 caused this event. However, resolution of the elevated blood pressure and tachycardia the day after stopping SPD489 suggests a causal link between drug and these events. Both elevated blood pressure and tachycardia have been associated with SPD489 treatment and are not considered new safety findings for this drug.

7.3.4 Other Significant Adverse Events

I identified one other significant adverse event from the ISS adverse event dataset (adae.xpt). Subject #208-036-006 experienced acute renal failure while receiving SPD489 treatment in trial SPD489-208. However, this event occurred after a fatal methamphetamine overdose and was unlikely related to SPD489. This subject was discussed above as a death.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The proportion of patients who experienced treatment-emergent adverse events (TEAEs) that were reported in 2% or more of SPD489-treated patients and at a rate at least twice the placebo rate within the pool of studies SPD489-343 and SPD489-344 are displayed in the table below.

TEAEs that are considered common and probably drug-related (SPD489 reporting rate $\geq 5\%$ and at least twice the placebo rate) were: dry mouth,

¹⁴ From information provided by the sponsor on September 9, 2014 (Serial #0138).

insomnia, decreased appetite, heart rate increased, constipation, feeling jittery, and anxiety.

| Table 15: Treatment-Emergent Adverse Event Reporting Rates (Pool of Trials SPD489-343 and SPD489-344)¹⁵ | | |
|---|---------------------------|----------------------------|
| Adverse Event | SPD489 (N=373) | Placebo (N=372) |
| Dry mouth | 36% | 7% |
| Insomnia ¹⁶ | 20% | 8% |
| Decreased appetite | 8% | 2% |
| Heart rate increased ¹⁷ | 7% | 1% |
| Feeling jittery | 6% | 1% |
| Constipation | 6% | 1% |
| Anxiety | 5% | 1% |
| Diarrhea | 4% | 2% |
| Weight decreased | 4% | 0% |
| Hyperhidrosis | 4% | 0% |
| Vomiting | 2% | 1% |
| Gastroenteritis | 2% | 1% |
| Paresthesia | 2% | 1% |
| Pruritis | 2% | 1% |
| Upper abdominal pain | 2% | 0% |
| Energy increased | 2% | 0% |
| Urinary tract infection | 2% | 0% |
| Nightmare | 2% | 0% |
| Restlessness | 2% | 0% |
| Oropharyngeal pain | 2% | 0% |

7.4.2 Laboratory Findings

Laboratory Assessments

In trials SPD489-343 and SPD489-344, fasting blood and urine specimens were required. Assays included the following:

- Hematology: hemoglobin, hematocrit, RBCs, MCH, MCV, MCHC, WBCs with differential, platelet count.
- Chemistry: total cholesterol, HDL, LDL, triglycerides, AST, ALT, GGT, total bilirubin, alkaline phosphatase, sodium, potassium, phosphorus, HbA_{1c}, BUN, creatinine, glucose, CPK, LDH, uric acid, albumin, total protein, TSH, insulin, leptin (“satiety hormone”), and ghrelin (“hunger hormone”).

¹⁵ TEAEs for which the placebo reporting rate was equal to or greater than that in the SP489 treatment arm after rounding were: upper respiratory tract infection, nasopharyngitis, sleep disorder, dizziness, and back pain.

¹⁶ Includes all preferred terms containing the word “insomnia.”

¹⁷ Includes the preferred terms “heart rate increased” and “tachycardia.”

- Urinalysis: specific gravity, pH, glucose, blood, ketones, protein, bilirubin, urobilinogen, leukocyte esterase (indicator of possible infection), and nitrite.

Hematology Findings

The number and percentage of patients with hematology values meeting a criterion for potential clinical importance (PCI) in the pool of trials SPD489-343 and SPD489-344 are shown in the table below. The proportion of SPD489 patients with a PCI value for lymphocytes/leukocytes (as a fraction of 1) was statistically significantly higher than for the placebo group: 2.9% vs 0.3%, $p=0.0112$ (2-tailed Fishers exact test). Of the 10 SPD489-treated patients with a PCI value, 4 had a high value at baseline. Also, 7 of the 10 values were not substantially higher than the PCI cutoff of 0.50, with values in the range of 0.50 to 0.53. Mean changes from baseline in lymphocytes/leukocytes were small in both treatment arms (fractions <0.01) and no patient dropped out because of an abnormality on this measure. Drug versus placebo differences on other hematology parameters were not statistically significant at the 0.100 level.

| Parameter | PCI Criteria | Placebo (N=327) | | SPD489 (N=339) | |
|----------------------------|-------------------|-----------------|------|----------------|------|
| | | n | % | n | % |
| Hemoglobin | <10 g/dL | 2 | 0.6% | 1 | 0.3% |
| Platelets | >500,000/ μ L | 1 | 0.3% | 2 | 0.6% |
| Leukocytes | <3,000/ μ L | 4 | 1.2% | 1 | 0.3% |
| Leukocytes | >16,000/ μ L | 0 | 0% | 1 | 0.3% |
| Neutrophils | <1,500/ μ L | 2 | 0.6% | 7 | 2.1% |
| Neutrophils/ Leukocytes | <0.4 | 2 | 0.6% | 6 | 1.8% |
| Lymphocytes | <800/ μ L | 1 | 0.3% | 3 | 0.9% |
| Lymphocytes/ Leukocytes | <0.1 | 1 | 0.3% | 1 | 0.3% |
| Lymphocytes/ Leukocytes | >0.5 | 1 | 0.3% | 10 | 2.9% |
| Eosinophils/ Leukocytes | >0.1 | 1 | 0.3% | 0 | 0% |

Mean changes from baseline in hematology parameters using both Last Observation Carried Forward and Observed Cases analyses were generally small and comparable between the SPD489 and placebo treatment arms.

No hematology abnormality led to discontinuation from the trial.

¹⁸ N= number of patients with a baseline and at least one post-baseline value, n= number of patients meeting a PCI criterion post-baseline, and %= (n/N) x 100%. PCI cutoffs have been converted from SI to conventional units.

Chemistry Findings

The number and percentage of patients with clinical chemistry values meeting a PCI criterion in the pool of trials SPD489-343 and SPD489-344 are shown in the table below.

| Parameter | PCI Criteria | Placebo (N=332) | | SPD489 (N=342) | |
|---------------|--|-----------------|------|----------------|------|
| | | n | % | n | % |
| Cholesterol | >301 mg/dL | 0 | 0% | 1 | 0.3% |
| Triglycerides | >2.5 xULN | 3 | 0.9% | 2 | 0.6% |
| AST | >2.5 xULN | 1 | 0.3% | 0 | 0% |
| Phosphate | <2.5 mg/dL | 5 | 1.5% | 4 | 1.2% |
| Phosphate | >5.0 mg/dL | 2 | 0.6% | 3 | 0.9% |
| ALT | >2.5 xULN | 4 | 1.2% | 0 | 0% |
| Sodium | >150 mEq/L | 1 | 0.3% | 0 | 0% |
| Potassium | <3.5 mEq/L | 1 | 0.3% | 1 | 0.3% |
| Potassium | >5.5 mEq/L | 3 | 0.9% | 3 | 0.9% |
| GGT | >2.5 xULN | 3 | 0.9% | 3 | 0.9% |
| Thyrotropin | <LLN | 5 | 1.5% | 11 | 3.2% |
| Thyrotropin | >2 xULN | 2 | 0.6% | 1 | 0.3% |
| Calcium | <8 mg/dL | 1 | 0.3% | 0 | 0% |
| Urate | >10 mg/dL (male) OR >8 mg/dL (female) | 7 | 2.1% | 5 | 1.5% |
| Bilirubin | >1.5 xULN | 1 | 0.3% | 3 | 0.9% |
| Glucose | <56 mg/dL | 1 | 0.3% | 0 | 0% |
| Glucose | >160 mg/dL | 0 | 0% | 1 | 0.3% |
| CPK | >2.5 xULN | 14 | 4.2% | 7 | 2.0% |

There were no statistically significant differences between SPD489 and placebo for any chemistry measure (2-tailed Fishers exact test, alpha=0.10).

Mean changes from baseline in chemistry parameters were generally small and comparable between the SPD489 and placebo treatment arms or greater in the placebo group. Mean changes in the metabolic parameters total cholesterol, HDL, LDL, and triglycerides are summarized in the table below.

¹⁹ N= number of patients with a baseline and at least one post-baseline value, n= number of patients meeting a PCI criterion post-baseline, and %= (n/N) x 100%. PCI cutoffs have been converted from SI to conventional units.

| Table 18: Mean Changes in Select Metabolic Parameters Phase 3 Placebo-Controlled Trials²⁰ | | | | |
|---|---------------|----------------------|----------------|----------------------|
| | SPD489 | | Placebo | |
| | N | Level (mg/dl) | N | Level (mg/dl) |
| Cholesterol | | | | |
| Baseline | 373 | 195 | 369 | 195 |
| Mean Δ BL to Wk 11/12 | 304 | -10.4 | 297 | -4.0 |
| HDL | | | | |
| Baseline | 373 | 60 | 369 | 62 |
| Mean Δ BL to Wk 11/12 | 304 | -1.1 | 297 | -1.5 |
| LDL | | | | |
| Baseline | 373 | 124 | 369 | 122 |
| Mean Δ BL to Wk 11/12 | 304 | -7.3 | 297 | -2.1 |
| Triglycerides | | | | |
| Baseline | 373 | 116 | 369 | 112 |
| Mean Δ BL to Wk 11/12 | 304 | -11.5 | 297 | +8.6 |

For reference, the normal ranges for these parameters were:

- cholesterol 0 to 200 mg/dl.
- HDL cholesterol \geq 40 mg/dl.
- LDL cholesterol \leq 100 mg/dl.
- triglycerides \leq 150 mg/dl.

With the exception of LDL cholesterol, the mean baseline values were within normal range. In the SPD489 treatment group, mean values improved from baseline at Weeks 11/12.

In the pool of trials SPD489-343 and SPD489-344, the proportion of patients with high cholesterol, LDL, or triglyceride values at baseline and who were in the normal range at Weeks 11/12 or who had a low HDL at baseline and who were in the normal range at Weeks 11/12 are shown in the table below. SPD489 was clearly superior to placebo in terms of shifts from high to normal levels of cholesterol and triglycerides.

²⁰ Figures have been converted from SI to conventional units. Baseline N's represent the total number of patients with values at baseline and, thus, are larger than the completers with values.

| Table 19: Proportion of Patients with Shift Changes in Select Metabolic Parameters: Phase 3 Placebo-Controlled Trials | | |
|--|----------------|----------------|
| | SPD489 | Placebo |
| | % Shift | % Shift |
| Cholesterol | | |
| Shift from BL High to Normal | 43% | 21% |
| HDL | | |
| Shift from BL Low to Normal | 27% | 39% |
| LDL | | |
| Shift from BL High to Normal | 16% | 11% |
| Triglycerides | | |
| Shift from BL High to Normal | 53% | 21% |

One patient in the SPD489 treatment group dropped out because of an abnormal chemistry value (increased GGT), which was elevated at baseline.

Urinalysis Findings

An enumeration of patients who met PCI criterion for a urinalysis result is displayed in the table below.

| Table 20: Enumeration of Patients With PCI Urinalysis Results (Pool of Trials SPD489-343 and SPD489-344)²¹ | | | | | |
|--|----------------------------------|------------------------|----------|-----------------------|----------|
| Parameter | PCI Criteria²² | Placebo (N=326) | | SPD489 (N=332) | |
| | | N | % | N | % |
| Glucose | Positive value | 1 | 0.3% | 1 | 0.3% |
| Protein | Positive value | 11 | 3.4% | 20 | 6.0% |
| Blood | Positive value | 18 | 5.5% | 18 | 5.4% |
| Leukocyte esterase | Positive value | 21 | 6.4% | 32 | 9.6% |

The proportions of SPD489-treated patients with protein or leukocyte esterase in the urine were higher than those for placebo. However, neither difference was statistically significant using a two-tailed Fishers exact test and an alpha of 0.100.

Mean changes from baseline in quantitative urinalysis results (specific gravity and pH) as well as qualitative findings (e.g., glucose, ketones, blood, and protein) were comparable between the SPD489 and placebo treatment arms.

No patient dropped out of study SPD489-343 or SPD489-344 because of an abnormal urinalysis finding.

²¹ N= number of patients with a baseline and at least one post-baseline value, n= number of patients meeting a PCI criterion post-baseline, and %= (n/N) x 100%.

²² Any positive value excluding a trace amount.

7.4.3 Vital Signs

Vital Sign Assessments

Vital sign measurements included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, temperature, and respiratory rate at each visit in trials SPD489-343 or SPD489-344. Temperatures were taken by mouth or by ear. Body weight was measured at each visit without shoes. Waist circumference was measured at the week 4/5 and week 11/12 visits.

Vital Sign Findings

An enumeration of patients meeting PCI criteria for vital sign values is depicted in the table below.

A significantly larger proportion of SPD489-treated patients experienced a PCI high DBP and high pulse rate at some point after baseline ($p=0.004$ and 0.007 , respectively, using a 2-tailed Fishers exact test). This is consistent with the sympathomimetic effect of amphetamine drugs. However, SPD489 was comparable to placebo when more stringent PCI criteria were applied (high value with a large increase from baseline on 2 consecutive visits including the last visit).

| Table 21: Enumeration of Patients With PCI Vital Sign Measurements (Pool of Trials SPD489-343 and SPD489-344)²³ | | | | |
|---|----------------------------|----------|---------------------------|----------|
| Measurement/ PCI Criteria | Placebo (N=370) | | SPD489 (N=370) | |
| | n | % | N | % |
| SBP (mmHg) | | | | |
| <100 | 117 | 32% | 84 | 23% |
| ≥140 | 21 | 6% | 26 | 7% |
| ≥140 and increased >10 from baseline on 2 consecutive visits including the last visit | 0 | 0% | 1 | 0.3% |
| DBP (mmHg) | | | | |
| <50 | 2 | 0.5% | 1 | 0.3% |
| ≥90 | 43 | 12% | 72 | 20% |
| ≥90 and increased >10 from baseline on 2 consecutive visits including the last visit | 2 | 0.5% | 0 | 0% |
| Pulse (bpm) | | | | |
| <50 | 9 | 2% | 2 | 0.5% |
| ≥110 | 2 | 0.5% | 13 | 4% |
| ≥110 and increased >15 from | 0 | 0% | 0 | 0% |

²³ N= number of patients with a baseline and at least one post-baseline value, n= number of patients meeting a PCI criterion post-baseline, and %= (n/N) x 100%.

| Table 21: Enumeration of Patients With PCI Vital Sign Measurements (Pool of Trials SPD489-343 and SPD489-344)²³ | | | | |
|---|----------------------------|----------|---------------------------|----------|
| Measurement/ PCI Criteria | Placebo (N=370) | | SPD489 (N=370) | |
| | n | % | N | % |
| baseline on 2 consecutive visits including the last visit | | | | |
| Temperature (degrees Celsius) | | | | |
| <35 | 3 | 0.8% | 2 | 0.5% |
| >39 | 1 | 0.3% | 0 | 0% |
| Body Weight (kg)²⁴ | | | | |
| ≥10% increase from baseline | 6 | 2% | 1 | 0.3% |
| ≥10% decrease from baseline | 2 | 0.5% | 75 | 20% |

Mean increases in SBP and DBP were seen in SPD489-treated patients compared to decreases in the placebo group: at the week 11/12 visit (or end of treatment for dropouts), the mean change from baseline in SBP was -2.5 mmHg for placebo and +0.8 mmHg for SPD489; the mean change from baseline in DBP was -1.4 mmHg for placebo and +1.4 mmHg for SPD489. On average, mean increases in pulse rate were seen in both treatment arms but were substantially greater in the SPD489 group. For example, at the week 11/12 visit (or end of treatment for dropouts), the mean change from baseline in pulse rate was +1.8 bpm for placebo and +5.4 bpm for SPD489.

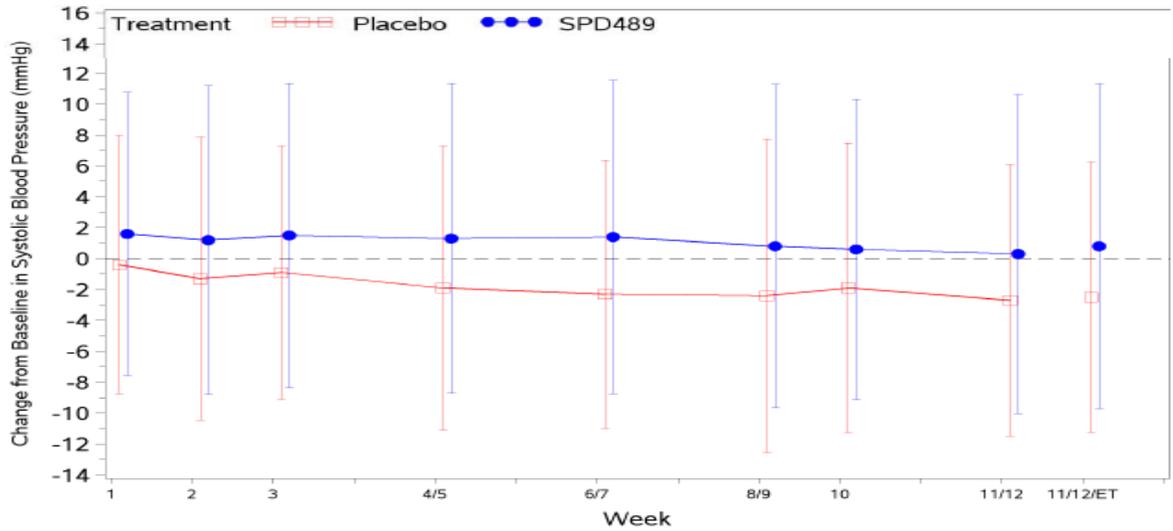
In the pool of these two trials, the proportion of patients who received a concomitant medication for elevated blood pressure was lower in the SPD489 group than in the placebo group: 4.3% (16/373) versus 5.9% (22/372).²⁵

Changes in blood pressure and pulse rate relative to placebo tended to remain stable over time throughout these trials, as shown in the following figures.

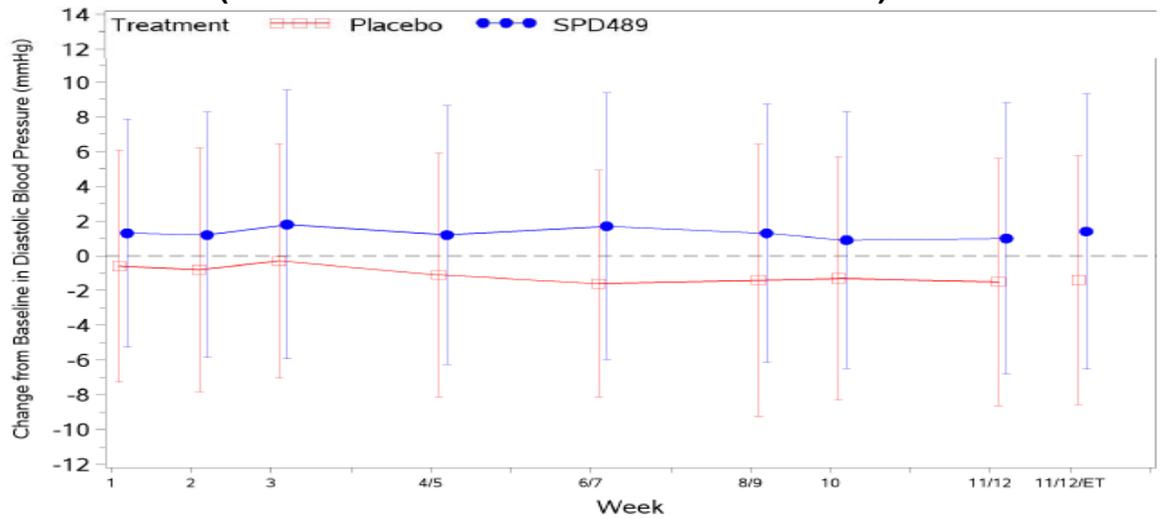
²⁴ Placebo N=372 and SPD489 N=373.

²⁵ These figures are based on data from the CM.xpt files for these trials, which were searched for the following indications (CMINDC) for the concomitant medication: high blood pressure, HTN, and hypertension.

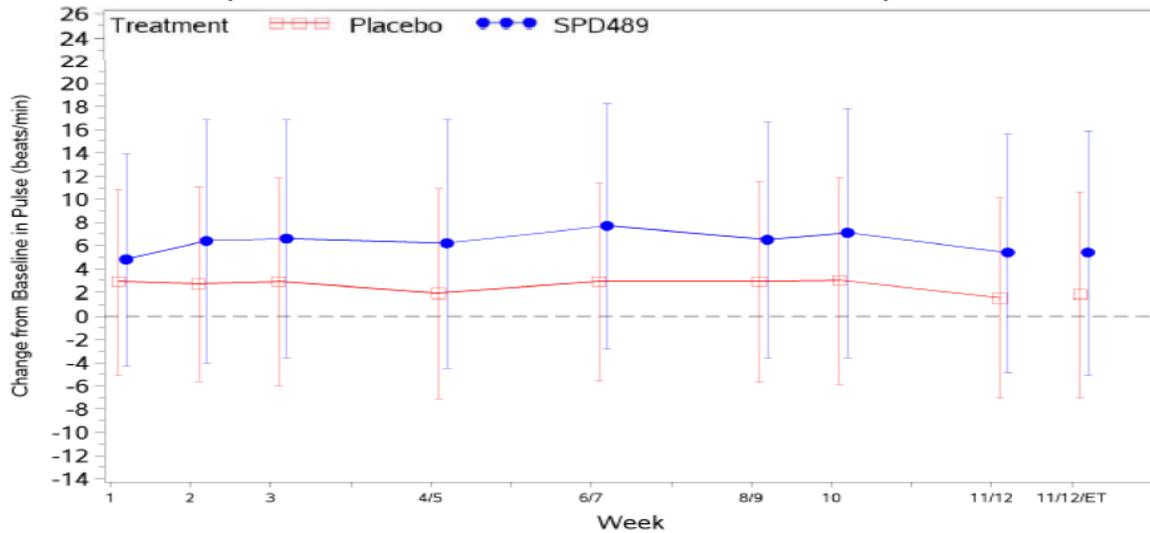
**Figure 4: Mean Change in Systolic Blood Pressure By Visit
(Pool of Trials SPD489-343 and SPD489-344)**



**Figure 5: Mean Change in Diastolic Blood Pressure By Visit
(Pool of Trials SPD489-343 and SPD489-344)**

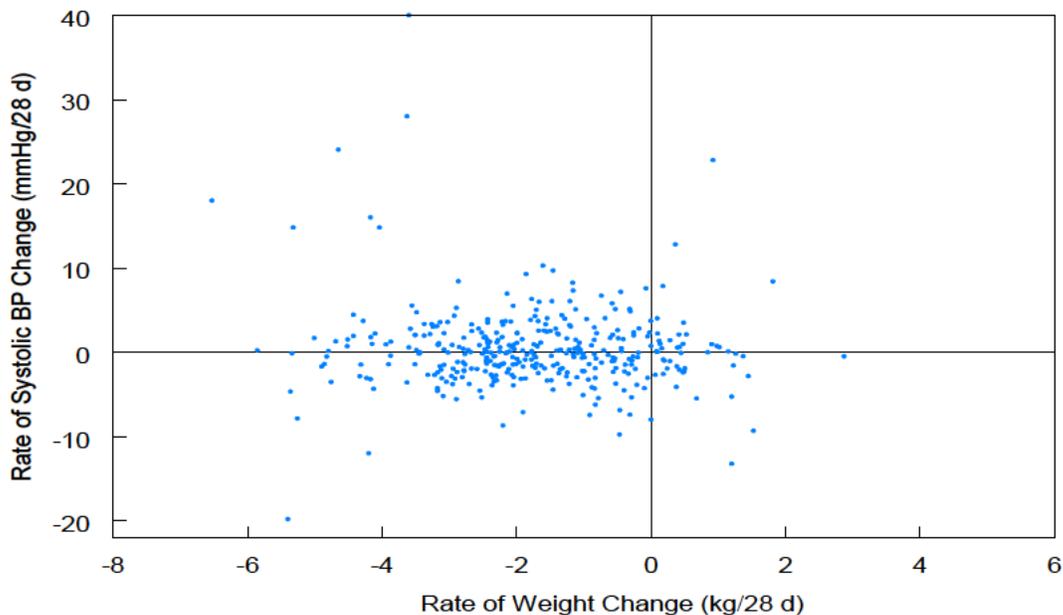


**Figure 6: Mean Change in Pulse By Visit
(Pool of Trials SPD489-343 and SPD489-344)**



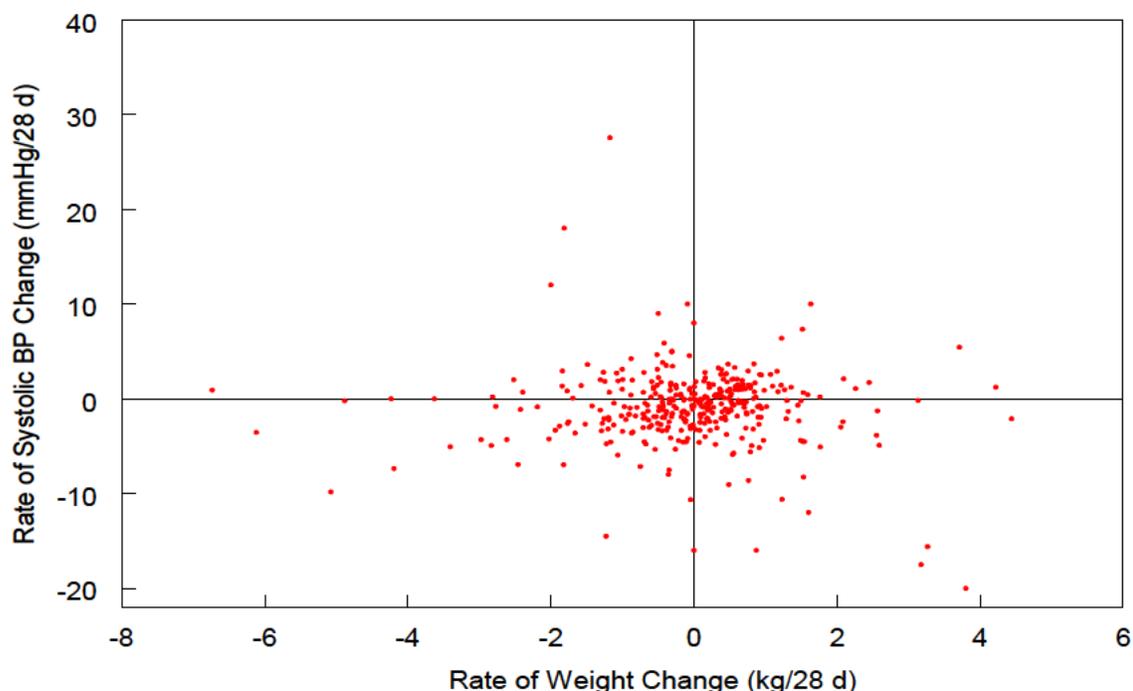
There was no correlation between the rate of change in systolic blood pressure and rate of change in body weight in either the SPD489-treated patients or the placebo group in the pool of trials SPD489-343 and SPD489-344, as seen in the following two figures.²⁶

Figure 7: Rate of Systolic BP Change vs. Rate of Weight Change (SPD489-Treated Patients)



²⁶ Scatterplots are the courtesy of Dr. Ellis Unger, ODE I Director.

Figure 8: Rate of Systolic BP Change vs. Rate of Weight Change (Placebo-Treated Patients)



Changes in respiratory rate were very small in both treatment groups.

A much larger proportion of patients in the SPD489 arm experienced substantial weight loss ($\geq 10\%$ baseline body weight) compared to the placebo arm (20% vs. <1%).

Baseline weight and BMI were comparable between groups for the pool of studies SPD489-343 and SPD489-344: 208.4 lbs for drug vs. 204.8 lbs for placebo and 33.8 kg/m^2 for drug vs. 33.2 kg/m^2 for placebo. Body weight changes from baseline at week 11/12 were -12.8 lbs in the SPD489 group versus +0.1 lbs in the placebo group. No SPD489-treated subject shifted to a BMI category of underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$). Weight decrease tended to occur gradually during the course of these short-term trials. Parallel changes from baseline in BMI and waist circumference were observed. In the long-term, open-label trial (SPD489-345), mean body weight decreased over time achieving a maximum decrease at week 28 (16.8 lbs on average) for those in the trial, with increases in mean body weight thereafter.²⁷

²⁷ As of the data cutoff February 28, 2014.

A few patients dropped out of trials SPD489-343 and SPD489-344 because of vital sign abnormalities. These are enumerated in the table below.

| Table 22: Enumeration of Dropouts (n(%)) Because of Vital Sign Abnormalities (Studies SPD489-343 and SPD489-344) | | |
|---|------------------------|-----------------------|
| Adverse Event Preferred Term | Placebo (N=372) | SPD489 (N=373) |
| Bradycardia | 1 (0.3%) | 0 (0%) |
| Blood pressure increased | 1 (0.3%) | 0 (0%) |
| Heart rate increased | 0 (0%) | 2 (0.5%) |
| Dyspnea | 0 (0%) | 1 (0.3%) |

7.4.4 Electrocardiograms (ECG's)

ECGs were obtained at baseline and at the week 4/5 and week 11/12 (or end of treatment) visits.

The incidence rates of PCI values on various ECG measures in the pool of trials SPD489-343 and SPD489-344 are displayed in the table below. Significantly more SPD489 patients had a heart rate of 100 bpm or greater at some point after baseline compared to placebo (4% vs. 0.3%; $p=0.0002$). This is consistent with the vital sign data discussed above and the pharmacological activity of this drug class. The proportion of SPD489 patients with an increase from baseline in QTcB of ≥ 30 but < 60 msec was also significantly greater than placebo at a 0.10 level of significance (9% vs. 5%, $p=0.07$). Otherwise, the rates of PCI values on ECG parameters were comparable between treatment arms.

Likewise, SPD489-treated patients experienced an increased mean change in heart rate on ECG compared to placebo: +3.6 vs. -0.8 bpm (at week 11/12 or end of treatment). Mean changes in PR, QRS, QT, QTcB, and QTcF intervals suggested no tendency for SPD489 to cause prolongation of these parameters.

| Table 23: Enumeration of Patients With PCI ECG Values (Pool of Trials SPD489-343 and SPD489-344)²⁸ | | | | |
|--|----------------------------|----------|---------------------------|----------|
| Measurement/ PCI Criteria | Placebo (N=357) | | SPD489 (N=360) | |
| | n | % | N | % |
| Heart rate | | | | |
| ≤50 bpm | 29 | 8% | 16 | 4% |
| ≥100 bpm | 1 | 0.3% | 16 | 4% |
| PR duration | | | | |
| ≥200 msec | 17 | 5% | 13 | 4% |
| QRS duration | | | | |
| ≥120 msec | 0 | 0% | 2 | 0.6% |
| QT duration | | | | |
| ≥480 msec | 1 | 0.3% | 2 | 0.6% |
| Increase from BL ≥30 but <60 msec | 38 | 11% | 36 | 10% |
| Increase from BL ≥60 msec | 3 | 0.8% | 2 | 0.6% |
| QTcB duration | | | | |
| ≥480 but <500 msec | 0 | 0% | 1 | 0.3% |
| ≥500 msec | 0 | 0% | 0 | 0% |
| Increase from BL ≥30 but <60 msec | 18 | 5% | 31 | 9% |
| Increase from BL ≥60 msec | 1 | 0.3% | 0 | 0% |
| QTcF duration | | | | |
| ≥480 but <500 msec | 0 | 0% | 0 | 0% |
| ≥500 msec | 0 | 0% | 0 | 0% |
| Increase from BL ≥30 but <60 msec | 4 | 1% | 6 | 2% |
| Increase from BL ≥60 msec | 0 | 0% | 0 | 0% |

No patient in these trials dropped out because of an ECG abnormality.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The common and probably drug-related treatment-emergent adverse events identified above from the pool of placebo-controlled Phase 3 trials were examined within the fixed dose trial SPD489-208 for dose dependency. The reporting rates for these events by dose group are displayed in the following table. These data provide some evidence for dose dependency for the following 2 adverse events: dry mouth and feeling jittery.

²⁸ N= number of patients with a baseline and at least one post-baseline value, n= number of patients meeting a PCI criterion post-baseline, and %= (n/N) x 100%.

| Table 24: Reporting Rates of Treatment-Emergent Adverse Events By Fixed Dose Group (Trial SPD489-208) | | | | |
|--|-------------------------|--------------------------|----------------------|----------------------|
| | Placebo N=66 | SPD489 Dose Group | | |
| | | 30mg N=68 | 50mg N=68 | 70mg N=68 |
| Dry mouth | 8% | 32% | 32% | 40% |
| Insomnia | 2% | 10% | 15% | 13% |
| Decreased appetite | 6% | 25% | 19% | 18% |
| Constipation | 2% | 9% | 4% | 7% |
| Feeling jittery | 0% | 2% | 4% | 7% |
| Anxiety | 0% | 6% | 6% | 2% |
| Initial insomnia | 0% | 3% | 3% | 4% |
| Increased heart rate | 0% | 2% | 2% | 3% |

7.5.2 Time Dependency for Adverse Events

The sponsor examined the time of onset of dry mouth, headache, insomnia, and decreased appetite in all placebo-controlled trials.²⁹ This examination revealed that most occurrences had onset during the first week of treatment (at the 30 mg/day dose), with fewer occurrences of onset or worsening in subsequent weeks despite increases in dose.

The sponsor also examined the timing of resolution of these 4 events and found that the majority of the occurrences resolved while the patient was on treatment or within 3 days of the last dose.

7.5.3 Drug-Demographic Interactions

The sponsor evaluated treatment-emergent adverse event incidence according to subgroups defined by age (<40 vs. ≥40 years), sex, race (white vs. non-white), ethnicity (Hispanic vs. non-Hispanic), region (U.S. vs. non-U.S.), and obesity (BMI <30 kg/m² vs. BMI ≥30 kg/m²).³⁰ However, subgroups based on ethnicity and region were considered too small to draw any meaningful conclusions.

In terms of age, nausea and irritability was reported more frequently in the younger age group compared to those 40 and older, as shown in the table below.

²⁹ These 4 adverse events occurred in at least 10% of all SPD489-treated patients in all placebo-controlled trials.

³⁰ Adverse events considered were those that were reported by at least 5% of SPD489-treated patients in all 3 placebo-controlled trials (SPD489-208, SPD489-343, and SPD489-344), specifically: dry mouth, headache, insomnia, decreased appetite, nausea, irritability, constipation, fatigue, feeling jittery, and anxiety.

| | <40 Years | | ≥40 Years | |
|--------------|----------------------------|---------------------------|----------------------------|---------------------------|
| | Placebo (N=227) | SPD489 (N=270) | Placebo (N=208) | SPD489 (N=233) |
| Nausea | 6.6% | 11.1% | 3.4% | 4.9% |
| Irritability | 5.3% | 9.2% | 5.3% | 3.0% |

Regarding sex, males comprised only 15% of the SPD489-treated group and no firm conclusions could be drawn from these analyses. With respect to race, non-whites constituted only 24% of the SPD489-treated group and no definitive conclusions could be drawn from this evaluation. About 29% of the SPD489-treated patients were non-obese (BMI <30kg/m²). Reporting rates of adverse events were comparable between subgroups.

7.6 Additional Safety Explorations

7.6.2 Human Reproduction and Pregnancy Data

This supplement provides no new information on the use of lisdexamfetamine during pregnancy.

According to Vyvanse labeling, there are no adequate and well-controlled studies with Vyvanse in pregnant women. Adverse outcomes, such as premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. Available data from women taking amphetamines during pregnancy do not show a clear increased risk of major congenital malformations. Two case control studies in over a thousand women exposed to amphetamines at different gestational ages did not show an increase in congenital abnormalities. Vyvanse should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In Phase 2/3 trials (with a total of 833 patients treated with SPD489), 6 SPD489-treated subjects had events termed “overdose” (n=3) or “accidental overdose” (n=3). For 5 of these 6 patients, only one additional capsule of study drug was ingested. In the remaining patient, the number of additional capsules could not be confirmed.

Lisdexamfetamine consists of L-lysine covalently linked to dextroamphetamine and is very stable outside the body. It is an inactive prodrug of the stimulant dextroamphetamine and, once absorbed, it is hydrolyzed to lysine and d-amphetamine, primarily by peptidases associated with red blood cells. Studies that subjected lisdexamfetamine, with and without excipients, to extreme acid and base hydrolytic conditions have demonstrated the difficulty that would be

involved in isolating and purifying dextroamphetamine from the resulting mixtures, hindering extraction. Human abuse liability studies with Vyvanse have indicated evidence of abuse liability at a oral dose of 150mg and an intravenous dose of 50mg. Lisdexamfetamine is a Schedule II controlled substance.

To further evaluate the abuse potential of SPD489, Shire commissioned a review of the potential for non-medical use of lisdexamfetamine in the context of BED.³¹ This evaluation entailed an assessment of abuse liability from the 3 completed Phase 2/3 placebo-controlled trials and preliminary data from the ongoing Phase 3 open-label trial. Information regarding study drug adherence, as assessed by the investigator, and drug accountability, as determined by the return of unused medication and product packaging by the patient at each visit, were collected in the BED trials. Neither measure suggested abuse or diversion of the product. Patients were considered compliant if they reportedly ingested 80%-120% of the prescribed medication. Compliance rates in study SPD489-343 were 98% in the drug and 100% in the placebo group. For study SPD489-344, compliance rates were 99% for both drug and placebo. With respect to drug accountability, the numbers of capsules dispensed, returned, and the differences between the two were similar between treatment groups, as shown in the table below.

| Table 26: Drug Accountability (Mean Number of Capsules) | | | | | | |
|--|------------------|-----------------|-------------------|------------------|-----------------|-------------------|
| Trial | SPD489 | | | Placebo | | |
| | Dispensed | Returned | Difference | Dispensed | Returned | Difference |
| SPD489-343 | 90.4 | 15.5 | 75.3 | 92.0 | 15.4 | 76.6 |
| SPD489-344 | 91.8 | 15.0 | 76.8 | 88.6 | 15.3 | 73.7 |

Additionally, treatment-emergent adverse events from all 3 placebo-controlled trials were examined to evaluate the occurrence of abuse/dependence, which entailed the preferred term “drug diversion” as well as the SMQ “drug abuse/dependence.” Abuse/dependence was reported by 0.7% (3/435) of placebo patients and 0.5% (3/569) of SPD489 patients in the pool of these trials.

These data suggest that SPD489 had no abuse or diversion. However, they are based largely on information from the patient and, thus, should be taken with a grain of salt.

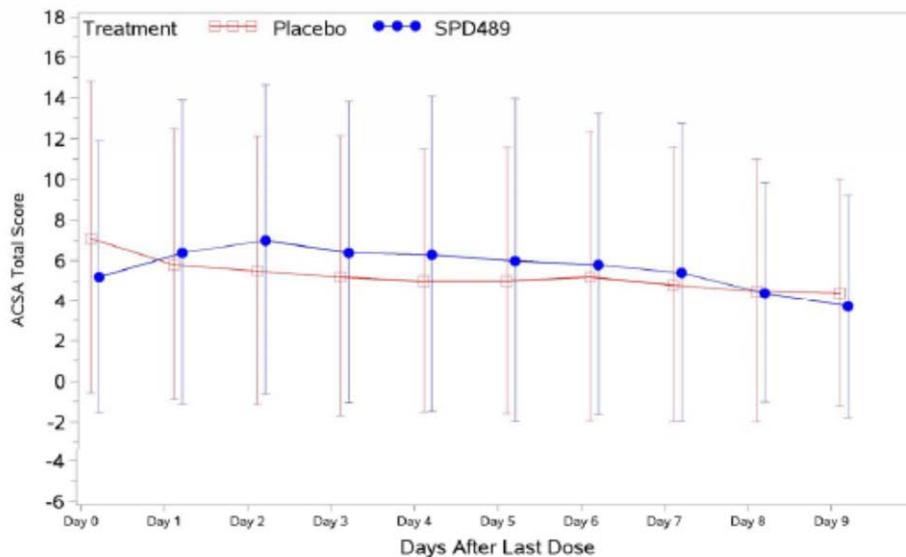
This report also described recent findings from postmarketing surveillance with the use of Vyvanse for ADHD. These data have been derived from various surveys of stimulant misuse and diversion as well as internet monitoring and suggest that lisdexamfetamine non-medical use and diversion have remained low since the approval of Vyvanse in 2007.

The Amphetamine Cessation Symptom Assessment (ACSA) is a self-reported scale for the assessment of withdrawal symptoms among amphetamine users.

³¹ The report was prepared by Pinney Associates and dated July 25, 2014. It is located in Module 5.3.5.4 of the sNDA submission.

This instrument is comprised of 16 symptom items each rated on a 5-point scale ranging from 0 (not at all) to 4 (extreme). The ACSA was assessed at baseline, at the final visit (week 11/12 or end of treatment), and daily thereafter until the follow-up visit in trials SPD489-343 and SPD489-344. The figure below depicts the mean ACSA total score for all patients in these two trials following the final dose of study medication. Scores remained low and comparable between the SPD489 and placebo treatment groups up to 9 days after the last dose.

Figure 9: Mean (SD) ACSA Total Scores Following the Last Dose of Study Medication (Trials SPD489-343 and SPD489-344)



“Withdrawal syndrome” was reported by 2/833 SPD489-treated patients in placebo-controlled Phase 2/3 trials (1 and 2 days after the last dose of SPD489). There were no such events in placebo patients.

There are no available data on rebound symptoms of binge-eating.

7.6.5 Suicidal Ideation and Behavior

The emergence of suicidal ideation and behavior was assessed at each visit using the Columbia-Suicide Severity Rating Scale (C-SSRS). An enumeration of positive responses to items on the C-SSRS in trials SPD489-343 and SPD489-344 is displayed in the table below. There were few positive responses and the rate of positive responses was not substantially higher for the SPD489 arm compared to placebo.

| Table 27: Enumeration of Patients With Positive C-SSRS Responses³² | | | | |
|--|----------------------------|----------|---------------------------|----------|
| Trial SPD489-343 | | | | |
| C-SSRS Item | Placebo (N=187) | | SPD489 (N=191) | |
| | N | % | n | % |
| Wish to be dead. | 1 | 0.5% | 2 | 1.0% |
| Non-specific active suicidal thoughts. | 2 | 1.1% | 0 | 0% |
| Active suicidal ideation without intent. | 1 | 0.5% | 0 | 0% |
| Any active suicidal ideation. | 2 | 1.1% | 0 | 0% |
| Trial SPD489-344 | | | | |
| C-SSRS Item | Placebo (N=183) | | SPD489 (N=179) | |
| | N | % | n | % |
| Wish to be dead. | 2 | 1.1% | 0 | 0% |
| Non-suicidal self-injurious behavior. | 0 | 0% | 1 | 0.6% |

There were no suicide-related treatment-emergent adverse events reported in the Phase 2/3 placebo-controlled trials.³³

7.7 Additional Submissions/Safety Issues

None.

8 POSTMARKETING EXPERIENCE

SPD489 has not been approved for the treatment of BED in any country.

All postmarketing data have been derived from ADHD patients. SPD489 has received marketing authorization for ADHD in 14 countries, including the U.S., and is marketed in 9 of those countries. As of August 31, 2014, the estimated cumulative worldwide exposure to SPD489 in ADHD patients is (b) (4) patient-years, primarily in the U.S. According to the sponsor, the postmarketing experience with SPD489 in the ADHD population is generally consistent with the clinical trial experience in BED.

³² There were no positive responses for C-SSRS items not listed in this table.

³³ There was one suicide attempt in a placebo-treated patient that occurred 7 days after completion of double-blind treatment that was not considered treatment-emergent.

9 APPENDICES

9.1 Literature Review

For purposes of this supplement, Shire conducted a literature search covering the period from February 24, 2014, to June 15, 2014, using the OvidSP Medline and Embase databases. (Previous time periods were covered by searches described in prior NDA Annual Reports). The search was performed by (b) (6) Senior Research Specialist, Knowledge Management Library Services, Shire Development LLC. The results were reviewed by the Medical Monitor for the Vyvanse Binge Eating Disorder Clinical Development Program, Maria Gasior, Ph.D. Dr. Gasior signed a warrant on June 30, 2014, that the review revealed no new potential adverse safety findings associated with lisdexamfetamine dimesylate and that the benefit-risk profile remains unchanged.

The Four-Month Safety Update Report describes a more recent search covering the period from June 15, 2014, to October 15, 2014. This search utilized the OvidSP Medline and Embase databases as well as both Quosa and PubMed. The search was performed by (b) (6), Senior Research Specialist, Knowledge Management Library Services, Shire Development LLC. The results were likewise reviewed by Dr. Gasior, who signed a warrant on November 6, 2014, that the review revealed no new potential adverse safety findings associated with lisdexamfetamine dimesylate. Shire concluded that the benefit-risk profile remains unchanged.

9.2 Labeling Recommendations

Section 1.2 (Indications and Usage/BED) - A Limitation of Use should be added to help insure that Vyvanse is not used as a weight loss product. The following language is suggested:

1.2 Binge Eating Disorder (BED)

Vyvanse is indicated for the treatment of moderate to severe BED in adults. The effectiveness of Vyvanse for long-term use in BED, i.e., for more than 12 weeks, has not been systematically evaluated in controlled trials.

Limitation of Use

The safety and effectiveness of Vyvanse as a weight loss product has not been adequately studied. Vyvanse should not be used for weight reduction.

This limitation of use should also be included under the Indications and Usage subsection of Highlights.

Section 8.4 (Pediatric Use) - Should clearly state that Vyvanse for the treatment of BED has not been studied in children.

9.3 Advisory Committee Meeting

This supplement was not taken to an Advisory Committee.

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/s/

GREGORY M DUBITSKY
01/09/2015

JING ZHANG
01/11/2015



Shari L. Targum, M.D.
Division of Cardiovascular and Renal Products

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: January 8, 2015

FROM: Shari L. Targum, M.D., Clinical Team Leader
Division of Cardiovascular and Renal Products

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products

TO: Hiren D. Patel, Pharm.D., Regulatory Project Manager, Division of Psychiatry Products
Gregory Dubinsky, M.D., Medical Officer, Division of Psychiatry Products

SUBJECT: NDA #21977/S-037
NAME OF PRODUCT: lisdexamfetamine or SPD489
TRADE NAME: Vyvanse®
FORMULATION: oral

RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: Attention-deficit hyperactivity disorder
SPONSOR: [REDACTED] (b) (4)

DOCUMENTS AVAILABLE FOR REVIEW: Consult request form; Supplement 037 (via electronic document room)

DATE CONSULT RECEIVED: 12 December 2014
DESIRED COMPLETION DATE: 9 January 2015
DATE CONSULT COMPLETED: 8 January 2015

REASON FOR CONSULTATION: We have been asked to address the following: 1. Evaluate the magnitude of cardiovascular risk of Vyvanse® in patients with binge eating disorder (BED) in view of the sponsor's Phase 2/3 clinical program; 2. Recommend any further pre-approval work-up or Postmarketing Requirements (PMRs) that should be requested to more fully characterize the cardiovascular risk/benefit ratio of Vyvanse® in this population.

BACKGROUND:
Vyvanse®, or lisdexamfetamine dimesylate, a prodrug of dextroamphetamine, is currently marketed for the treatment of attention-deficit hyperactivity disorder in patients over six years of age. The current package insert for Vyvanse® contains a boxed warning for a high abuse potential, in addition to warnings for cardiovascular risk and increases in heart rate and blood pressure.

The first and second bullets in the Warnings and Precautions section contain the following respective cardiovascular risk information:

- “*Serious Cardiovascular Reactions*: Sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke and myocardial infarction in adults reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease.”
- “*Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic.”

The BED clinical program included four studies (see Table 1, below): one Phase 2 dose-finding trial (study 208), two Phase 3, twelve-week placebo-controlled trials (studies 343 and 344) and one Phase 3, 12-month, ongoing, open-label extension study (study 345). The study population, adults with moderate to severe BED, was mostly obese and female. In the Phase 3 placebo-controlled trials, increases in systolic and diastolic blood pressure (on average about 2-3 mm Hg versus placebo) and heart rate (5.4 beats per minute [bpm] on drug versus 1.8 bpm on placebo) were observed. These changes were not clearly dose-related but tended to persist over time (12 weeks). In these trials, Vyvanse® also produced significant weight reduction and decreased fasting triglyceride levels. If approved, patients with BED are likely to take Vyvanse® for several months to years.

Please note that SPD489 and Vyvanse® are used interchangeably in this review.

| Table 1: Phase 2/3 Studies Presented in Support of the Safety of SPD489 for the Treatment of Binge Eating Disorder | | | | | |
|---|--|--|------------------------------|-----------------------|--|
| Study / Phase / Design / Status | Randomized Treatment Arms | SPD489 Titration Schedule^a | Optimized Dose Levels | Study Duration | Total Subjects in Safety Analysis Set^b |
| SPD489-208 Phase 2 Randomized, double-blind Completed | Placebo SPD489 30mg SPD489 50mg SPD489 70mg | Week 1: 30mg Week 2: 50mg (only for those subjects randomized to 50 or 70mg) Week 3: 70mg (only for those subjects randomized to 70mg) Weeks 4-11: SPD489 30mg, 50mg or 70mg (fixed dose as randomized) | Not applicable | 11 weeks | 259 ^c |
| SPD489-343 Phase 3 Randomized, double-blind Completed | Placebo SPD489 | Week 1: 30mg Week 2: 50mg Week 3: 50 or 70mg Weeks 4-12: SPD489 50mg or 70mg (optimized dose) | 50mg or 70mg | 12 weeks | 379 |

| Table 1: Phase 2/3 Studies Presented in Support of the Safety of SPD489 for the Treatment of Binge Eating Disorder | | | | | |
|---|----------------------------------|--|------------------------------|-----------------------|--|
| Study / Phase / Design / Status | Randomized Treatment Arms | SPD489 Titration Schedule^a | Optimized Dose Levels | Study Duration | Total Subjects in Safety Analysis Set^b |
| SPD489-344 Phase 3 Randomized, double-blind Completed | Placebo SPD489 | Week 1: 30mg Week 2: 50mg Week 3: 50 or 70mg Weeks 4-12: SPD489 50mg or 70mg (optimized dose) | 50mg or 70mg | 12 weeks | 366 ^c |
| SPD489-345 ^d All SPD489, open-label Ongoing | Not applicable | Week 1: 30mg Week 2: 50mg Week 3: 50 or 70mg Weeks 4-52: SPD489 50mg or 70mg (as tolerated) | 50mg or 70mg | 52 weeks | 599 ^e |

^a Subjects randomized to placebo were titrated in the same manner as SPD489 subjects in order to maintain the blind.

^b The Safety Analysis Set includes all randomized or enrolled subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

^c All 11 subjects enrolled at Site 015 were excluded from the Safety Analysis Set.

^d Ongoing study enrolling subjects who completed 1 of the 3 antecedent studies. Number of subjects in the Safety Analysis Set is based on data available as of the cutoff date of 28 Feb 2014.

^e As of the data cutoff date (28 Feb 2014), a total of 604 subjects had enrolled in SPD489-345: 52 subjects had completed this study, 188 had discontinued, and 364 were ongoing (refer to the [ISS, Module 5.3.5.3, Table 1.2.1](#)).

Note: Number of subjects in Safety Analysis Set for SPD489-208 obtained from [SPD489-208 CSR Addendum](#) (located in Module 5.3.5); numbers of subjects in the Safety Analysis Set for other studies obtained from the respective CSRs (also located in Module 5.3.5).

Subjects were excluded if they had a history of moderate to severe hypertension or elevated blood pressure at screening or baseline. Subjects with diabetes were also excluded; additional cardiac exclusions included a “known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormality, coronary artery disease, known family history of sudden cardiac death or ventricular arrhythmia or clinically significant ECG prior to the baseline visit.” Thus, the Phase 3 controlled studies were designed to enroll subjects at lower risk for cardiovascular events.

Use of caffeine and tobacco was permitted; in study 343 about 14% of placebo and 16% of SPD489 subjects were active smokers, and in study 344 about 16% of placebo and 12% of SPD489 subjects were active smokers.

A total of 79% of subjects in placebo and SPD489 completed the phase 3 controlled studies and 21% in both placebo and SP489 discontinued prematurely.

Across the studies, the mean age ranged from 37 to 39 years (relatively young compared to a more typical coronary artery disease population, where the incidence increases with age); the highest proportions of study subjects were female (>75%), White (>70%), and obese (>66%). The mean BMI ranged from 33.3 to 35.1 kg/m² and 20% were morbidly obese.

Deaths: One subject (study 208) died (verbatim term: methamphetamine and amphetamine toxicity). The postmortem toxicology report showed methamphetamine and amphetamine levels consistent with methamphetamine overdose.

Serious adverse events (SAE): Among 569 subjects in the SPD489 group, SAE occurred in 7 subjects. Two subjects had syncope. One SAE was fatal as noted above. Other SAEs occurred in a single subject each and included pancreatitis, appendicitis, cholecystitis, and lumbar vertebral fracture. Except for the case of appendicitis, each of these events led to discontinuation from the study. In the placebo group (N=435), 4 subjects experienced 6 treatment-emergent SAEs, including conversion disorder, anaphylactic reaction, agitation and anxiety (one subject), and syncope/fibula fracture (one subject). All 4 subjects were discontinued from the study. There appears to be no cardiovascular SAE signal, based on these few events.

Table 14: Cardiovascular Events of Special Interest Occurring in 2 or More SPD489 Subjects - Presented for the Combined Placebo-controlled Studies (Safety Analysis Set)

| AESI SubCategory Preferred Term | SPD489-208/-343/-344 | |
|--------------------------------------|-----------------------------|---|
| | Placebo (N=435) n (%) | SPD489 All Doses (N=569) n (%) |
| Vasculitis/Raynaud's Syndrome | 2 (0.5) | 11 (1.9) |
| Paraesthesia | 2 (0.5) | 10 (1.8) |
| Syncope | 1 (0.2) | 7 (1.2) |
| Hypotension | 0 | 4 (0.7) |
| Syncope | 1 (0.2) | 2 (0.4) |
| Angina/Ischemia | 3 (0.7) | 4 (0.7) |
| Chest Discomfort | 1 (0.2) | 2 (0.4) |

Note: Percentages are based on all subjects in the Safety Analysis Set.

Note: Subjects were counted once per category and preferred term.

Note: This table only includes AESI categories and events (based on Preferred Term) that were reported for 2 or more subjects in the SPD489 group.

Note: AESI categories are ordered by decreasing frequency based on the SPD489 All Doses Group. Similarly, Preferred Terms within each category are ordered by decreasing frequency based on the SPD489 All Doses Group.

AESI = adverse event of special interest

Source: [Module 2.7.4, Section 2.1.6.1](#) and [Module 5.3.5.3 \(ISS\), Table 4.1.2.12](#).

Except for vasculitis/Raynaud's Syndrome (paresthesia) and syncope (including hypotension, with seemingly counterintuitive results), the cardiovascular event rates are low in both active drug and placebo groups, limiting the meaningfulness of any conclusions. Possible reasons for these low event rates include: enrollment of a "less vulnerable" study population, a sample size underpowered to detect such a signal, or inadequate study duration.

Table 15: Vital Signs Events of Special Interest Occurring in 2 or More SPD489 Subjects - Presented for the Combined Placebo-controlled Studies (Safety Analysis Set)

| AESI SubCategory Preferred Term | SPD489-208/-343/-344 | |
|------------------------------------|-----------------------------|---|
| | Placebo (N=435) n (%) | SPD489 All Doses (N=569) n (%) |
| | n (%) | |
| Tachycardia | 5 (1.1) | 34 (6.0) |
| Heart Rate Increased | 5 (1.1) | 23 (4.0) |
| Tachycardia | 0 | 12 (2.1) |
| Increased Blood Pressure | 10 (2.3) | 24 (4.2) |
| Blood Pressure Increased | 7 (1.6) | 16 (2.8) |
| Blood Pressure Diastolic Increased | 1 (0.2) | 3 (0.5) |
| Hypertension | 2 (0.5) | 3 (0.5) |

Note: Percentages are based on all subjects in the Safety Analysis Set.

Note: Subjects were counted once per category and preferred term.

Note: This table only includes AESI categories and events (based on Preferred Term) that were reported for 2 or more subjects in the SPD489 group.

Note: AESI categories are ordered by decreasing frequency based on the SPD489 All Doses Group. Similarly, Preferred Terms within each category are ordered by decreasing frequency based on the SPD489 All Doses Group.

AESI = adverse event of special interest

Source: [Module 2.7.4, Section 2.1.6.1](#) and [Module 5.3.5.3 \(ISS\), Table 4.1.2.12](#).

According to the sponsor, among the 569 subjects in the SPD489 group, small mean increases from baseline in systolic BP and DBP (approx. 1 mm Hg) were seen at all visits; among the 436 placebo subjects, small decreases from baseline in systolic and diastolic BP (1-3 mm Hg) were seen at most visits. Mean increases from baseline in pulse rate (5-7 bpm) were seen in the SPD489 group at most visits. From Week 2 onward, the mean increases in the SPD489 group were about 3-4 bpm higher than those in the placebo group.

Increases in pulse rate and blood pressure have been noted previously, since these findings appear as warnings in the package insert.

| Table 9: Summary of Treatment-emergent Adverse Events Across Combined Placebo-controlled Studies (Safety Analysis Set) | | |
|---|--------------------------------------|---|
| Category of TEAE | SPD489-208/-343/-344 | |
| | Placebo (N=435) n (%) | SPD489 All Doses (N=569) n (%) |
| Any TEAE | 241 (55.4) | 464 (81.5) |
| Related TEAEs ^a | 146 (33.6) | 401 (70.5) |
| Severe TEAEs | 15 (3.4) | 33 (5.8) |
| TEAEs Leading to Dose Discontinuation | 9 (2.1) | 25 (4.4) |
| Serious TEAE | 4 (0.9) | 7 (1.2) |
| Deaths | 0 | 1 (0.2) |

^a An AE was considered to be related to the investigational product based on assessment by the investigator.

Note: Percentages are based on all subjects in the Safety Analysis Set.

Note: Subjects were counted once per category per treatment.

Note: An AE was considered treatment-emergent if it had a start date on or after the first dose of double-blind investigational product or if it has a start date before the date of the first dose of double-blind investigational product, but increased in severity on or after the date of the first dose of double-blind investigational product. An AE that occurs more than 3 days after the date of the last dose of double-blind investigational product was not counted as a TEAE.

Note: Dose discontinuation also resulted in discontinuation from the study.

AE=adverse event; TEAE = treatment-emergent adverse event

The most commonly reported adverse events were those associated with gastrointestinal, psychiatric and nervous system disorders. The most commonly reported adverse events (active drug higher than placebo) were drug mouth, headache, insomnia, and decreased appetite.

Table 10: Treatment-emergent Adverse Events Occurring in $\geq 5\%$ of SPD489 Subjects Across Combined Placebo-controlled Studies (Safety Analysis Set)

| Preferred Term | SPD489-208/-343/-344 | |
|--------------------|-----------------------------|---|
| | Placebo (N=435) n (%) | SPD489 All Doses (N=569) n (%) |
| Any TEAE | 241 (55.4) | 464 (81.5) |
| Dry mouth | 32 (7.4) | 207 (36.4) |
| Headache | 39 (9.0) | 81 (14.2) |
| Insomnia | 21 (4.8) | 78 (13.7) |
| Decreased appetite | 13 (3.0) | 70 (12.3) |
| Nausea | 22 (5.1) | 47 (8.3) |
| Irritability | 23 (5.3) | 36 (6.3) |
| Constipation | 6 (1.4) | 35 (6.2) |
| Fatigue | 21 (4.8) | 31 (5.4) |
| Feeling jittery | 2 (0.5) | 30 (5.3) |
| Anxiety | 3 (0.7) | 29 (5.1) |

Note: Percentages are based on all subjects in the Safety Analysis Set

Note: Subjects were counted once per Preferred Term.

Note: TEAEs are ordered by decreasing frequency based on the SPD489 All Doses Group.

Source: [Module 5.3.5.3 \(ISS\), Table 4.1.2.2.8](#)

COMMENTS:

1. Evaluate magnitude of cardiovascular risk of Vyvanse® in patients with binge eating disorder (BED) in view of the sponsor's Phase 2/3 clinical program.

The BED phase 2/3 program included a short-term (11-12 week) randomized, double-blind period and excluded high-risk patients (e.g., diabetes, patients with coronary artery disease). The study results do not reveal a cardiovascular safety signal. However, the low cardiovascular event rates, including low event rates in the placebo group, limit any reassurance in these results.

It is also difficult to quantify the magnitude of cardiovascular risk given the low cardiovascular event rates in the available placebo-controlled studies. Use of BP curves to estimate cardiovascular risk might, perhaps incorrectly, assume that this drug has no other cardiovascular effect. It is not clear whether other risk assessment tools such as the Framingham (10-year) risk score (which has been modified over decades and uses multiple variables such as systolic BP, smoking use, and total cholesterol) have a useful role with regard to calculating cardiovascular risk of Vyvanse® use. Based on previous outcome study experience, it would be difficult to predict the net result of alternations to various risk factors (e.g., increased BP and HR but reductions in lipids and weight); however, we have yet to see a reduction in cardiovascular risk resulting from weight reduction.

2. Further pre-approval workup or PMR to characterize cardiovascular risk

1. Vyvanse®, a stimulant, already carries warnings for serious cardiovascular reactions and blood pressure and heart rate increases for the ADHD indication. It is reasonable to assume that the cardiovascular risk will not be eliminated when Vyvanse® is administered to the binge eating

disorder population, particularly when taken chronically by those at elevated cardiovascular risk (e.g., diabetes and/or other cardiovascular risk factors).

2. What really matters is the absolute risk in higher-risk subsets, compared with benefits perceived. If the condition being treated seems debilitating, benefits might make life markedly better for those with modest risk.
3. The risks could be addressed to some extent, if necessary, through monitoring and treating blood pressure, limiting treatment duration, and avoiding use in patients at particularly high baseline risk. These strategies could be appropriately communicated to prescribers via labeling (and perhaps other risk communication mechanisms). We recommend this approach.

Thank you. If you have any further questions please feel free to contact us.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARI L TARGUM
01/09/2015

NORMAN L STOCKBRIDGE
01/09/2015

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

DATE: November 7, 2014

FROM: Julie Golden, M.D.

SUBJECT: Consult for Division of Psychiatry Products

TO: Hiren Patel, Pharm.D.

THROUGH: James Smith, M.D., M.S., Deputy Division Director (Acting)

Introduction

DPP is reviewing lisdexamfetamine, a prodrug of dextroamphetamine, for the treatment of binge eating disorder (BED) in adults. Lisdexamfetamine is currently marketed as Vyvanse for the treatment of attention-deficit hyperactivity disorder (ADHD). DPP noted the following in their review, and have asked for DMEP's input:

The BED clinical program is comprised of four studies: one Phase 2 dose-finding trial (208), two Phase 3 12-week placebo-controlled trials (343 and 344), and one Phase 3 12-month open-label extension study (345). BED subjects were mostly obese and female. In Phase 2/3 placebo-controlled trials (11-12 weeks in duration), there was one report of cholecystitis and another of cholelithiasis on drug (N=569) and none on placebo (N=435). In the 12-month study, there were 4 reports of cholecystitis and one of cholelithiasis, all on drug (N=599). Most of these cases were classified as serious. In short-term trials, SPD489 caused appreciable weight loss and reduced fasting triglyceride and total cholesterol levels. In view of these reports, the possibility that drug-related cholecystitis may have a delayed time to symptom onset, the BED sample studied, and the propensity of SPD489 to decrease weight, triglycerides, and total cholesterol, please provide your opinion as to whether SPD489 may be causally related to the cases of cholecystitis and cholelithiasis. If a causal link is plausible, please suggest language for labeling this risk.

Background

Lisdexamfetamine is a prodrug of dextroamphetamine, a non-catecholamine sympathomimetic amine that acts as a stimulant in the central nervous system. It is believed to exert its effects by blocking reuptake of dopamine and norepinephrine at nerve terminals. Lisdexamfetamine is

approved as Vyvanse for ADHD at a dose range of 20 to 70 mg daily. Decreased appetite and weight loss are described adverse reactions in the Vyvanse label.

In the clinical program evaluating lisdexamfetamine for BED, adverse events of cholelithiasis and cholecystitis were noted in association with the drug. This finding has not been previously described with Vyvanse (as per the prescribing information) and a literature search of 'lisdexamfetamine' or 'amphetamine' and 'gallstone' or 'cholelithiasis' did not reveal any relevant articles.

Gallstones are very common in adults in Western societies. Estimates range from 10 to 20% of the adult population that have or will have gallstones; of these, 20% are estimated to develop symptoms (biliary pain) or complications (e.g., acute cholecystitis, cholangitis, or pancreatitis).¹ Gallstones are diagnosed with ultrasonography, and when symptomatic, are generally treated with cholecystectomy.

Gallstones are classified by their composition; the majority of gallstones are 'cholesterol' stones indicating cholesterol content of $\geq 70\%$.² Conditions that support formation of gallstones include cholesterol supersaturation of bile, pronucleating factors exceeding antinucleating factors (such as bile salt concentrations), and decreases in gallbladder motility.³ Risk factors for cholesterol stone formation include female sex, increasing age, genetics/ethnicity (prevalence highest in Native Americans), obesity, and rapid weight loss. Metabolic disorders associated with abdominal obesity such as insulin resistance, hypertriglyceridemia, and low HDL-cholesterol have been described in association with cholelithiasis, but the independent effects of each of these factors in the pathogenesis is unclear.⁴ Obesity is associated with increased saturation of cholesterol in the bile and this is thought to be increased during weight loss. Gallstone development during 8 to 16 weeks of weight loss with a very low calorie diet (~500 kcal/day; ~2 kg body weight loss/week) has been reported to range from 11 to 26%.^{5,6,7} It has been suggested that rates of weight loss above 1.5 kg/week are associated with "dramatically" higher rates of gallstone formation than rates below 1.5 kg/week.⁸ In addition, and perhaps relevant to a population of patients with binge eating disorder, weight cycling has been suggested as a possible risk factor for gallstones, independent of BMI.^{9,10}

¹ Stinton LM and Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver*. 2012; 6(2): 172-87.

² Qiao T, et al. The systematic classification of gallbladder stones. *PLoS One*. 2013; 8(10): e74887.

³ Gurusamy KS and Davidson BR. Gallstones. *BMJ*, 2014; 348: g2669.

⁴ Shaffer EA. Epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol*. 2006; 20(6): 981-96.

⁵ Broomfield PH, et al. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. *N Engl J Med*. 1988; 319: 1567-72.

⁶ Yang H, et al. Risk factors for gallstone formation during rapid loss of weight. *Dig Dis Sci*. 1992; 37(6): 912-8.

⁷ Little RA, et al. Gallstone formation during weight-reduction dieting. *Arch Intern Med*. 1989; 149: 1750-3.

⁸ Weinsier RL, et al. Medically safe rate of weight loss for the treatment of obesity: a guideline based on risk of gallstone formation. *Am J Med*. 1995; 98: 115-7.

⁹ Syngal S, et al. Long-term weight patterns and risk for cholecystectomy in women. *Ann Intern Med*. 1999; 130(6): 471-7.

¹⁰ Tsai CJ, et al. Weight cycling and risk of gallstone disease in men. *Arch Intern Med*. 2006; 166(21): 2369-74.

Drugs may have effects on gallstone formation via their effects on body weight or lipid metabolism, or via changes in gallbladder motility. For example, fibrates are thought to be lithogenic; however, statins are not.¹¹ Orlistat has been described to increase the risk of gallstones;¹² it is unclear if this is related to weight loss or independent effects on gallbladder motility.¹³ Similarly, liraglutide (approved for treatment of type 2 diabetes; currently under review for treatment of obesity) was associated with a greater incidence of acute gallbladder disease (cholelithiasis and cholecystitis) in trials in obese patients.¹⁴

Lisdexamfetamine Efficacy Supplement

The lisdexamfetamine BED clinical development program includes data from 4 trials, including one phase 2 trial, two phase 3 trials, and one open-label extension (for patients who completed one of the 3 prior trials):

Table 1. Studies in the BED Clinical Development Program

| Study Type | Study Identifier/ Location of Study Report | Primary Study Objective | Study Design and Type of Control | Investigational Product: Dosage Regimen, Route of Administration | Number of Subjects Enrolled | Diagnosis (Population) | Duration of Treatment | Study Status; Type of Report |
|--------------------------|--|--|---|--|--|------------------------------|-----------------------|------------------------------|
| Completed Studies | | | | | | | | |
| Efficacy | SPD489-208 ^a 5.3.5.1 | Evaluate efficacy of SPD489 compared to placebo based on number of binge days per week as assessed by clinical interview based on diary data | Phase 2 dose-finding, proof of concept study, which used a randomized, double-blind, placebo-controlled, parallel-group study design. This study consisted of a screening period, a double-blind treatment phase (including forced-dose titration and dose-maintenance periods), and a follow-up phone call. | <i>SPD489</i> 30, 50, and 70mg oral, once daily capsules <i>Placebo</i> oral, once daily capsules | 260 (placebo, 64; SPD489 30mg, 66; SPD489 50mg, 65; SPD489 70mg, 65) | BED (adults, 18 to 55 years) | 11 weeks | Complete; Full |

¹¹ Caroli-Bosc FX, et al. Role of fibrates and HMG Co-A reductase inhibitors in gallstone formation: epidemiological study in an unselected population. *Dig Dis Sci*. 2001; 46(3): 540-4.

¹² Xenical prescribing information

¹³ Mathus-Vliegen EMH, et al. *Aliment Pharmacol Ther*. 2004; 19: 601-11.

¹⁴ Liraglutide EMDAC briefing information 11 Sep 2014.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs/AdvisoryCommittee/ucm413316.htm>

| Study Type | Study Identifier/ Location of Study Report | Primary Study Objective | Study Design and Type of Control | Investigational Product: Dosage Regimen, Route of Administration | Number of Subjects Enrolled | Diagnosis (Population) | Duration of Treatment | Study Status; Type of Report |
|-------------------------|--|---|--|--|---------------------------------|---|-----------------------|------------------------------|
| Efficacy | SPD489-343 5.3.5.1 | Demonstrate efficacy of SPD489 compared to placebo based on number of binge days per week as assessed by clinical interview based on diary data | Phase 3 double-blind, randomized, placebo-controlled, parallel-group, dose-optimization study. This study consisted of a screening phase, a double-blind treatment phase (including dose-optimization and dose-maintenance periods), and a follow-up visit. | SPD489 30 ^b , 50, and 70mg oral, once daily capsules Placebo oral, once daily capsules | 383 (placebo, 191; SPD489, 192) | BED (adults, 18 to 55 years) | 12 weeks | Complete; Full |
| Efficacy | SPD489-344 5.3.5.1 | Demonstrate efficacy of SPD489 compared to placebo based on number of binge days per week as assessed by clinical interview based on diary data | Phase 3 double-blind, randomized, placebo-controlled, parallel-group, dose-optimization study. This study consisted of a screening phase, a double-blind treatment phase (including dose-optimization and dose-maintenance periods), and a follow-up visit. | SPD489 30 ^b , 50, and 70mg oral, once daily capsules Placebo oral, once daily capsules | 390 (placebo, 195; SPD489, 195) | BED (adults, 18 to 55 years) | 12 weeks | Complete; Full |
| Ongoing Studies | | | | | | | | |
| Safety and Tolerability | SPD489-345 ^c 5.3.5.2 | Evaluate long-term safety and tolerability of SPD489 based on TEAEs; the C-SSRS; and blood pressure, pulse, weight, waist circumference, clinical laboratory evaluations, and ECG results | Phase 3 open-label extension study. This study consists of a screening period, a dose-optimization period, a dose-maintenance period, and a follow-up visit. | SPD489 30 ^b , 50, and 70mg oral, once daily capsules | 604 (as of 28 Feb 2014) | BED (adults, 18 to 55 years) ^d | 52 weeks | Ongoing; Preliminary |

Source: Tabular Listing of Clinical Studies – SPD489, Table 1

Clinical Findings

At baseline, across the phase 2 and 3 trials, the mean age was 38.7 years. The majority of patients were female (86%) and white (76%). Mean weight was 95 kg and ranged from 49 to 176 kg; mean BMI was 34 kg/m² and ranged from 20 to 45 kg/m². The majority (71%) of patients were obese (BMI ≥ 30 kg/m²).

In the controlled phase 2 and 3 trials (208, 343, and 344), 569 patients received active drug and 435 patients received placebo. Including the open label extension (trial 345), a total of 833 patients received any dose of active drug (N=599 in trial 345).

Seven events were identified of interest, related to or potentially related to gallstones, all in patients treated with active drug (7/833, 0.8%). Two events occurred in the randomized controlled periods (2/569, 0.4% lisdexamfetamine vs. 0/435 placebo) and five occurred in the open label extension (5/599, 0.8%). Patients with adverse events were females 24 to 49 years

of age; 5 were white, 2 were black. All patients were obese (BMI 34 to 44 kg/m²). A summary of the adverse events is presented in the table below:

Table 2. Summary of Patients with Adverse Events of Interest, Safety Analysis Set

| Trial | Patient | Sex/age/race/BMI BL chol/TG | Dose | PT | Severity | Serious | Action | Outcome | Study Day |
|-------|--------------------|--------------------------------|------|------------------------|----------|---------|---------------------|--------------------------------------|------------------------|
| 208 | SPD489208-012-0023 | F/49/B/43.9 192.2/95.7 | 30 | PANCREATITIS ACUTE | SEVERE | Y | DRUG WITHDRAWN | RECOVERED/ RESOLVED | 58 |
| 343 | SPD489343-095-3001 | F/32/W/42.6 251.4/110.7 | 70 | CHOLECYSTITIS | SEVERE | Y | DRUG WITHDRAWN | NOT RECOVERED/ NOT RESOLVED | 82 |
| 345 | SPD489208-032-0012 | F/43/W/36.0 234.3/208.1 | 50 | CHOLECYSTITIS | MODERATE | N | DOSE NOT CHANGED | RECOVERED/ RESOLVED | 309 |
| 345 | SPD489343-052-3006 | F/24/W/43.2 224.3/205.5 | 30 | CHOLECYSTITIS ACUTE | SEVERE | Y | DOSE NOT CHANGED | RECOVERED/ RESOLVED | 2 (+ 83d in RCT) |
| 345 | SPD489343-066-3016 | F/42/W/33.6 143.1/97.4 | 70 | CHOLECYSTITIS ACUTE | SEVERE | Y | DRUG WITHDRAWN | RECOVERED/ RESOLVED | 172 |
| 345 | SPD489344-027-4004 | F/47/W/40.6 231.2/64.7 | 70 | CHOLELITHIASIS | MILD | N | DOSE NOT CHANGED | NOT RECOVERED/ NOT RESOLVED | 69 |
| 345 | SPD489344-102-4007 | F/48/B/36.6 178.3/408.3 | 70 | CHOLECYSTITIS | SEVERE | Y | DOSE NOT CHANGED | RECOVERED/ RESOLVED | 121 |

Source: ISS AE Datasets

Narratives for the SAEs are presented below (patient-level weight profiles are shown in Figure 2):

- Patient SPD489208-012-0023 was a 49-year-old black female with a baseline BMI of 44 kg/m² randomized to 30 mg of active treatment. She presented to the emergency department after approximately 1 month of treatment with mid-epigastric pain and was admitted with pancreatitis. Laboratory tests revealed a lipase level of 1.956u/L (reference range 10-60) [**reviewer comment: value presumed to be 1956 U/L**], lactate dehydrogenase (LDH) level of 236u/L (reference range 60-200), and other chemistries (aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase) were within normal limits. A gallbladder ultrasound showed cholelithiasis without cholecystitis and hepatic steatosis with no ductal enlargement.

The acute pancreatitis was considered by the Investigator to be not related to investigational product, but related to concomitant medication (hydrochlorothiazide) that was introduced 10 days prior to the SAE of acute pancreatitis.

Reviewer comment: Pancreatitis has been described with hydrochlorothiazide (as noted in the Microzide capsules label). Although gallstones were observed in this patient, there was no biliary dilatation seen on abdominal ultrasound. The relationship of the gallstones to pancreatitis is unclear, but considered possible.

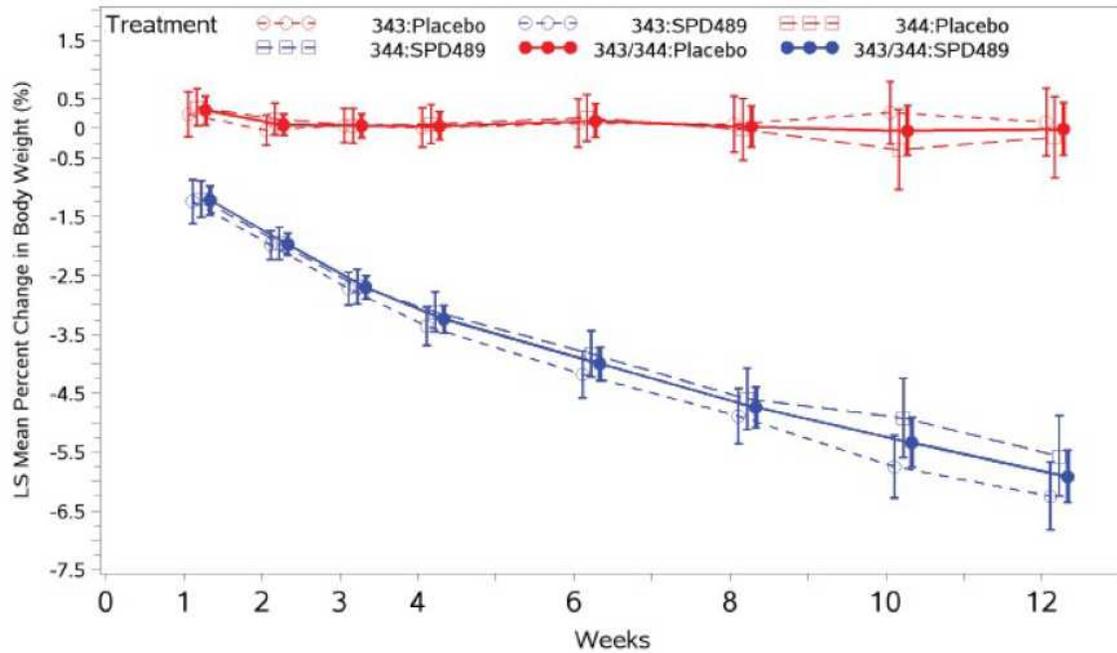
- Patient SPD489343-095-3001 was a 32-year-old white female with a baseline BMI of 42.6 kg/m² randomized to active drug; she was initiated on 30 mg, and then titrated weekly to

50 mg and then 70 mg. Approximately 2 months after being treated at the 70 mg dose, the patient had epigastric pain, nausea, and vomiting, and was admitted to the hospital for a cholecystectomy due to cholecystitis. Investigational product was discontinued due to the event.

- Patient SPD489343-052-3006 was a 24-year-old white Hispanic female with a baseline BMI of 43.2 kg/m². The patient had received active drug in study 343; she enrolled in the open label study (345) 8 days after completing 343. Two days later (while receiving the 30 mg dose), the patient was admitted to the hospital for an “acute gall bladder attack” (PT: cholecystitis acute). She was treated with cholecystectomy and the following day, a remaining gallstone that was stuck in the common bile duct was removed by endoscopy. Therapy with investigational product was continued uninterrupted.
- Patient SPD489343-066-3016 was a 42-year-old white female with a baseline BMI of 33.6 kg/m². The patient had received placebo in study 343; 9 days after completing this trial she enrolled in the open label study (345), during which time she was titrated to 70 mg. On study day 172, the patient was admitted to the hospital for acute cholecystitis. Investigational product was discontinued due to the event.
- Patient SPD489344-102-4007 was a 49-year-old black female with a baseline BMI of 36.6 kg/m². The patient had received placebo in study 344; 8 days later she enrolled in the open label study (345) and was titrated up to the 70 mg dose. On study day 121, the patient had severe abdominal pain and was taken to the emergency room via ambulance. The patient was diagnosed with cholecystitis, and needed to have emergency surgery to remove her gallbladder. Therapy with investigational product was continued uninterrupted.
- Patient SPD489344-027-4004 was a 48-year-old white female with a baseline BMI of 40.6 kg/m². She reported an AE of cholelithiasis on study day 69, which was not considered serious (therefore, there was not a narrative for this event). However, it is noted that she underwent an elective vertical sleeve gastrectomy on study day 189. The patient’s weight fluctuations can be seen in figure 2, below.

Over the 12 weeks of studies 343 and 344 combined, mean weight decreased by -5.92 kg in patients treated with drug, compared with -0.01 kg in patients treated with placebo (difference in LS mean -5.91; 95% CI: -6.54, -5.28). Mean weight over time is presented in Figure 1:

Figure 1. LS Mean (95% CI) Percent Change from Baseline Over Time in Body Weight Presented by Separate and Combined Phase 3 Study and by Treatment Group (Full Analysis Set)



CI=confidence interval; LS=least squares

Source: Summary of Clinical Efficacy, Figure 7

Changes in serum triglycerides (roughly, a 15% decrease from baseline) and serum total cholesterol (roughly, 2 to 4% decrease from baseline) are shown in the tables below; these changes are generally consistent with the weight loss observed.

Table 3. Mean Change from Baseline at Week 12 /ET in Triglycerides Presented by Separate and Combined Phase 3 Study and by Treatment Group (Full Analysis Set)

| Time Point Statistical Parameter | Separate Phase 3 Study | | | | Combined Phase 3 Studies | |
|-------------------------------------|------------------------|-------------------|--------------------|-------------------|-------------------------------|-------------------|
| | Study SPD489-343 | | Study SPD489-344 | | Studies SPD489-343/SPD489-344 | |
| | Placebo (N=184) | SPD489 (N=190) | Placebo (N=176) | SPD489 (N=174) | Placebo (N=360) | SPD489 (N=364) |
| Triglycerides in mmol/L | | | | | | |
| Baseline | | | | | | |
| n | 183 | 190 | 176 | 174 | 359 | 364 |
| mean (SEM) | 1.3 (0.05) | 1.3 (0.05) | 1.3 (0.05) | 1.3 (0.06) | 1.3 (0.03) | 1.3 (0.04) |
| SD | 0.68 | 0.73 | 0.60 | 0.74 | 0.64 | 0.74 |
| Week 12/ET | | | | | | |
| n | 171 | 181 | 153 | 156 | 324 | 337 |
| mean (SEM) | 1.4 (0.06) | 1.3 (0.05) | 1.3 (0.06) | 1.1 (0.06) | 1.4 (0.04) | 1.2 (0.04) |
| SD | 0.82 | 0.70 | 0.78 | 0.76 | 0.80 | 0.73 |
| Change from Baseline at Week 12 | | | | | | |
| n | 170 | 181 | 153 | 156 | 323 | 337 |
| mean (SEM) | 0.1 (0.04) | -0.1 (0.04) | 0.1 (0.04) | -0.1 (0.05) | 0.1 (0.03) | -0.1 (0.03) |
| SD | 0.56 | 0.55 | 0.56 | 0.60 | 0.56 | 0.57 |
| Based on ANCOVA: ^a | | | | | | |
| LS Mean (SEM) | 0.12 (0.04) | -0.08 (0.04) | 0.06 (0.05) | -0.13 (0.04) | 0.09 (0.03) | -0.11 (0.03) |
| Difference in LS Mean | | -0.20 | | -0.20 | | -0.20 |
| 95% CI of the Difference in LS Mean | | -0.31, -0.09 | | -0.32, -0.07 | | -0.28, -0.11 |

^a From an ANCOVA model with change from baseline to Week 12/ET as outcome variable; treatment group and study as a factor and baseline value as a covariate. Difference in LS Means is calculated as SPD489 - Placebo.

Note: The normal reference range for triglycerides is 0 to 1.69mmol/L.

ANCOVA=analysis of covariance; CI=confidence interval; ET=early termination; LS=least squares; SD=standard deviation; SEM=standard error of the mean

Source: Summary of Clinical Efficacy, Table 25

Table 4. Mean Change from Baseline at Week 12/ET in TC Presented by Separate and Combined Phase 3 Study and by Treatment Group (Full Analysis Set)

| Time Point Statistical Parameter | Separate Phase 3 Study | | | | Combined Phase 3 Studies | |
|-------------------------------------|------------------------|-------------------|--------------------|-------------------|-------------------------------|-------------------|
| | Study SPD489-343 | | Study SPD489-344 | | Studies SPD489-343/SPD489-344 | |
| | Placebo (N=184) | SPD489 (N=190) | Placebo (N=176) | SPD489 (N=174) | Placebo (N=360) | SPD489 (N=364) |
| Total Cholesterol in mmol/L | | | | | | |
| Baseline | | | | | | |
| n | 183 | 190 | 176 | 174 | 359 | 364 |
| Mean (SEM) | 5.1 (0.07) | 5.1 (0.07) | 5.0 (0.07) | 5.1 (0.07) | 5.0 (0.05) | 5.1 (0.05) |
| SD | 0.98 | 0.96 | 0.92 | 0.98 | 0.95 | 0.97 |
| Week 12/ET | | | | | | |
| n | 171 | 181 | 153 | 156 | 324 | 337 |
| Mean (SEM) | 5.0 (0.07) | 4.8 (0.06) | 4.8 (0.08) | 4.8 (0.07) | 4.9 (0.05) | 4.8 (0.05) |
| SD | 0.89 | 0.87 | 0.99 | 0.91 | 0.94 | 0.89 |
| Change from Baseline at Week 12 | | | | | | |
| n | 170 | 181 | 153 | 156 | 323 | 337 |
| Mean (SEM) | -0.1 (0.05) | -0.3 (0.05) | -0.1 (0.05) | -0.2 (0.05) | -0.1 (0.04) | -0.3 (0.03) |
| SD | 0.65 | 0.63 | 0.63 | 0.57 | 0.64 | 0.6 |
| <i>Based on ANCOVA:^a</i> | | | | | | |
| LS Mean (SEM) | -0.09 (0.04) | -0.30 (0.04) | -0.13 (0.05) | -0.20 (0.05) | -0.11 (0.03) | -0.26 (0.03) |
| Difference in LS Mean | | -0.21 | | -0.08 | | -0.14 |
| 95% CI of the Difference in LS Mean | | -0.33, -0.09 | | -0.20, 0.05 | | -0.23, -0.06 |

^a From an ANCOVA model with change from baseline to Week 12/ET as outcome variable; treatment group and study as a factor and baseline value as a covariate. Difference in LS Means is calculated as SPD489 - Placebo.

Note: The normal reference range for total cholesterol is 0 to 5.17mmol/L.

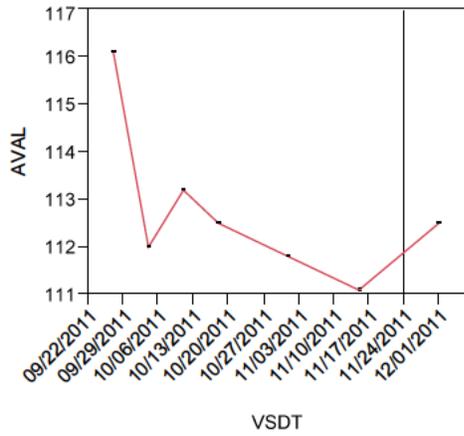
ANCOVA=analysis of covariance; CI=confidence interval; ET=early termination; LS=least squares; SD=standard deviation; SEM=standard error of the mean

Source: Summary of Clinical Efficacy, Table 26

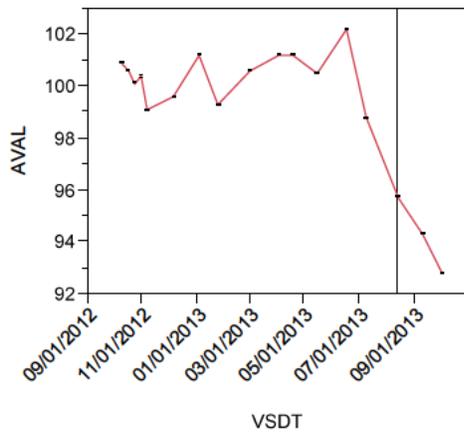
The trajectory of weight for each patient with an AE of interest over the course of the trial is shown in the figures below; the date of the AE of interest is identified with the vertical reference line for each patient:

Figure 2. Body Weight Over Time, Patients with AEs of Interest

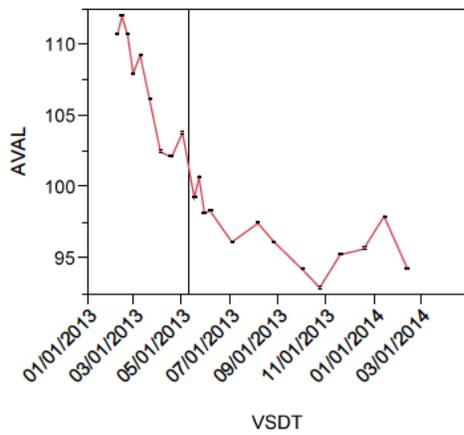
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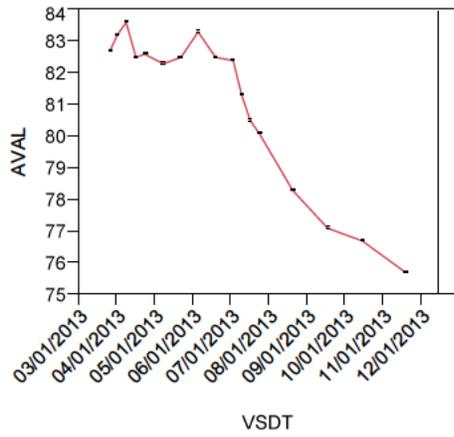
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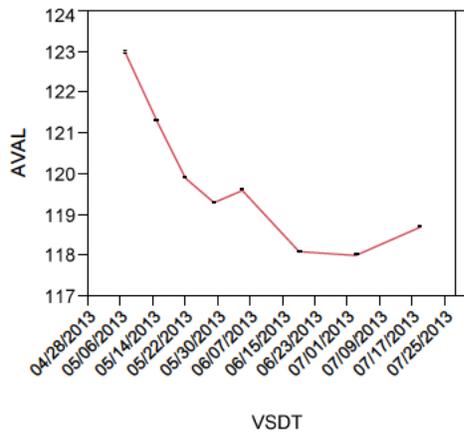
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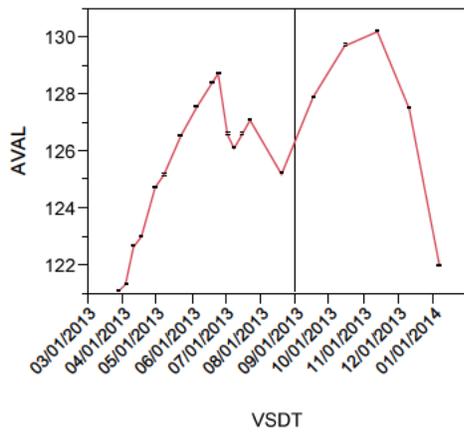
SPD489343-066-3016



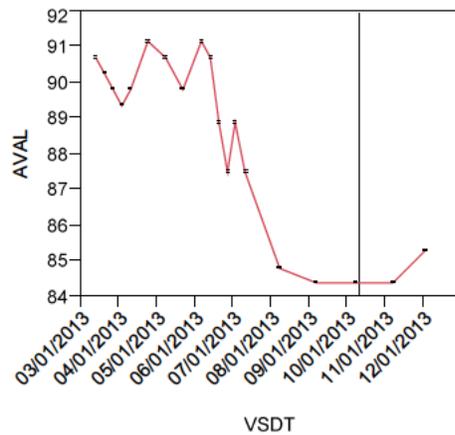
SPD489343-095-3001



SPD489344-027-4004



SPD489344-102-4007



Source: ISS VS datasets

Reviewer comment: *Most patients lost body weight prior to the adverse event, which could be consistent with, although not definitive proof of, an association between weight loss due to study drug and the adverse event.*

Summary and Recommendations

A number of adverse events of cholelithiasis or its complications (cholecystitis and potentially pancreatitis) were noted in the clinical development program for lisdexamfetamine in the treatment of binge eating disorder. The studied patient population is at risk for gallstones: female and obese; perhaps even binge eating is a risk factor. In addition, weight loss can increase risk. It is plausible that lisdexamfetamine, via its effects on dietary intake and weight, may increase the risk of cholelithiasis in this patient population that is already predisposed to gallstones. Because patients did not have baseline evaluations for gallstones, it is unknown if these patients with adverse events had cholelithiasis prior to receiving active treatment. Of note, the degree of lipid alterations associated with this drug is consistent with its effect on weight; an independent effect on lipid metabolism is unknown but seems less likely. A mechanism whereby amphetamines or amphetamine congeners might have independent effects on gallbladder motility is unknown and cannot be established without dedicated study.

For products in our division that have been associated with gallstone-related adverse events in clinical trials (obesity drugs and fibrates), the risk is labeled in Warnings and Precautions. This is because (1) there is a plausible causal link, and (2) complications can be serious or even life-threatening, and early recognition of signs/symptoms related to gallbladder disease might mitigate the risks of serious morbidity. Addressing gallstone-related adverse events with lisdexamfetamine in labeling for binge-eating disorder should be consistent with this approach, given similar considerations.

Recommendations:

1. Consider describing “Acute Gallbladder Disease” in the W&P section of the label, and include the adverse event data from the clinical trials. We would recommend including a statement for risk mitigation, such as, “If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.”

If weight loss is described in the adverse reactions section, you could consider including a statement that weight loss can be associated with the development of gallstones. (b) (4)



2. Consider consulting OSE for an assessment of post-marketing reports of gallstone-related disease, including cholecystitis, cholangitis, and pancreatitis with Vyvanse. Post-marketing reports, prior to inclusion in labeling and prior to approval in the BED population (both of which might lead to stimulated reporting and complicate the interpretation of these reports), would be informative and could further guide labeling or post-marketing evaluation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE K GOLDEN
11/12/2014

JAMES P SMITH
11/12/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---------------|--|-----|----|----|---------------------------|
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 SPD489-343 Phase 3, MC, R, DB, PG, PC, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years with Moderate to severe BED Indication: BED Pivotal Study #2 SPD489-344 Phase 3, MC, R, DB, PG, PC, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years with Moderate to severe BED Indication: BED | X | | | BED=Binge Eating Disorder |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | X | | | SCE page125. |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | X | | | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | | | X | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | | | X | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-----------------------------|--|------------|-----------|-----------|----------------------|
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | X | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | | | X | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | X | Most sites were U.S. |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|---------|
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None identified at this point in time from a clinical standpoint.

[See electronic signature]

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Reviewing Medical Officer

Date

[See electronic signature]

[See electronic date]

Clinical Team Leader

Date

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/s/

GREGORY M DUBITSKY
08/08/2014

JING ZHANG
08/11/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DATE: 5 JAN 2015

TO: NDA 21977 /S-37

THROUGH: Hasmukh Patel Ph.D., Branch Chief, ONDQA/DNDQA-1

FROM: David J. Claffey, Ph.D., CMC Lead, ONDQA/DNDQA-1

SUBJECT: CMC assessment of efficacy supplement for treatment of Binge Eating Disorder

The supplement does not provide for any changes to the drug product, manufacturing process, or specifications and there are no CMC-related labeling changes. A claim for categorical exclusion under 21 CFR Part 25.31(b) is included in the submission.

Recommend approval of this application from a CMC perspective.

David J. Claffey
-S

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ou=FDA, ou=People,
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cn=David J. Claffey -S
Date: 2015.01.05 15:09:39 -05'00'

For Hasmukh Patel:

Nallaperumal
Chidambaram -S

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MARY GRACE LUBAO
02/10/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #: 21,977

Supplement #: 37

Drug Name: VYVANSE (Lisdexamfetamine dimesylate, SPD489) 30 mg, 50 mg and 70 mg capsules

Indication(s): Binge Eating Disorder (BED)

Applicant: Shire Development Inc.

Date(s): Submitted: 08/01/2014
PDUFA due date: 02/01/2015

Review Priority: Priority

Biometrics Division: Division of Biometrics I

Statistical Reviewer: Thomas Birkner, Ph.D.

Concurring Reviewers: Peiling Yang, Ph.D. (Team leader)
H. M. James Hung, Ph.D. (Division director)

Medical Division: Division of Psychiatry Products

Clinical Team: Gregory M. Dubitsky, M.D.
Jing Zhang, M.D.

Project Manager: Hiren Patel, Pharm. D.

Keywords: mixed models, nonparametric/dist. free tests, sensitivity analyses, worst case analysis

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1 EXECUTIVE SUMMARY

The sponsor submitted results of three randomized, double-blind studies to support a claim for Lisdexamfetamine (trade name Vyvanse; hereafter referred to as SPD489 or LDX) in the treatment of binge eating disorder. SPD489 is already approved for the treatment of ADHD in pediatric and adult patients. The review of studies SPD489-208, SPD489-343, and SPD489-344 found adequate statistical evidence to support a claim for SPD489 (50 and 70 mg) for moderate to severe binge eating disorder in adults.

Study SPD489-208 (a Phase 2 proof-of-concept study; hereafter referred to as Study 208) suggests that SPD489 has a treatment effect at the end of the 11 week double-blind treatment phase based on the primary endpoint, the log transformed change in the number of binge days per week, for patients with moderate to severe binge eating disorder randomized to the 50 and 70 mg groups compared to placebo patients. The 30 mg group did not differ in a statistically significant way from the placebo group on the primary endpoint.

The identically designed and analyzed flexible dose (50 or 70 mg) Phase 3 pivotal studies (SPD489-343 and SPD489-344, hereafter referred to as Study 343 and Study 344) provide evidence of a treatment effect of SPD489 in patients with moderate to severe binge eating disorder at the end of the 12 week double-blind treatment period given the results for the primary endpoint, i.e., the change in the number of binge eating days per week, and also for a number of key secondary endpoints (e.g., Percent improved on the Clinical Global Impression - Improvement scale, Percent with 4-week binge cessation, and Improvement on the Yale-Brown Obsessive Compulsive Scale modified for BED).

2 INTRODUCTION

2.1 Overview

Lisdexamfetamine (trade name: Vyvanse; referred to as SPD489 or LDX in this review) is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adult and pediatric patients. The sponsor is seeking a new indication “Treatment of Binge Eating Disorder (BED)”. BED is included in DSM-V (for the first time) as distinct eating disorder. No other drug has been approved for the treatment of BED so far. Table 1 lists the three studies included in this review.

Table 1. Studies Included In Analysis

| Study ID | Phase and Design | Treatment Period | # of Subjects per Arm | Study Population |
|------------|--|------------------|---|--|
| SPD489-208 | Phase 2, randomized, double-blind, parallel-group, placebo controlled, fixed dose | 11 weeks | Placebo: 65 SPD489 (30 mg): 68 (50 mg): 67 (70 mg): 66 | Male or female, 18 - 55 years of age with moderate to severe Binge Eating Disorder |
| SPD489-343 | Phase 3, randomized, double-blind, parallel-group, placebo controlled, flexible dose | 12 weeks | Placebo: 184 SPD489 (50 or 70 mg): 190 | |
| SPD489-344 | Phase 3, randomized, double-blind, parallel-group, placebo controlled, flexible dose | 12 weeks | Placebo: 176 SPD489 (50 or 70 mg): 174 | |

2.1.1 Study 208

Study 208 was considered a proof-of-concept study. It was a Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration study to evaluate the efficacy, safety, and tolerability of SPD489 in adults aged 18-55 years with Binge Eating Disorder (BED). The study was conducted at 31 sites in the US between May 2011 and January 2012. The primary objective of this study was to evaluate the efficacy of three doses of SPD489 (30, 50, or 70 mg) compared to placebo in the treatment of moderate to severe BED. The primary endpoint was the change from baseline in Binge Eating Days (defined as days during which at least 1 binge episode occurred) per Week at week 11 assessed by clinical interview based on subject diary.

Subsequent to the issuance of the original study report site 15 (11 randomized subjects) was removed from the analysis for reasons unrelated to the study. Results excluding site 15 are presented in an addendum to the study report and do not change the original conclusions.

The summary and statistical review of Study 208 has been placed in the appendix.

2.1.2 Studies 343 and 344

Studies 343 and 344 were considered pivotal studies. Both were multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible dose (50 or 70 mg) Phase 3 studies to evaluate the efficacy, safety, and tolerability of SPD489 in adults aged 18-55 years with moderate to severe Binge Eating Disorder (BED).

Study 343 was conducted at 50 sites in the US, Germany, Sweden, and Spain between November 2012 and September 2013. Study 344 was conducted at 41 sites in the US and two sites in Germany also from November 2012 to September 2013.

The primary endpoint for both Phase 3 studies was the change from baseline in the number of binge eating days per week at week 12. Both studies also included the following five key secondary endpoints:

1. Clinical Global Impression of Improvement (CGI-I)
2. 4-week cessation from binge eating
3. Body weight
4. Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score
5. Triglycerides

2.2 Data Sources

Original Submission (includes datasets and SAS code):

<\\CDSESUB1\evsprod\NDA021977\0131>

Site 66 (Study 343) closure: <\\CDSESUB1\evsprod\IND110503\0137>

Response to information request: [only email submission (12/24) so far]

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The randomization process for both Phase 3 studies appears to have been executed properly (besides two mis-randomizations in Study 343). See Figures A4 and A5 in the appendix for a depiction of the treatment assignments over time. Data quality assurance measures employed by the sponsor and the Contract Research Organization (CRO) are described in the study reports (section 6). A listing of audits conducted by the sponsor is provided. The inspection of selected clinical study sites by FDA's Office of Scientific Investigation did not reveal any major issues. Statistical Analysis Plans were submitted prior to database lock (Study 343: study completion date 09/25/2013, SAP Version 1.0 effective 03/28/2013; Study 344: study completion date 09/20/2013, SAP Version 3.0 effective 09/25/2013). Processing of the sponsor submitted datasets did not pose any problems. This reviewer obtained similar results for the primary analysis when starting with the listing dataset versus the analysis dataset.

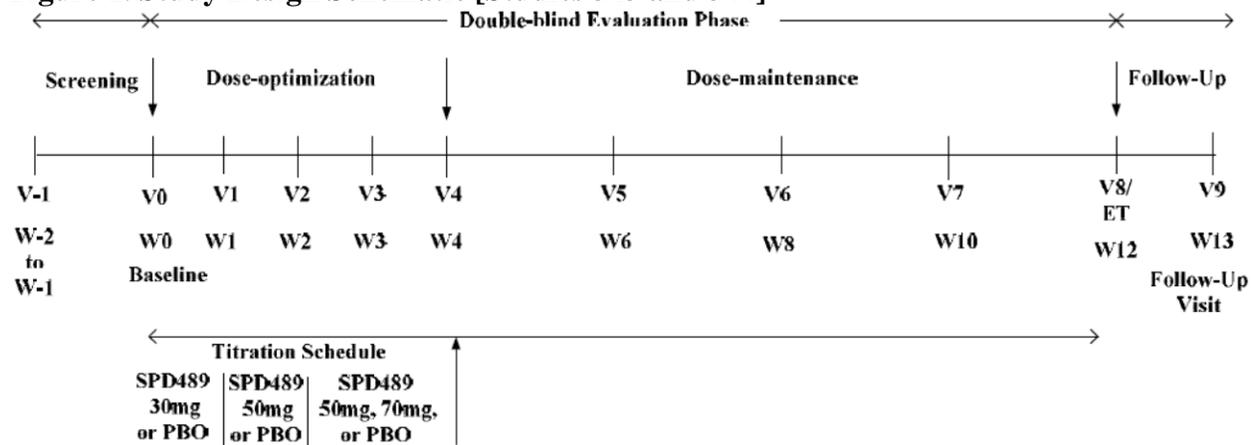
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies 343 and 344

The study design and statistical methodology are identical in both Phase 3 studies. Figure 1 displays the study design. The studies consisted of a 2- to 4-week Screening Period, a 4-week Dose-optimization Period, and an 8-week Dose-maintenance Period. The 4-week Dose-optimization Period and the 8-week Dose-maintenance Period comprised the 12-week, Double-blind Treatment Phase of the study. Subjects who provided informed consent and met all study entry criteria were enrolled in the study and were subsequently randomized (1:1) to receive either SPD489 or placebo. During the 4-week Dose-optimization Period, all subjects randomized to SPD489 started at a daily dose of 30 mg and were titrated to their optimal dose (either 50 or 70 mg/day) based on efficacy and tolerability. One downward titration was permitted during this 4-week period, with 50 mg being the lowest dose allowed once down-titration occurred. The optimized dose then remained fixed for the duration of the 8-week Dose-maintenance Period.

Figure 1. Study Design Schematic [Studies 343 and 344]



(Source: Study 343 Protocol p. 45)

3.2.2 Statistical Methodologies

Studies 343 and 344

Primary endpoint

The primary efficacy endpoint is defined as the change from baseline to Visit 8 (Weeks 11 and 12) in the number of binge eating days per week. The diary data from the time period spanning Weeks 11 and 12 are used. Baseline is defined as the weekly average of the number of binge eating days per week for the 14 days prior to the Baseline Visit (Visit 0); i.e., the number of binge eating days in the 14 days prior to baseline multiplied by 7 and divided by the number of days in the Baseline Period, with diaries confirmed by the clinical interview.

Binge eating days per week for a period between two scheduled visits in the Double-blind Treatment Phase is the number of binge eating days multiplied by 7 and divided by the number of days in the period, with diaries confirmed by the clinical interview. The null hypothesis for the primary efficacy endpoint is that there is no difference at Visit 8 (Weeks 11 and 12) in the change from baseline in the number of binge eating days per week between the SPD489 and placebo groups.

The primary efficacy analysis was conducted over the Full Analysis Set using an MMRM analysis over all post-baseline visits during the Double-blind Treatment Phase, with change from baseline in number of binge eating days per week as the outcome variable; treatment group, visit, and their interaction as factors; baseline binge eating days per week as a covariate; and its

interaction with visit included in the model. The null hypothesis was to be rejected if the statistical analysis resulted in a 2-sided p-value for treatment at Visit 8 (Weeks 11 and 12) that was ≤ 0.05 . Least squares means were calculated for each treatment group for each visit.

A note on the calculation of number of binge days per week: Binge Days per Week for Baseline, Visit 5 (Weeks 5 and 6), Visit 6 (Weeks 7 and 8), Visit 7 (Weeks 9 and 10), and Visit 8 (Weeks 11 and 12) are averaged over two weeks, whereas Binge days per Week for Visit 1 (Week 1), Visit 2 (Week 2), Visit 3 (Week 3) and Visit 4 (Week 4) are not averaged (just a count over the respective one week period). An adjustment is applied in both cases should any diary entries be missing (see SAP for Study 343 p. 25). Note that the averaging over the two week periods will smooth possible weekly fluctuations.

Sensitivity and Supportive Analyses for the Primary Endpoint

The robustness of the primary efficacy analysis was investigated using several alternative analytical methods:

- Permutation test – The primary analysis using MMRM, as described above, was based on a normal approximation of the bounded endpoint. The permutation test was used to confirm the robustness of the primary analysis results in case of a deviation from the normality assumption required in the primary analysis.
- Completer analysis – This analysis repeated the primary analysis described above using subjects in the Completer Set.
- Analyses based on MNAR assumptions:

The primary efficacy analysis described above was based on the assumption of a missing at-random (MAR) mechanism, namely, missingness was not related to the data not observed, though it may have been related to baseline covariates and observed post-baseline data. Two sensitivity analysis models were used to examine the robustness of these primary analysis results. The sensitivity analysis models assume different MNAR mechanisms and are within the pattern-mixture model framework. The first model utilized multiple imputations based on the distribution of placebo group responses over time. The second model utilized multiple imputations with penalties applied to subjects who discontinued from the study.

Analysis of the Key Secondary Endpoints

CGI-I at Week 12 (Visit 8/ET)

The CGI-I, dichotomized as improved (including categories of ‘very much improved’ and ‘much improved’) or not improved (other categories excluding ‘not assessed’), was compared between treatment groups at Week 12 (Visit 8/ET) using the Chi-square test.

Proportion of Subjects with 4-week Cessation of Binge Eating for the Last 28 Days Prior to Week 12 (Visit 8/ET)

Four-week cessation of binge eating was defined as no binge episodes for 28 consecutive days prior to the last study visit. If a subject discontinued from the study prior to having 28 days of diary information or the subject had missing diary information, then the subject was considered not to have had 4-week cessation of binge eating. The difference between treatment groups in proportions of subjects with 4-week binge cessation was compared at Week 12 (Visit 8/ET) using the Chi-square test.

Percent Change from Baseline in Body Weight at Week 12 (Visit 8)

The percent change from baseline (Visit 0) in body weight was compared between the SPD489 group and the placebo group using the MMRM method, with treatment group, visit, and their interaction as factors; weight at the Baseline Visit (Visit 0) as a covariate; and its interaction with visit included in the model. The statistical inference of interest is based on the p-value for treatment at Week 12 (Visit 8).

Change from Baseline in Y-BOCS-BE Total Score at Week 12 (Visit 8)

The change from baseline (Visit 0) in Y-BOCS-BE total score was compared between the SPD489 group and the placebo group using the MMRM method with treatment group, visit, and their interaction as factors; the corresponding Y-BOCS-BE total score at the Baseline Visit (Visit 0) as a covariate; and its interaction with visit included in the model. The statistical inference of interest is based on the p-value for treatment at Week 12 (Visit 8).

Change from Baseline in Triglycerides at Week 12 (Visit 8/ET)

Triglyceride values were compared between the SPD489 and placebo groups using an ANCOVA model. In the model, the outcome variable is the change from baseline (Visit -1) to Week 12 (Visit 8/ET) in triglyceride values based on fasted samples. Treatment group was included as a factor in the model with the Baseline Visit (Visit -1) value included as a covariate.

Multiplicity Adjustment

In order to maintain study-wide Type I error control, a hierarchical testing procedure was used in the comparisons between the SPD489 and placebo groups on the primary and key secondary efficacy endpoints.

Specifically, testing was conducted in the following order:

1. Change from baseline in the number of binge eating days per week (the primary efficacy endpoint)
2. CGI-I score (dichotomized)
3. Proportion of subjects with 4-week binge eating cessation
4. Percent change from baseline in body weight
5. Change from baseline in Y-BOCS-BE total score
6. Change from baseline in Triglycerides

A later test was reported as statistically significant only if all earlier tests were also statistically significant at the 2-sided 0.05 level.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 343

The Full Analysis Set for Studies 343 and 344 was defined as all subjects who took at least one dose of investigational product and who had one post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least one week).

Study 343 randomized 383 subjects across 50 sites from the US and Europe (US: 44 sites with 342 subjects; Sweden: 3 sites with 29 subjects; Spain: 1 site with 10 subjects; Germany: 2 sites with 3 subjects). A total of 68 (17.8%) randomized subjects did not complete the study, with

similar proportions in the placebo and SPD489 groups (Table 2). The Full Analysis Set contains 374 subjects (Placebo: n=184, SPD489: n=190).

Table 2. Subject Disposition [Study 343]

| | Placebo n (%) | SPD489 n (%) | Total n (%) |
|-------------------------------------|--------------------------|-------------------------|------------------------|
| Screened Set | | | 642 |
| Randomized Set | 191 | 192 | 383 |
| Safety Analysis Set ^{a, b} | 187 (97.9) | 192 (100) | 379 (99.0) |
| Full Analysis Set ^c | 184 (96.3) | 190 (99.0) | 374 (97.7) |
| Completed Follow-up Visit | 162 (84.8) | 172 (89.6) | 334 (87.2) |
| Completed Study | 157 (82.2) | 158 (82.3) | 315 (82.2) |
| Completer Set ^d | 157 (82.2) | 158 (82.3) | 315 (82.2) |
| Did Not Complete Study | 34 (17.8) | 34 (17.7) | 68 (17.8) |
| Primary Reason for Discontinuation | | | |
| Withdrawal by Subject | 14 (7.3) | 12 (6.3) | 26 (6.8) |
| Adverse Event | 5 (2.6) | 12 (6.3) | 17 (4.4) |
| Lost to Follow-up | 8 (4.2) | 3 (1.6) | 11 (2.9) |
| Protocol Violation | 4 (2.1) | 2 (1.0) | 6 (1.6) |
| Lack of Efficacy | 1 (0.5) | 0 | 1 (0.3) |
| Other Reasons | 2 (1.0) | 5 (2.6) | 7 (1.8) |

^a The Safety Analysis Set includes all randomized subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

^b Four placebo subjects were excluded from the Safety Analysis Set. Of these 4 subjects, 2 were lost to follow-up prior to receiving investigational product (055-3002 and 803-3008) and 2 were withdrawn due to a protocol violation (mis-randomization) prior to receiving investigational product (064-3004 and 072-3006).

^c The Full Analysis Set includes all subjects in the Randomized Set who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment.

^d The Completer Set includes all subjects in the Full Analysis Set who completed the Visit 8 (Week 12) assessments.

Note: All proportions are based on the Randomized Set.

Note: Primary reasons for withdrawal are presented by decreasing frequency based on the SPD489 group.

(Source: 343 Study Report p. 78)

Table 3 summarizes demographic and baseline characteristics. They appear balanced between treatment groups. For the safety analysis set the mean age was 38.1 years. The majority of subjects were female and white. The mean weight was 93.5 kg and the mean BMI was 33.5.

Table 3. Demographic and Baseline Characteristics – Safety Set [Study 343]

| | Placebo (N=187) | SPD489 (N=192) | Total (N=379) |
|---|-----------------------|-------------------|------------------|
| Demographic Parameter | Baseline Value | | |
| Age (years) ^a | | | |
| n | 187 | 192 | 379 |
| Mean (SD) | 37.6 (10.21) | 38.5 (10.40) | 38.1 (10.30) |
| Median | 38.0 | 38.0 | 38.0 |
| Min, Max | 19, 55 | 19, 55 | 19, 55 |
| Age Category (years) n (%) | | | |
| <40 years | 102 (54.5) | 98 (51.0) | 200 (52.8) |
| ≥40 years | 85 (45.5) | 94 (49.0) | 179 (47.2) |
| Sex n (%) | | | |
| Male | 24 (12.8) | 27 (14.1) | 51 (13.5) |
| Female | 163 (87.2) | 165 (85.9) | 328 (86.5) |
| Ethnicity n (%) | | | |
| Hispanic or Latino | 21 (11.2) | 27 (14.1) | 48 (12.7) |
| Not Hispanic or Latino | 166 (88.8) | 165 (85.9) | 331 (87.3) |
| Race n (%) | | | |
| White | 144 (77.0) | 150 (78.1) | 294 (77.6) |
| Non-White | 43 (23.0) | 41 (21.4) | 84 (22.2) |
| Black or African American | 29 (15.5) | 33 (17.2) | 62 (16.4) |
| Native Hawaiian or other Pacific Islander | 1 (0.5) | 2 (1.0) | 3 (0.8) |
| Asian | 5 (2.7) | 3 (1.6) | 8 (2.1) |
| American Indian or Alaska Native | 2 (1.1) | 2 (1.0) | 4 (1.1) |
| Multiple | 6 (3.2) | 1 (0.5) | 7 (1.8) |
| Missing | 0 | 1 (0.5) | 1 (0.3) |
| Weight (kg) | | | |
| n | 187 | 192 | 379 |
| Mean (SD) | 92.70 (19.331) | 94.30 (19.732) | 93.51 (19.526) |
| Median | 92.99 | 90.27 | 91.60 |
| Min, Max | 49.2, 140.2 | 54.7, 148.8 | 49.2, 148.8 |
| Height (cm) | | | |
| n | 187 | 192 | 379 |
| Mean (SD) | 166.93 (8.065) | 167.22 (8.168) | 167.08 (8.108) |
| Median | 166.37 | 167.64 | 167.50 |
| Min, Max | 143.8, 193.0 | 144.8, 190.5 | 143.8, 193.0 |

Table 3. Continued

| | Placebo (N=187) | SPD489 (N=192) | Total (N=379) |
|--|-----------------------|-------------------|------------------|
| Demographic Parameter | Baseline Value | | |
| Body Mass Index (kg/m ²) | | | |
| n | 187 | 192 | 379 |
| Mean (SD) | 33.21 (6.234) | 33.68 (6.292) | 33.45 (6.260) |
| Median | 33.39 | 33.30 | 33.34 |
| Min, Max | 18.5, 44.6 | 19.9, 44.8 | 18.5, 44.8 |
| Body Mass Index Category n (%) ^b | | | |
| Underweight/Normal (<25.0 kg/m ²) ^c | 22 (11.8) | 14 (7.3) | 36 (9.5) |
| Pre-obesity (≥25.0 to <30.0 kg/m ²) | 39 (20.9) | 49 (25.5) | 88 (23.2) |
| Obesity Class I (≥30.0 to <35.0 kg/m ²) | 49 (26.2) | 48 (25.0) | 97 (25.6) |
| Obesity Class II (≥35.0 to <40.0 kg/m ²) | 47 (25.1) | 43 (22.4) | 90 (23.7) |
| Obesity Class III (≥40.0 kg/m ²) | 30 (16.0) | 38 (19.8) | 68 (17.9) |

^a Age was calculated as the difference between date of birth and date of informed consent, truncated to years.

^b BMI category was based on World Health Organization BMI categories for adults.

^c Subjects who had a BMI <18 were excluded from study participation.

BMI=body mass index; SD=standard deviation

(Source: 343 Study Report p. 81-82)

3.2.3.2 Study 344

A total of 390 subjects were randomized across 41 sites in the US (370 subjects) and 2 sites in Germany (20 subjects) in Study 343. The subject disposition table (Table 4) and the demographic and baseline characteristic table (Table 5) exclude the 11 subjects from the closed Site 15 from the safety analysis set. A total of 96 randomized subjects (24.6%) did not complete the study. The most frequently reported primary reason for discontinuation were lost to follow-up in the placebo group; and lost to follow-up and withdrawal by subject in the SPD489 group.

All subjects enrolled at Sites 15 (11 subjects) and 79 (12 subjects) were excluded from the efficacy analyses as reported in the main body of the study report. The sponsor excluded all data from Site 15 for reasons unrelated to the study. The data from the 12 subjects at site 79 was excluded from the efficacy analysis due to Good Clinical Practice (GCP) infractions, failure to follow study procedures, improper entry of subject data, and inadequate oversight (344 Study report p. 79). Results based on all data are provided in section 14.3 of the study report and are

very similar to the results reported when excluding subjects from sites 15 and 79 from the efficacy analyses.

Reviewer's Notes: During the IND review stage, the sponsor informed FDA about removing specific sites for various reasons. In principle, all randomized patients should be included in the primary analysis set. Those associated with a protocol violation should still be in the primary analysis, but should be excluded from the per-protocol analysis set. We responded to the sponsor that this would be a matter of review when the NDA comes in and that results from both analysis sets should be included in the study report.

Table 4. Subject Disposition [Study 344]

| | Placebo n (%) | SPD489 n (%) | Total n (%) |
|--|------------------|-----------------|----------------|
| Screened Set | | | 700 |
| Randomized Set | 195 | 195 | 390 |
| Safety Analysis Set ^{a, b, c} | 185 (94.9) | 181 (92.8) | 366 (93.8) |
| Sensitivity Safety Analysis Set ^d | 178 (91.3) | 177 (90.8) | 355 (91.0) |
| Full Analysis Set ^{e, f} | 176 (90.3) | 174 (89.2) | 350 (89.7) |
| Completed Follow-up Visit | 153 (78.5) | 160 (82.1) | 313 (80.3) |
| Completed Study | 147 (75.4) | 147 (75.4) | 294 (75.4) |
| Completer Set ^{g, h} | 142 (72.8) | 145 (74.4) | 287 (73.6) |
| Did Not Complete Study | 48 (24.6) | 48 (24.6) | 96 (24.6) |
| Primary Reason for Discontinuation | | | |
| Lost to Follow-up | 18 (9.2) | 15 (7.7) | 33 (8.5) |
| Withdrawal by Subject | 7 (3.6) | 13 (6.7) | 20 (5.1) |
| Adverse Event | 5 (2.6) | 7 (3.6) | 12 (3.1) |
| Protocol Violation | 4 (2.1) | 2 (1.0) | 6 (1.5) |
| Lack of Efficacy | 1 (0.5) | 0 | 1 (0.3) |
| Other Reasons ⁱ | 13 (6.7) | 11 (5.6) | 24 (6.2) |

^a The Safety Analysis Set includes all randomized subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

^b All subjects enrolled at Site 015 (11 subjects) were excluded from the Safety Analysis Set.

^c In addition to the 11 subjects from Site 015 who were excluded from the Safety Analysis Set, 12 subjects had not been treated and 1 subject (SPD489) had been treated but did not have any safety follow-up assessments.

^d The Sensitivity Safety Analysis Set includes all subjects in the Safety Analysis Set, with the exception of 11 subjects from Site 079 (the twelfth subject from Site 079 had already been excluded from the Safety Analysis Set).

^e The Full Analysis Set includes all subjects in the Randomized Set who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment.

^f All subjects enrolled at Sites 015 (11 subjects) and 079 (12 subjects) were excluded from the Full Analysis Set.

^g The Completer Set includes all subjects in the Full Analysis Set who completed the Visit 8 (Week 12) assessments.

^h Seven subjects (2 from Site 015 and 5 from Site 079) completed the study. However, because these subjects were excluded from the Full Analysis Set, they were also excluded from the Completer Set.

ⁱ Other primary reasons for withdrawal include discontinuation due to sponsor request, which was reported for 8 subjects enrolled at Site 015 (SPD489, 5 subjects and placebo, 3 subjects).

Note: All proportions are based on the Randomized Set.

Note: Primary reasons for withdrawal are presented by decreasing frequency based on the SPD489 group.

(Source: 344 Study Report p. 81)

Demographic and baseline characteristics appear balanced between the two treatment groups (Table 5). The mean age was 37.9 years. The majority of subjects were female and white. The mean weight was 93.9 kg and the mean BMI was 33.5.

Table 5. Demographic and Baseline Characteristics – Safety Set [Study 344]

| Demographic Parameter | Placebo (N=185) | SPD489 (N=181) | Total (N=366) |
|---|--------------------|-------------------|------------------|
| Baseline Value | | | |
| Age (years) ^a | | | |
| n | 185 | 181 | 366 |
| Mean (SD) | 38.7 (10.01) | 37.1 (10.00) | 37.9 (10.02) |
| Median | 40.0 | 36.0 | 37.5 |
| Min, Max | 18, 56 | 18, 56 | 18, 56 |
| Age Category (years) n (%) | | | |
| <40 years | 90 (48.6) | 108 (59.7) | 198 (54.1) |
| ≥40 years | 95 (51.4) | 73 (40.3) | 168 (45.9) |
| Sex n (%) | | | |
| Male | 32 (17.3) | 22 (12.2) | 54 (14.8) |
| Female | 153 (82.7) | 159 (87.8) | 312 (85.2) |
| Ethnicity n (%) | | | |
| Hispanic or Latino | 24 (13.0) | 21 (11.6) | 45 (12.3) |
| Not Hispanic or Latino | 161 (87.0) | 160 (88.4) | 321 (87.7) |
| Race n (%) | | | |
| White | 137 (74.1) | 130 (71.8) | 267 (73.0) |
| Non-White | 48 (25.9) | 51 (28.2) | 99 (27.0) |
| Black or African American | 32 (17.3) | 43 (23.8) | 75 (20.5) |
| Native Hawaiian or other Pacific Islander | 0 | 2 (1.1) | 2 (0.5) |
| Asian | 4 (2.2) | 3 (1.7) | 7 (1.9) |
| American Indian or Alaska Native | 4 (2.2) | 0 | 4 (1.1) |
| Multiple | 8 (4.3) | 3 (1.7) | 11 (3.0) |
| Weight (kg) | | | |
| n | 185 | 181 | 366 |
| Mean (SD) | 93.05 (20.330) | 94.75 (21.745) | 93.89 (21.030) |
| Median | 90.72 | 93.10 | 91.34 |
| Min, Max | 50.3, 157.2 | 51.9, 175.6 | 50.3, 175.6 |
| Height (cm) | | | |
| n | 185 | 181 | 366 |
| Mean (SD) | 167.21 (8.646) | 166.83 (8.627) | 167.02 (8.627) |
| Median | 166.37 | 165.50 | 166.19 |
| Min, Max | 146.0, 190.5 | 147.3, 200.7 | 146.0, 200.7 |
| Body Mass Index (kg/m ²) | | | |
| n | 185 | 181 | 366 |
| Mean (SD) | 33.20 (6.341) | 33.85 (6.202) | 33.52 (6.273) |
| Median | 32.82 | 33.84 | 33.15 |
| Min, Max | 20.8, 45.2 | 19.7, 45.2 | 19.7, 45.2 |

Table 5. Continued

| Demographic Parameter | Placebo (N=185) | SPD489 (N=181) | Total (N=366) |
|--|--------------------|-------------------|------------------|
| Body Mass Index Category n (%) ^b | | | |
| Underweight/Normal (<25.0 kg/m ²) ^c | 21 (11.4) | 13 (7.2) | 34 (9.3) |
| Pre-obesity (≥25.0 to <30.0 kg/m ²) | 36 (19.5) | 43 (23.8) | 79 (21.6) |
| Obesity Class I (≥30.0 to <35.0 kg/m ²) | 54 (29.2) | 48 (26.5) | 102 (27.9) |
| Obesity Class II (≥35.0 to <40.0 kg/m ²) | 39 (21.1) | 41 (22.7) | 80 (21.9) |
| Obesity Class III (≥40.0 kg/m ²) | 35 (18.9) | 36 (19.9) | 71 (19.4) |

^a Age was calculated as the difference between date of birth and date of informed consent, truncated to years.

^b BMI category was based on World Health Organization BMI categories for adults.

^c Subjects who had a BMI <18 were excluded from study participation.

(Source: 344 Study Report p. 83-85)

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's results

Dose response

The sponsor states that the results based on an ANCOVA LOCF model for Study 208 for the primary endpoint with treatment as factor and baseline as covariate support a linear dose response relationship (208 Study Report p. 80). Note however that there is almost no difference in the primary endpoint results of the 50 and 70 mg groups. Figure A2 in the appendix provides a depiction of the primary endpoint estimates from the MMRM on the untransformed data.

Studies 343 and 344

Primary efficacy: Number of Binge Days per Week

The primary efficacy variable was the change from Baseline at Week 12 in the Number of Binge Days per week. The means at baseline were generally between 4.6 or 4.8. The LS mean changes from baseline were all negative, suggesting improvement for each treatment arm in both Phase 3 studies. Specifically, for the placebo arms, the improvements were between 2 to 3 days, but for the LDX arms they were near 4 days. The differences between treatment arms (approx. 1.5 days) were statistically significant with very small p-values ($p < 0.001$).

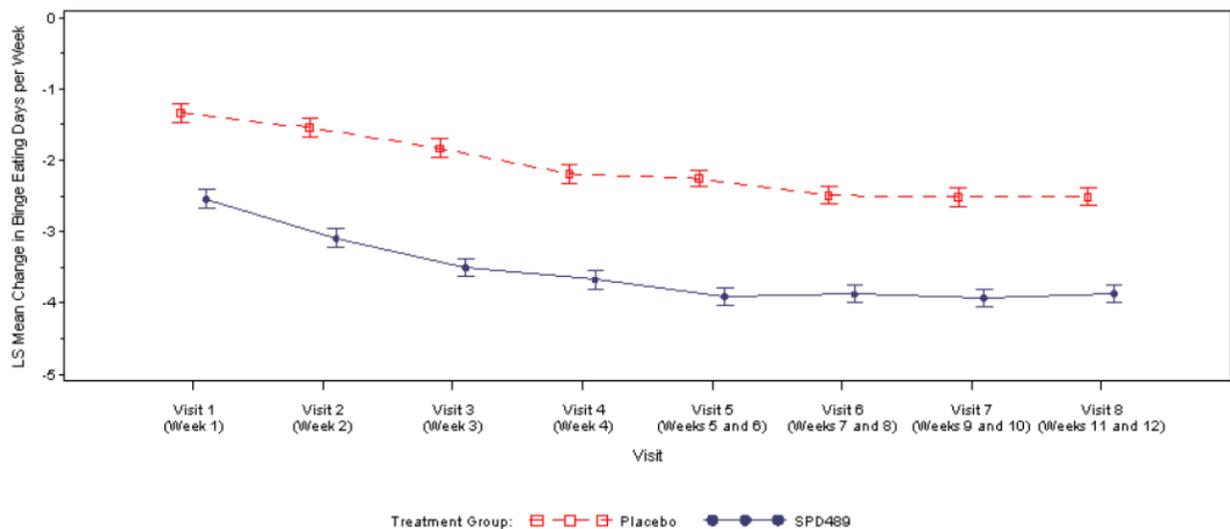
Table 6. Primary Endpoint: Change in Binge Eating Days per Week – FAS [Studies 343 and 344]

| Study # | 343 | | 344 | |
|------------------------------|----------------------|-------------|----------------------|-------------|
| | Placebo (N=184) | LDX (N=190) | Placebo (N=176) | LDX (N=174) |
| Baseline Mean | 4.60 | 4.79 | 4.82 | 4.66 |
| LS Mean Change from Baseline | -2.51 | -3.87 | -2.26 | -3.92 |
| LS Mean Diff.* (95% CI) | -1.35 (-1.70, -1.01) | | -1.66 (-2.04, -1.28) | |

(Source: 343 Study report p. 98, 344 Study report p. 101; results replicated by reviewer; *Diff = LDX – Placebo; negative value indicates greater improvement for LDX patients compared to Placebo patients)

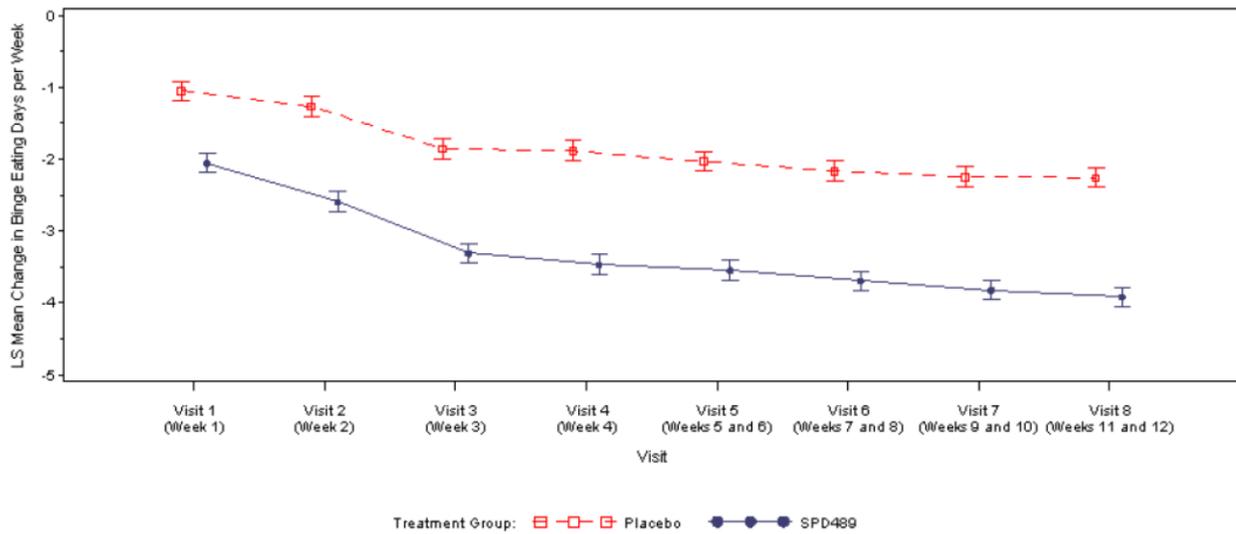
Figure 2 and Figure 3 display the LS Mean trajectories of Change in Binge Days per Week over the course of the 12 week double-blind studies. It is noticeable that most of the mean decrease in Binge Days occurs early and the curves are relatively flat after Visit 3 or 4.

Figure 2. LS Mean (SEM) Change from Baseline in Number of Binge Days per Week Over Time by Treatment Group - FAS [Study 343]



(Source: 343 Study Report p. 103)

Figure 3. LS Mean (SEM) Change from Baseline in Number of Binge Days per Week Over Time Presented by Treatment Group – FAS [Study 344]



(Source: 344 Study Report p. 106)

Analyses were re-run including sites 15 and 79 for Study 344. Results are provided in Section 14.3 of the study report (p. 1264 - 2430) and are consistent with the results presented in the body of the report excluding those sites from the efficacy analyses.

Sensitivity Analyses:

1) Permutation Test

Due to the novelty of the primary outcome measure and some concerns about the goodness of the normality approximation FDA had recommended to conduct a permutation test to support the primary analysis. For the permutation tests, the sponsor created 10,000 datasets by randomly assigning pseudo-treatment group designations. The number of between-group pseudo LS mean differences with absolute values greater than or equal to the absolute value of the between-group LS mean differences at Visit 8 from the primary analysis (i.e., 1.35 [Study 343] or 1.66 [Study 344]) was 0, showing that no randomly generated dataset had a between-group difference that was more extreme than that of the primary data (see Study Reports p. 104 [343], p. 106 [344]). This reviewer replicated the permutation test results.

2) Sensitivity analysis based on the Completer Set

A second sensitivity analysis was conducted by repeating the primary MMRM model over all subjects in the Completer Set. The results are similar to those obtained from the FAS for both Phase 3 studies.

3) Two Sensitivity Analysis based on Missing Not At Random assumption:

- a) Assuming all dropouts followed the distribution of the placebo responses (i.e., the means and the intra-subject correlations based on the placebo responses will apply).

Results from this sensitivity analysis are consistent with those of the primary efficacy analysis in that the LS mean decrease from baseline at Week 12 in the number of binge days per week was of greater magnitude for SPD489 subjects compared to placebo subjects (Study 343: -3.84 vs. -2.52 days [primary analysis estimates: -3.87 vs. -2.51]; Study 344: -3.84 vs. -2.26 days [primary analysis estimates: -3.92 vs. -2.26]).

- b) Assuming subjects who were discontinued had changes from baseline that were worse than predicted under Missing at Random (MAR) using a penalty. Results from this sensitivity analysis (for both Studies 343 and 344) are also consistent with those of the primary efficacy analysis. Regardless of the penalty applied (0.25 *SD to 1*SD), the LS mean decrease from baseline at Week 12 in number of binge days per week was of statistically significantly greater magnitude for the SPD489 group compared to the placebo group.

Key Secondary Efficacy Measures

The testing of the five key secondary efficacy measures in Studies 343 and 344 was conducted following a fixed sequence to control the overall type 1 error.

1st Key Secondary: Dichotomized CGI-I

The first key secondary endpoint was the Clinical Global Impression-Improvement (CGI-I) scale. The CGI-I is a clinician's global evaluation of a subject's improvement or worsening over time relative to the baseline state. The clinician rates the change as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

The endpoint at hand is the percentage improved at Week 12/ET (ET = Early Termination Visit), where “improved” includes very much improved and much improved. The complementary category is “not improved” including minimally improved, no change, minimally worse, much worse, and very much worse.

The CGI-Severity (CGI-S) score can be used to gauge a patient’s baseline state: In Study 343 for example about 90% of subjects were moderately mentally ill or markedly mentally ill (see Table 7 below). Note the following inclusion criteria in both Phase 3 studies: CGI-S score ≥ 4 (i.e., at least moderately ill) at Screening and Baseline Visit.

Table 7. Clinical Global Impression-Severity (CGI-S) at Baseline by Treatment Group – FAS [Study 343]

| CGI-S | Placebo (N=184) n (%) | SPD489 (N=190) n (%) |
|---|--------------------------|-------------------------|
| [1] Normal, not at all ill | 0 | 0 |
| [2] Borderline mentally ill | 0 | 0 |
| [3] Mildly ill | 0 | 0 |
| [4] Moderately ill | 86 (46.7) | 98 (51.6) |
| [5] Markedly ill | 83 (45.1) | 78 (41.1) |
| [6] Severely ill | 13 (7.1) | 14 (7.4) |
| [7] Among the most extremely ill subjects | 2 (1.1) | 0 |

(Source: study report p. 382)

A sizeable percentage of patients in each treatment group did improve. Specifically, for the placebo arms, percent improved were 47 and 43, but for the LDX arms percent improved was greater 80 in each study. At week 12 there were roughly twice as many LDX patients in the improved category compared to placebo patients. The differences between treatment arms (of approx. 30 to 40 percentage points) were statistically significant with very small p-values ($p < 0.001$).

Table 8. 1st Key Secondary: Percent of Improved Patients Based on Dichotomized CGI-I – FAS [Studies 343 and 344]

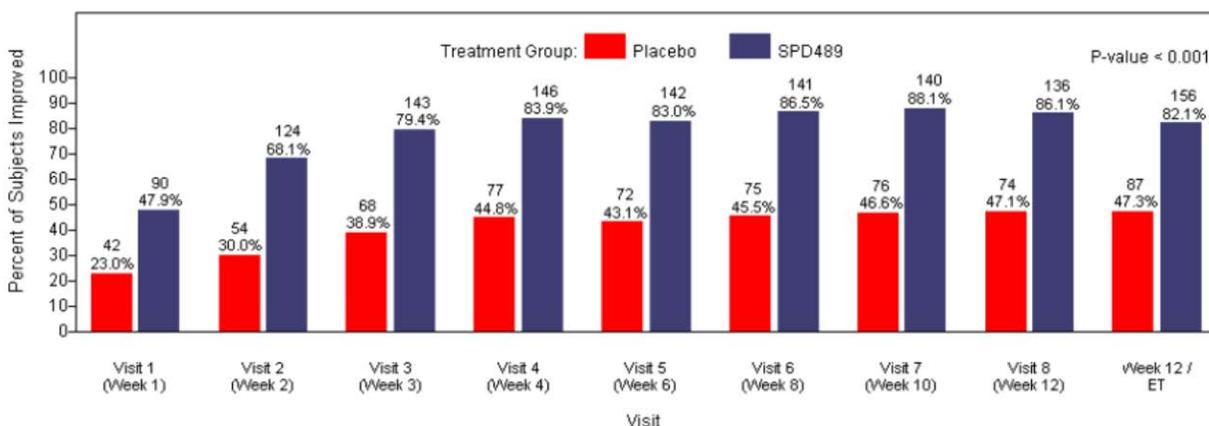
| Study # | 343 | | 344 | |
|---------|---------|-----|---------|-----|
| | Placebo | LDX | Placebo | LDX |
| | | | | |

| | | | | |
|-------------------------|----------------------|-------------------|----------------------|-------------------|
| Percent Improved | 47.3 (87/184) | 82.1 (156/190) | 42.9 (75/176) | 86.2 (150/174) |
| Diff. (95% CI) | 34.8 (25.8, 43.9) | | 43.3 (34.4, 52.3) | |

(Source: 343 Study Report p. 111, 344 Study Report p. 113, and Reviewer’s analysis; Sponsor’s results replicated by reviewer)

Figure 4 displays the proportion of improved subjects at each visit for Study 343.

Figure 4. Proportions of Improved Subjects (based on dichotomized CGI-I) over Time by Treatment Group – FAS [Study 343]



(Source: Study report p. 112)

2nd Key Secondary: 4-Week Binge Eating Cessation

The second key secondary endpoint is 4-week binge eating cessation, defined as no binge episodes for 28 consecutive days prior to the last study visit (week 12 or early termination visit). If a subject withdrew from the study prior to collecting 28 days of diary data or the subject has missing diary data, then the subject is counted as no cessation.

The percentage of subjects with 4-week cessation is 13 to 14 percent in the Placebo groups, and 36 to 40 percent in the LDX groups (Table 9).

The estimated differences of 23 and 26 percent are highly statistically significant ($p < 0.001$). The percentage of subjects with a 4-week cessation is roughly three times larger for patients on LDX.

Table 9. 2nd Key Secondary: Percent of Patients with a 4-week Cessation of Binge Eating – FAS [Studies 343 and 344]

| Study # | 343 | | 344 | |
|---------------------------|----------------------|------------------|----------------------|------------------|
| | Placebo | LDX | Placebo | LDX |
| Percent Cessation | 14.1 (26/184) | 40.0 (76/190) | 13.1 (23/176) | 36.2 (63/174) |
| Diff. (95% CI) | 25.9 (17.3, 34.5) | | 23.1 (14.4, 31.8) | |

(Source: 343 Study Report p. 113, 344 Study Report p. 115, and Reviewer’s analysis; Results replicated by reviewer)

3rd Key Secondary: Body Weight

The change from baseline to week 12 in body weight was the third key secondary endpoint. The means at baseline were between 205 and 209 pounds (93 to 95 kg). The LS mean percent changes from baseline were essentially zero for placebo subjects, and roughly minus six for LDX patients at week 12 (Table 10). The differences between treatment arms were highly statistically significant ($p < 0.001$) for both Study 343 and Study 344.

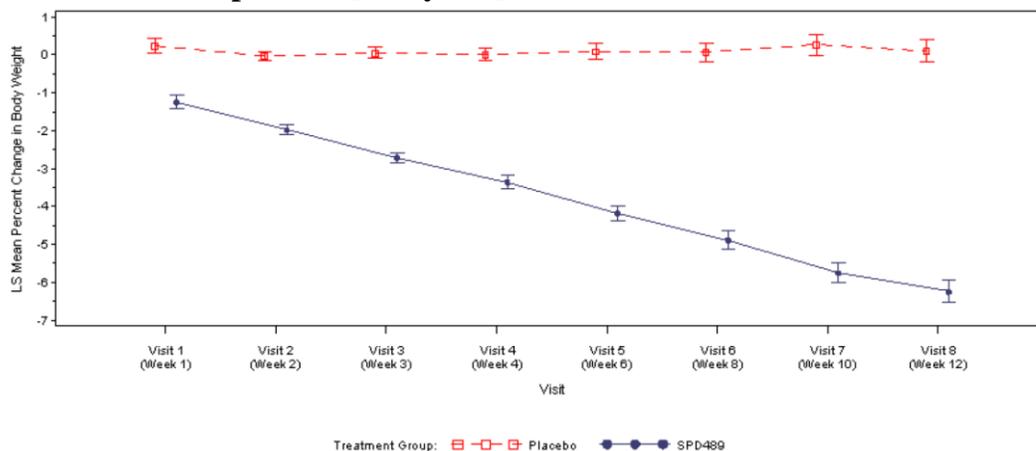
Table 10. 3rd Key Secondary: Percent Change in Body Weight - FAS [Studies 343 and 344]

| Study # | 343 | | 344 | |
|--------------------------------------|-------------------------|----------------|-------------------------|----------------|
| | Placebo (N=184) | LDX (N=190) | Placebo (N=176) | LDX (N=174) |
| Baseline Mean | lbs | 204.8 | 205.3 | 208.9 |
| | kg | 92.9 | 94.0 | 93.1 |
| LS Mean Percent Change from Baseline | 0.11 | -6.25 | -0.15 | -5.57 |
| LS Mean Percent Diff.* (95% CI) | -6.35 (-7.17, -5.54) | | -5.41 (-6.39, -4.44) | |

(Source: 343 Study Report p. 115, 344 Study Report p. 118; Results replicated by reviewer; *Diff = LDX – Placebo; negative value indicates greater improvement for LDX patients compared to Placebo patients)

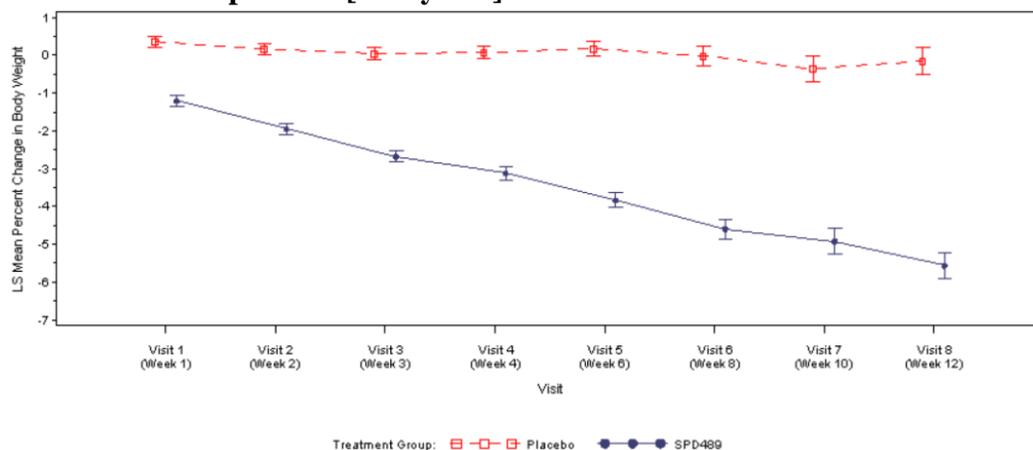
Figure 5 and Figure 6 display the LS mean percent change trajectories in body weight over the duration of the double-blind period. Note the flat shape of the placebo curves and the steadily decreasing curves for the LDX groups.

Figure 5. LS Mean Percent Changes (SEM) from Baseline in Body Weight by Visit and Treatment Group – FAS [Study 343]



(Source: Study report Figure 3.2.3.1; SEM = standard error of the mean; LS Mean Percent Changes calculated by MMRM model with percent change from baseline in weight as the outcome variable, treatment group, visit, and their interaction as factors; baseline weight as a covariate and its interaction with visit also in the model. Note Figure 7 presented in the study report for Study 343 is actually the figure for Study 344. Figure 7 (p. 106) in the Summary of Clinical Efficacy is correctly displaying the estimates for both studies.)

Figure 6. LS Mean Percent Changes (SEM) from Baseline in Body Weight by Visit and Treatment Group – FAS [Study 344]



(Source: 344 Study Report p. 1221)

4th Key Secondary: Y-BOCS-BE Total Score

The Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (Y-BOCS-BE) is a clinician-rated, 10-item scale, with each item rated from 0 (no symptoms) to 4 (extreme symptoms). This scoring results in a range from 0 to 40. The scale contains questions about obsessions and compulsions (how much time a patient spends on those, how much impairment or distress they experience, how much resistance or control they have over those thoughts).

The total score places a patient into the following categories: 0-7 sub-clinical, 8-15 mild, 16-23 moderate, 24-31 severe, and 32-40 extreme.

This key secondary endpoint was assessed at baseline, week 4, 8 and 12. The data were analyzed by a Mixed Model Repeated Measures approach where the change from baseline at week 12 was the dependent variable.

The means at baseline were generally between 21 or 22 [moderate category]. The LS mean changes from baseline were all negative, suggesting improvement for each treatment arm in both studies. Specifically, for the placebo arms, the improvements were between 7 and 8 points, but for the LDX arms they were between 15 and 16 points (Table 11). The differences between treatment arms (7 to 8 points) were statistically significant with very small p-values. Placebo

subjects remained in the moderate category or improved to mild, whereas LDX subjects improved from moderate to sub-clinical or at least mild.

Table 11. 4th Key Secondary: Y-BOCS-BE Total Score - FAS [Studies 343 and 344]

| Study # | 343 | | 344 | |
|-------------------------------------|----------------------|----------------|----------------------|----------------|
| | Placebo (N=184) | LDX (N=190) | Placebo (N=176) | LDX (N=174) |
| Baseline Mean | 21.5 | 21.8 | 21.5 | 21.1 |
| LS Mean Change from Baseline | -8.3 | -15.7 | -7.4 | -15.4 |
| LS Mean Diff.* (95% CI) | -7.4 (-8.9, -5.9) | | -7.9 (-9.5, -6.4) | |

(Source: 343 Study Report p. 118, 344 Study Report p. 120; Results replicated by reviewer;

*Diff = LDX – Placebo; negative value indicates greater improvement for LDX patients compared to Placebo patients)

5th Key Secondary: Triglycerides

Triglyceride levels were determined from fasted blood samples. Triglycerides were assessed only at baseline and at week 12 or the early termination visit. The means at baseline were generally between 111 and 118 mg/dL. The LS mean changes from baseline to week 12 estimated from an ANCOVA model were positive for placebo subjects and negative for LDX subjects. Specifically, for the placebo arms, the increase was between 5 and 11 mg/dL, whereas the decrease for the LDX subjects was between 6 and 12 mg/dL (Table 12). The differences between trt arms (around 17 mg/dL) were statistically significant with very small p-values.

Reviewer’s Notes: Since there was only one post-baseline assessment, the analysis would become a completer analysis, which is problematic if the dropout rate is non-negligible.

Table 12. 5th Key Secondary: Change from Baseline in Triglycerides (mg/dL) – FAS [Studies 343 and 344]

| Study # | 343 | | 344 | |
|-------------------------------------|------------------------|----------------|------------------------|----------------|
| | Placebo (N=184) | LDX (N=190) | Placebo (N=176) | LDX (N=174) |
| Baseline Mean | 112.9 | 118.0 | 111.5 | 113.2 |
| LS Mean Change from Baseline | 10.8 | -6.8 | 5.5 | -11.8 |
| LS Mean Diff.* (95% CI) | -17.6 (-27.4, -7.8) | | -17.3 (-28.4, -6.2) | |

(Source: 343 Study Report p. 119, 344 Study Report p. 123; Results replicated by reviewer; results converted from mmol/L to mg/dL; *Diff = LDX – Placebo; negative value indicates greater improvement for LDX patients compared to Placebo patients)

Study 344 Ad-hoc analysis including subjects from sites 15 and 79 (n = 360)

Results of the ad-hoc analysis (due to FDA request) including subjects from sites 15 (n = 10) and 79 (n = 0; [3 FAS subjects, but no baseline data]) are provided in the Study 344 study report in section 14.3. The ad-hoc results are very similar to the results presented in the main body of the report. Below is a snap-shot of those results (all statistically significant):

- Primary Endpoint: LS mean difference in change in binge eating days per week: -1.68 (95% CI: -2.06, -1.30) [p. 1404]
- CGI-I Improved: SPD489 85.5%, Placebo 41.4% [p. 1439]
- 4-week Cessation: SPD489 36.3%, Placebo 12.7% [p. 1451]
- LS mean difference in Percent Change in Body Weight: -5.41 [p. 1456]
- LS mean difference in Change in Y-BOCS-BE total score: -8.01 [p. 1460]

3.2.4.2 Reviewer's analysis

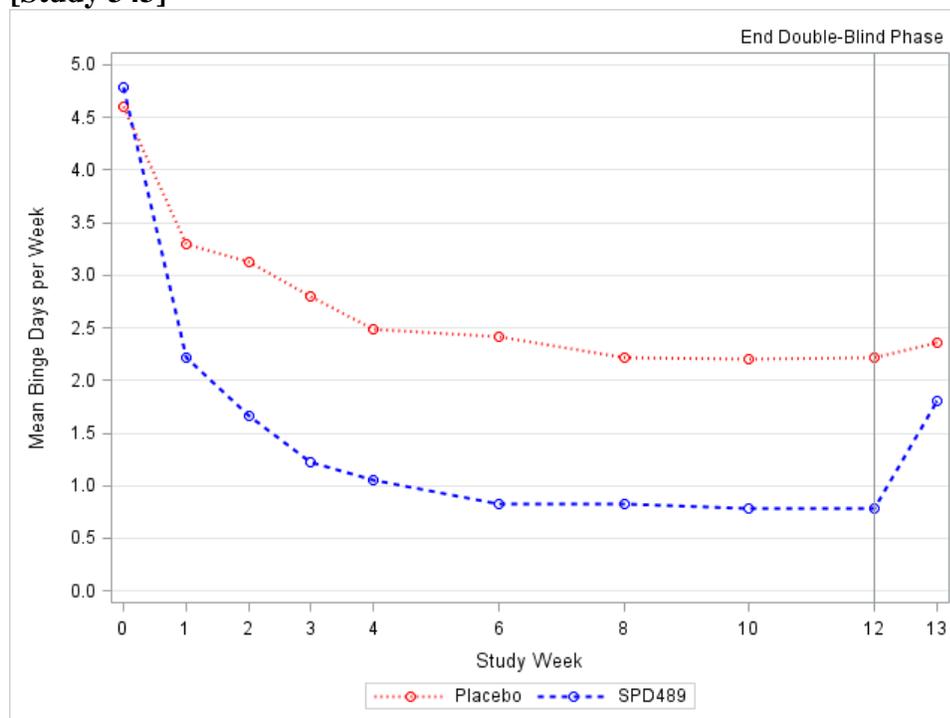
Studies 343 and 344

Primary Endpoint: Number of Binge Days per Week

The number of binge days per week is based on patient diaries. Completeness of those entries is crucial. It appears that entries are missing for only 1.2 to 1.4 percent of all diary days during the double-blind period in Studies 343 and 344.

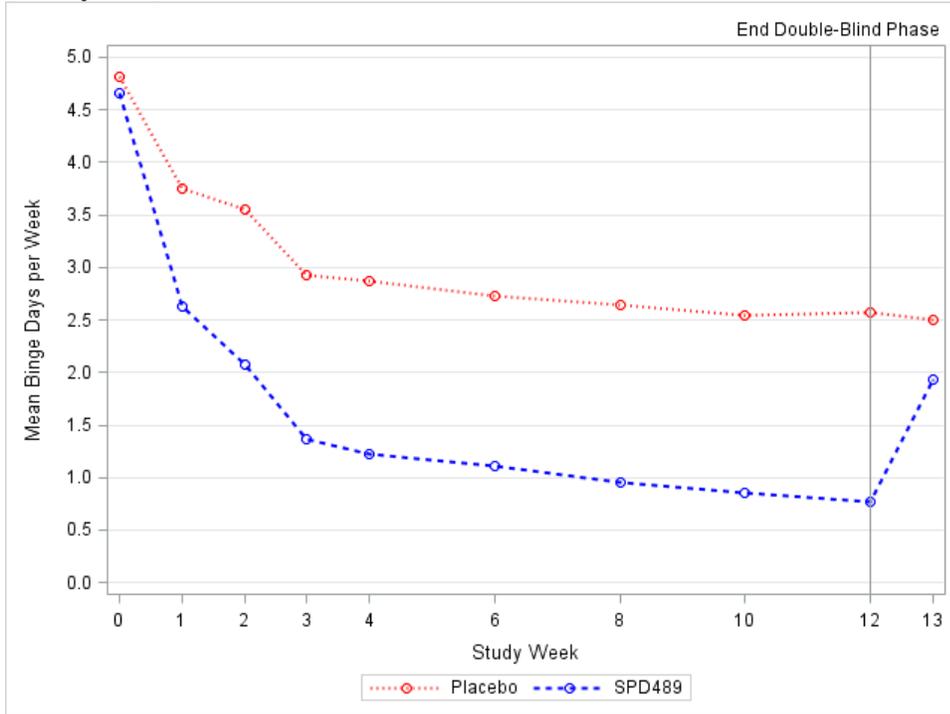
Figure 7 and Figure 8 display the mean number of binge days calculated from the observed data for Studies 343 and 344. Note the large decrease during the first three weeks of the double-blind period for both LDX and placebo groups, with the decrease for the LDX group being clearly larger. The curves are almost flat after week three indicating that there was no further change in binge days on average. It appears that after stopping LDX (Study week 12) the number of binge days is increasing again quickly. Note however, that this last finding is somewhat exaggerated by the inclusion of a number of drop-outs in the Week 13 mean calculation.

Figure 7. Mean Number of Binge Days per Week by Study Week (Observed values) - FAS [Study 343]



(Source: Reviewer, see also Table 15 study report [343]; Note that the Follow-up visit at week 13 included some subjects that had dropped out earlier in the study.)

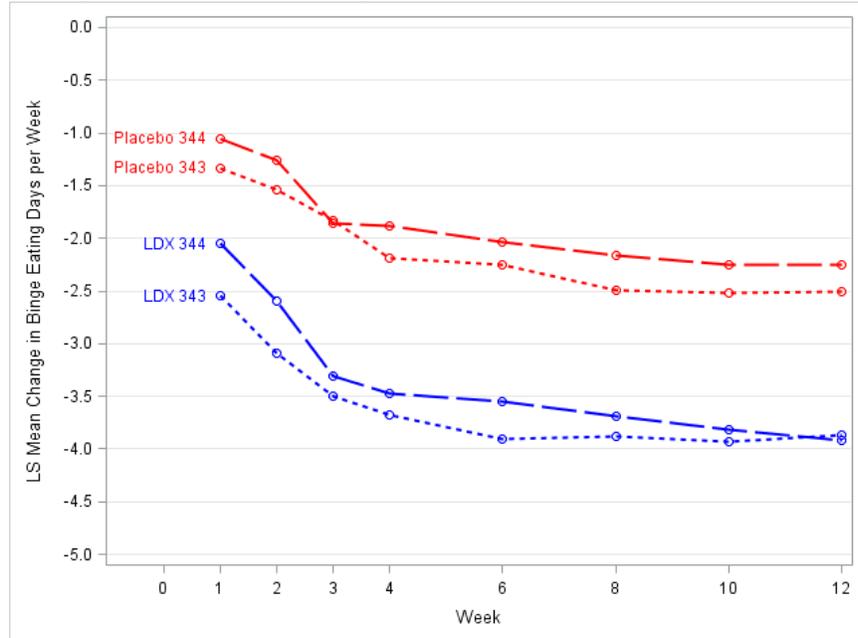
Figure 8. Mean Number of Binge Days per Week by Study Week (Observed values) - FAS [Study 344]



(Source: Reviewer, see also Table 15 study report [344]; Note that the follow-up visit at week 13 included some subjects that had dropped out earlier in the study.)

Figure 9 contains the LS mean changes from baseline in the number of binge days for both Phase 3 studies. The LS mean trajectories are very similar across Studies 343 and 344 and show that most of the decrease in binge days occurs shortly after treatment initiation. A substantive placebo response is noticeable as well.

Figure 9. Primary Endpoint: LS Mean Changes from Baseline in Number of Binge Days – FAS [Studies 343 and 344]

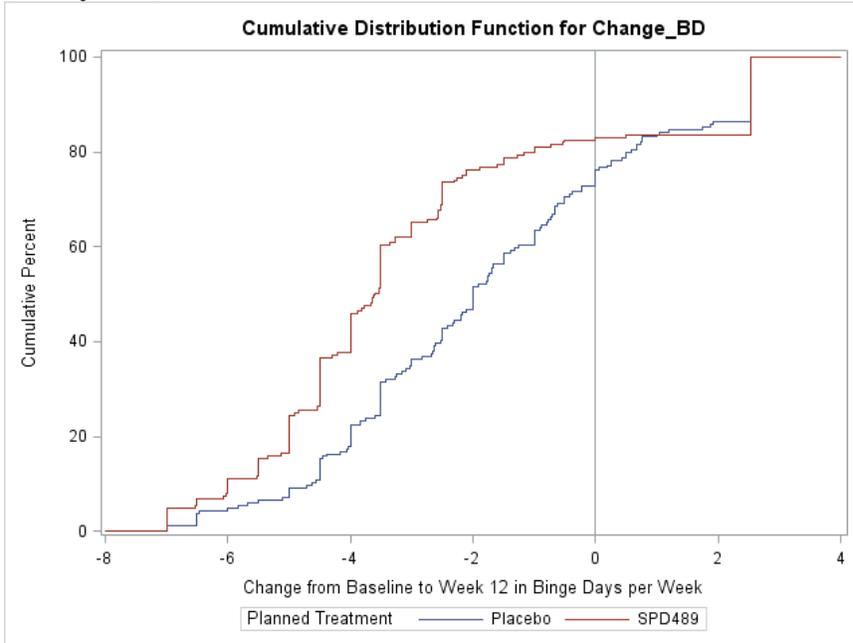


(Source: Reviewer)

Exploration of the Impact of Drop-Outs

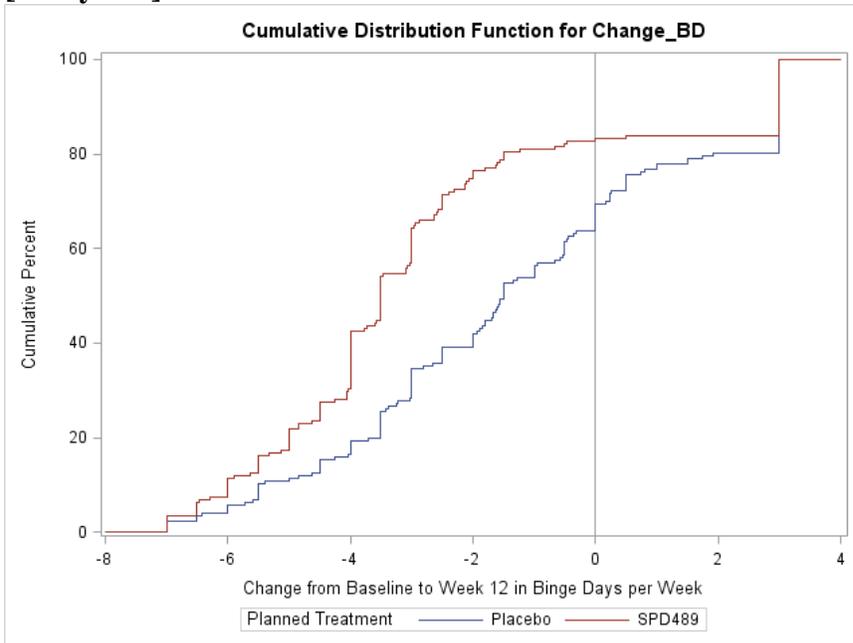
About 14.7 (17.7) percent of patients in the Full Analysis Sets of Study 343 (Study 344) dropped out of the respective study before the final visit (Week 12) in the double-blind period. To assess the impact of the drop-outs on the primary efficacy variable this reviewer conducted a worst case analysis by imputing the worst observed change (i.e., the most extreme increase in binge days) for the missing data points at Week 12 (i.e., Study 343: +2.53 and for Study 344: +3.0). The probability of having a change in binge less or equal to x days remains substantially larger for the SPD489 treated group compared to the placebo group over the entire desired range of x (i.e., where x is negative, indicating a decrease in binge days) (Figure 10 and Figure 11). For different ways to display those results and for worst case scenario results by visit see appendix figures A20 through A29.

Figure 10. Change in Binge Days at Week 12 (Worst Case Imputation for Dropouts) – FAS [Study 343]



(Source: Reviewer)

Figure 11. Change in Binge Days at Week 12 (Worst Case Imputation for Dropouts) – FAS [Study 344]



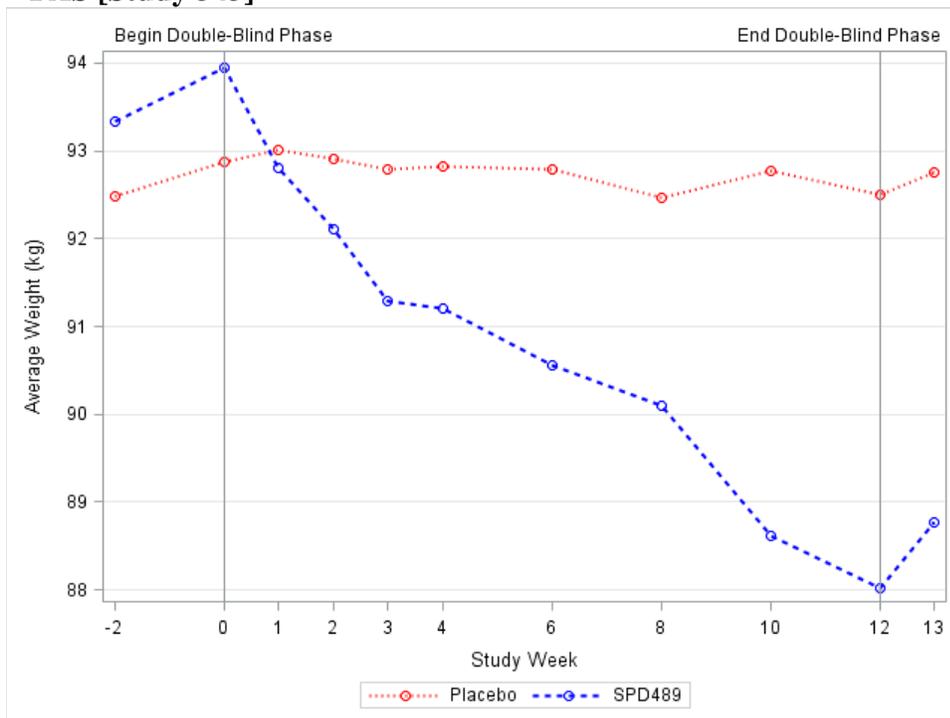
(Source: Reviewer)

Selected Key Secondary Endpoints

Body Weight

Figure 12 provides the mean weight (kg) trajectories by treatment group calculated from observed data for Study 343. The divergence between the SPD489 and Placebo treated patients is striking, with body weight remaining essentially unchanged for the Placebo group, but substantially decreasing over the entire double-blind period for the SPD489 group.

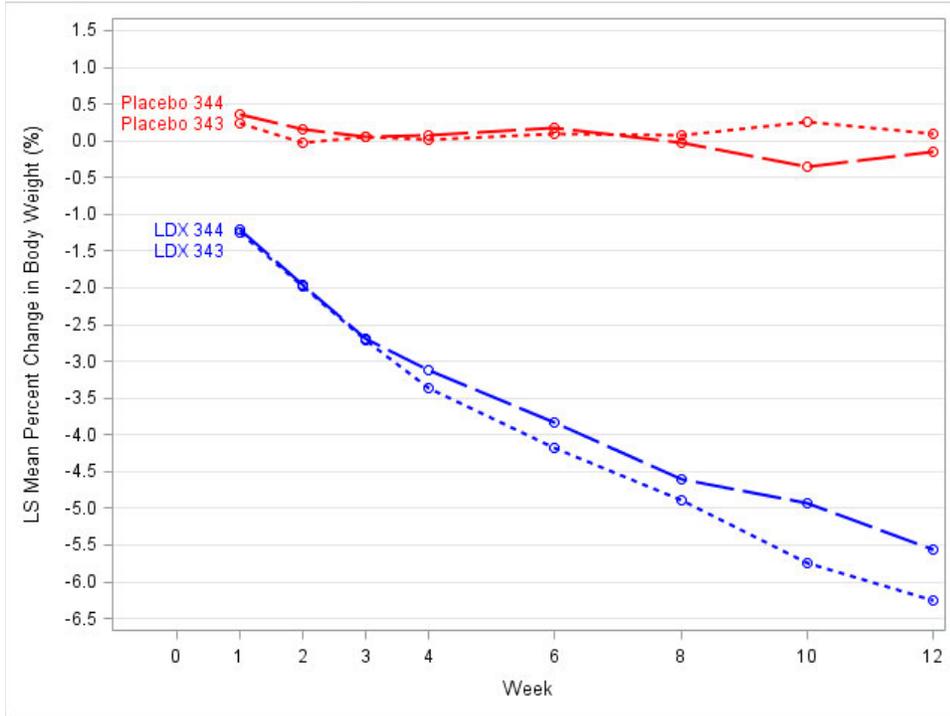
Figure 12. Average Body Weight by Treatment Group and Study Week (Observed values) – FAS [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343; Follow-up visit for SPD489 group includes 12 more subjects compared to Week 12 visit [weight increase from Week 12 to follow-up visit is somewhat smaller for complete analysis]; Compare to Table 22, Figure 7 and Figure 22 in study report)

The finding of clearly diverging effects on body weight are confirmed by the model based mean estimates of percent change in body weight as shown in Figure 13 for both Phase 3 studies. Patients treated with LDX experience weight loss on average (starting at week 1 and continuing throughout the 12 week study), whereas patients treated with Placebo do not see any change in body weight on average. Again, the findings on weight are fairly consistent across Studies 343 and 344.

Figure 13. 3rd Key Secondary: LS Mean Percent Change from Baseline in Body Weight – FAS [Studies 343 and 344]

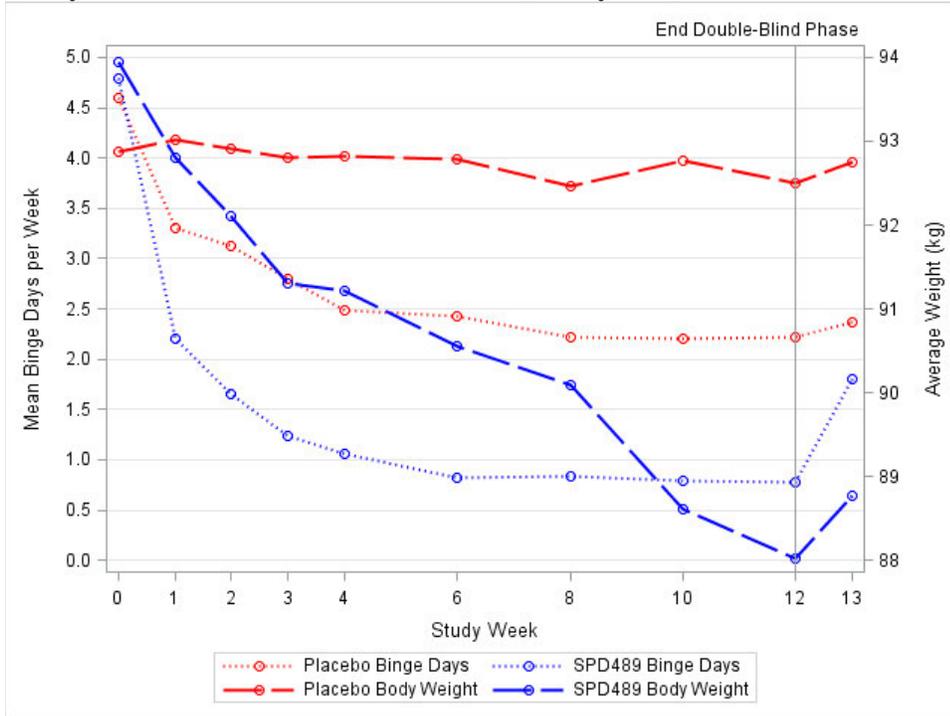


(Source: Reviewer)

Change in Binge in Days vs. Change in Body Weight

The following three figures explore the relationship of the change in binge days and the change in body weight. Figure 14 overlays the mean trajectories of binge days per week and body weight in kg for Study 343 based on observed data. Note that the average decrease by about 2.5 binge days at week 12 for Placebo patients is not associated with a decrease in weight, whereas the comparably larger reduction in binge days for SPD489 patients appears to go hand in hand with weight loss (almost 3 kg in first 3 weeks). The weight loss in the SPD489 group continues after the average number of binge days stabilizes.

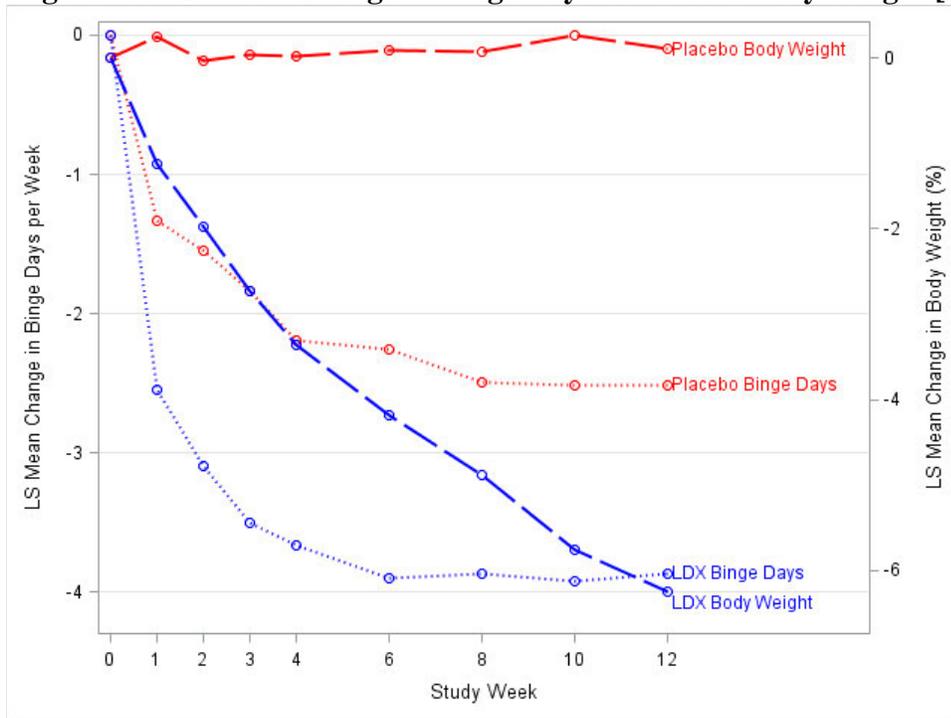
Figure 14. Average Binge Days per Week and Body Weight by Treatment Group and Study Week (Observed values) – FAS [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343)

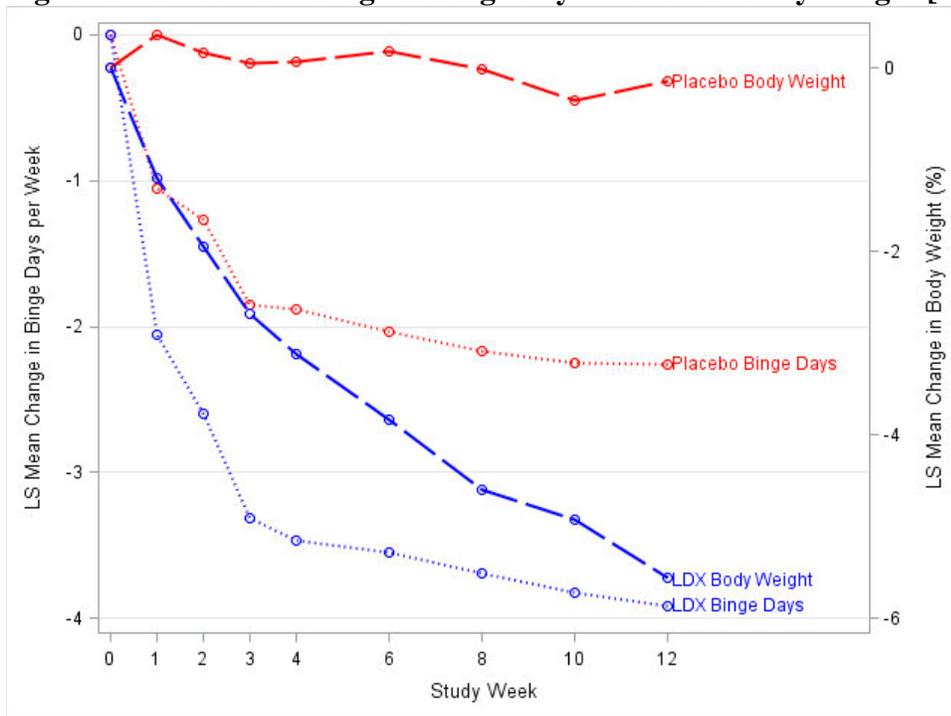
Figure 15 and Figure 16 also display the overlaid mean trajectories, this time based on the model estimates for change in binge days and percent change in weight. The finding reported in connection with Figure 14 – some disconnect between the reduction in binge days observed for both treatment groups albeit to different degrees and a reduction in mean body weight only observed for patients treated with SPD489 – is confirmed by those graphs.

Figure 15. LS Mean Change in Binge Days vs Percent Body Weight [Study 343]



(Source: Reviewer, program: Eff_key_sec_3_wgtm_dropout_expl_343)

Figure 16. LS Mean Change in Binge Days vs Percent Body Weight [Study 344]

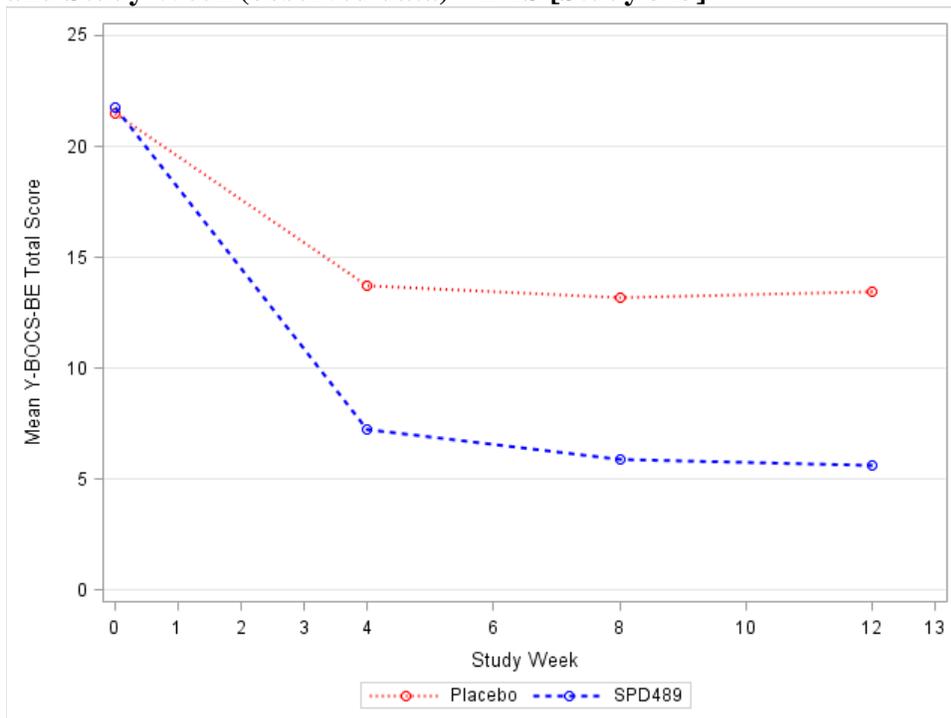


(Source: Reviewer, program: Eff_key_sec_3_wgtm_dropout_expl_343)

Y-BOCS-BE Total Score

The Y-BOCS-BE total score was measured at baseline, week 4, 8 and 12. Figure 17 displays the actual scores at those times for Study 343, whereas the sponsor's figure 8 depicts LS mean change based on the MMRM model. The conclusions are similar: the reduction in the total score occurs early (by week 4) with both treatment groups experiencing improvements. The mean score by treatment group remains flat for the remainder of the study.

Figure 17. Mean Changes from Baseline in Y-BOCS-BE Total Score by Treatment Group and Study Week (observed data) – FAS [Study 343]



(Source: Reviewer; program Eff_key_sec_4_yboc_343, compare to Figure 8 in study report)

Exploratory Primary Analysis by Optimized Dose (50 vs. 70 mg)

Study 344

The proportions of subjects by optimized dose are (344 study report p. 147): 28.7% on 50 mg, 62.4 % on 70 mg, and 8.8 % (16 subjects) did not reach their optimized dose/discontinued. There is almost no difference in the results for the primary endpoint between the 50 and 70 mg groups. Note that patients for whom 50 mg was the optimal dose are on average 10 kg lighter compared to patients with 70 mg as the optimal dose (86.7 kg versus 97.9 kg).

See appendix for:

- Scatterplot: BMI at baseline vs. BMI at end of study
- Scatterplot: Change in Weight vs. Change in Binge Days
- Residual diagnostics for log-transformed vs. untransformed primary endpoint
- Worst case analyses to evaluate impact of missing data

3.3 Evaluation of Safety

The reader is referred to the clinical review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor conducted subgroup analyses by gender, age, sex and race. No generalization is possible due to the small sample sizes (i.e., for Non-US subjects and males [Table 13]; also no patient older 55 years was enrolled) and the lack of stratification by those factors.

4.1 Gender, Race, Age, and Geographic Region

Table 13. Number of Subjects by Subgroup – FAS [Studies 343 and 344]

| Subgroup | Number of Subjects | |
|---------------|--------------------|-----------|
| | Study 343 | Study 344 |
| Region | | |
| US | 334 | 330 |
| Non-US | 40 | 20 |
| Sex | | |
| Females | 325 | 302 |
| Males | 49 | 48 |
| Age Category | | |
| < 40 Years | 199 | 187 |
| ≥ 40 Years | 175 | 163 |
| Race Category | | |
| White | 291 | 259 |
| Non-White | 82 | 91 |

(Source: 343 Study Report p. 108, 344 Study Report p. 110)

The sponsor explored consistency of treatment effects with respect to the change from baseline to Week 12 in the number of binge days per week using the MMRM models described above for

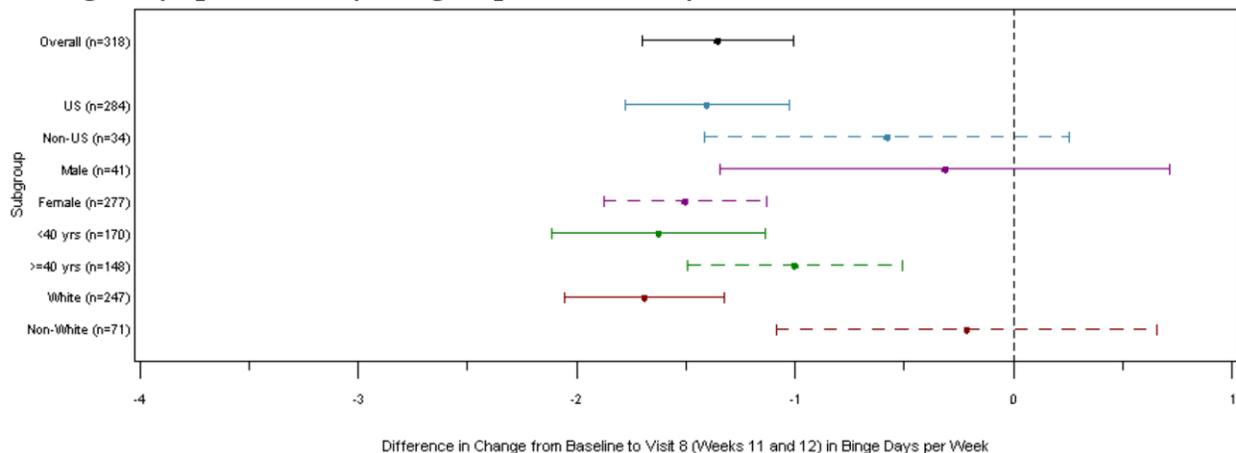
region (US and non-US), sex, age (<40 years and ≥40 years), and race (White and non-White). For each variable, an MMRM model was applied for each subgroup.

For all subgroups, LS mean decreases from baseline at Week 12 in number of binge days per week were noted for both treatment groups and were of numerically greater magnitude for the SPD489 group compared to placebo, which is consistent with the primary efficacy results based on the Full Analysis Set.

A graphic representation of LS mean differences (95% CIs) in change from baseline at Visit 8 is presented for all subgroups in Figure 18 (Study 343) and Figure 19 (Study 344). For the majority of subgroups, the 95% CIs fell left of zero, which indicates a greater mean improvement for subjects receiving SPD489 compared to placebo. However, the 95% CIs for non-US subjects (Studies 343 and 344), males (Study 343), and non-whites (Study 343) were relatively wide (potentially because of a relatively small sample size) and crossed zero, which indicates similarity between treatment groups.

However, because the randomization was not stratified based on subgroup, the number of subjects within a subgroup was not consistently balanced. Therefore, a definitive conclusion regarding efficacy results based on subgroup cannot be drawn (see 343/344 Study Reports p. 108/111).

Figure 18. LS Mean Difference (95% CI) in Change from Baseline at Week 12 in Number of Binge Days per Week by Subgroup – FAS [Study 343]

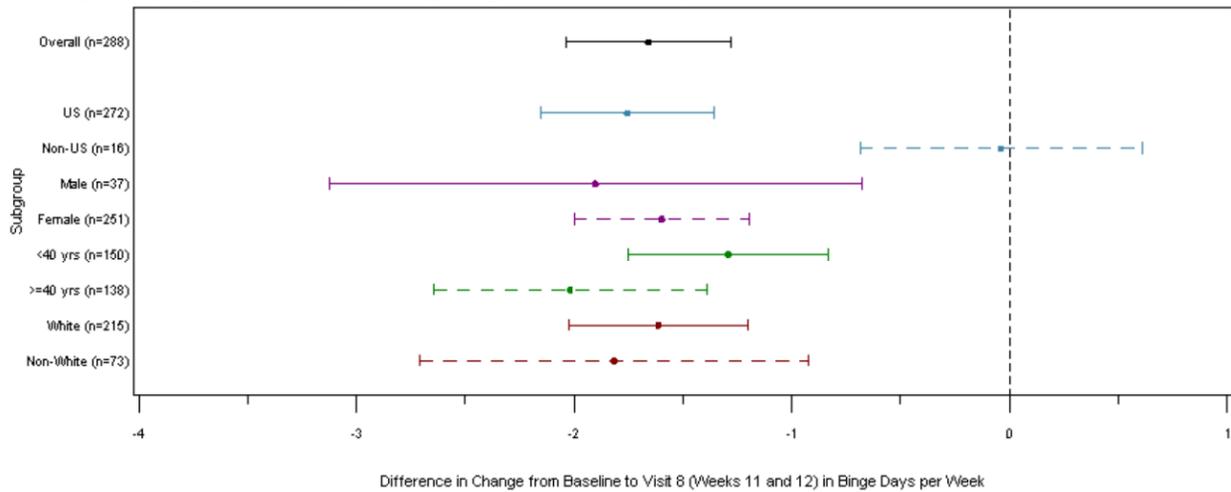


Reference line refers to no difference between SPD489 and Placebo in change from baseline number of binge days per week. Negative improvement indicates more improvement from baseline for SPD489 than placebo. n represents the number of subjects in the Full Analysis Set with a valid result at Visit 8 for each subgroup. Reference: Tables 3.1.1.1 and 3.1.2.6-3.1.2.9. Program: f_a-fchg.sas, Output: f_a-fchg.rtf, Generated on: 26NOV2013 08:23 Page 1 of 1

LS=least squares; US=United States

(Source: 343 Study Report p. 109)

Figure 19. LS Mean Difference (95% CI) in Change from Baseline at Week 12 in Number of Binge Days per Week by Subgroup – FAS [Study 344]



Reference line refers to no difference between SPD489 and Placebo in change from baseline number of binge days per week. Negative improvement indicates more improvement from baseline for SPD489 than placebo.
 Reference: Tables 3.1.1.1 and 3.1.2.8-3.1.2.9.
 Program: f_a-fchg.sas, Output: f_a-fchg.rtf, Generated on: 27NOV2013 05:45
 (Source: 344 Study Report p. 112)

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were discovered during the review.

5.2 Collective Evidence

The results obtained by proof-of-concept study 208, and the two pivotal studies 343 and 344 have to be viewed in light of the patient population enrolled: mostly female, white and obese (only Studies 343 and 344 randomized about 10 percent normal weight patients). A patient's binge eating disorder had to be of at least moderate severity (i.e., at least three binge eating days per week for the 14 days prior to randomization) to be eligible for the trials.

The 30 mg group in Study 208 did not show a statistically significant improvement at the 0.05 significance level over placebo on the primary endpoint. A marked placebo response was observed for most endpoints. Nonetheless, the results for the SPD489 (50 and 70 mg) treated

groups demonstrated statistically significant improvements over the placebo treated patient groups. For example the reduction in the number of binge days per week (the primary endpoint in both Phase 3 studies) was about 2.5 days at week 12 for the placebo groups, but close to 4 days for the SPD489 groups. The statistical significant results for all key secondary endpoints in the Phase 3 trials also provide support for a treatment effect of SPD489. For example, at week 12 there were roughly twice as many SPD489 treated patients in the improved category of the dichotomized CGI-I compared to placebo patients. The percentage of subjects with a 4-week cessation at the end of study is roughly three times larger for patients on SPD489.

5.3 Conclusions and Recommendations

The statistical results of Studies 208, 343, and 344 provide adequate evidence to support a claim for SPD489 in the treatment of moderate to severe binge eating disorder in adults.

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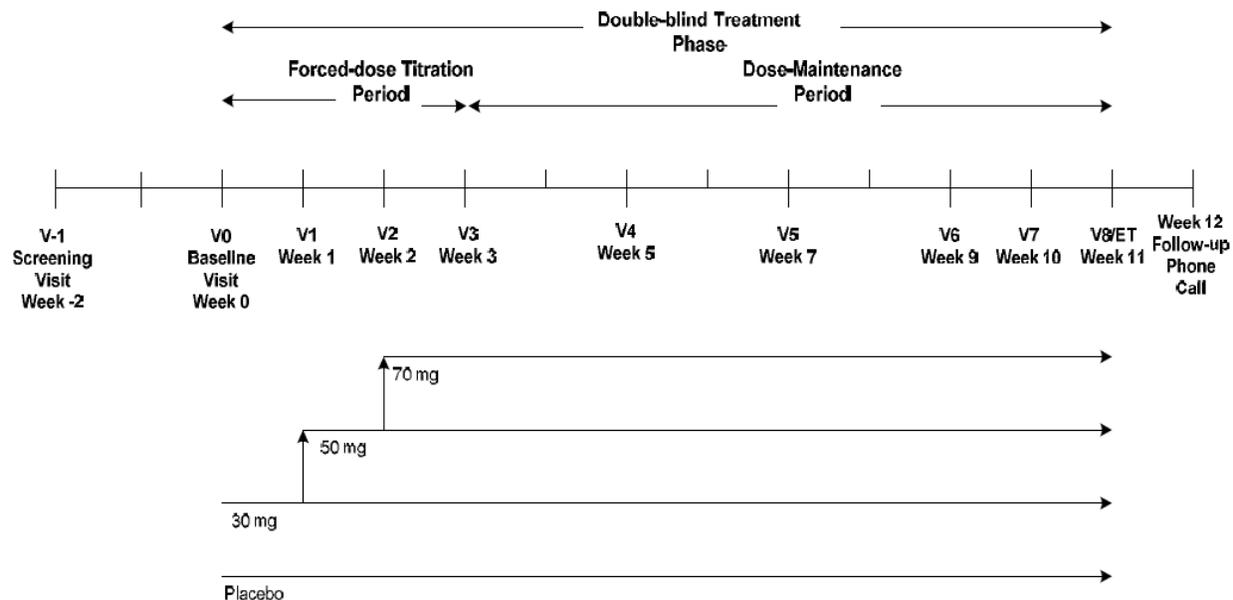
Study 208

Study Design and Endpoints

Study 208 (Proof-of-Concept Study)

Adult patients (18-55 years of age) with moderate to severe BED were randomized (1:1:1:1) to SPD489 30, 50, or 70mg/day, or placebo and treated for 11 weeks to evaluate safety and efficacy. The study consisted of 3 periods, as follows: a Screening Period (2 weeks), an 11-week Double-blind Treatment Phase (consisting of a 3-week Forced-dose Titration Period followed by a maximum 8-week Dose-Maintenance Period), and a 1-week Follow-up Period. A design schematic is provided in Figure A1.

Figure A1. Study Design Schematic [Study 208]



(Source: Study 208 Protocol p. 34)

Primary endpoint

The primary efficacy endpoint is the change from baseline at Visit 8 (Week 11) in the log transformed number of binge days per week.

Secondary endpoints

Selected secondary endpoints are: the number of binge episodes per week, 4-week remission, Clinical Global Impressions of Severity and Improvement scales (CGI-S and CGI-I), and the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (YBOCS-BE).

Statistical Methodologies

The primary efficacy endpoint is the change from baseline at Visit 8 (Week 11) in the log transformed number of binge days per week. The primary efficacy analysis is based on a mixed-effects model for repeated measures (MMRM) analysis over all post-baseline visits, with change from baseline in log (number of binge days per week +1) as the outcome variable. The model includes fixed factors for treatment and visit, the interaction of treatment and visit, a covariate of log (baseline number of binge days per week + 1) and the interaction of the baseline covariate and visit. P-values for the comparison between each SPD489 group and placebo are generated for Visit 8 (Week 11). The primary efficacy analysis is performed on the Full Analysis Set. In order to control the study-wise Type I error rate, a hierarchical testing procedure, starting with the highest dose, was used to compare each dose group with placebo.

Reviewer's Notes: Since the target indication is relatively new, there was very limited data to evaluate the suitability of statistical analyses for a primary endpoint candidate. We asked the sponsor to explore the statistical properties associated with a few primary endpoint candidates in this proof-of-concept study; for example, the transformed vs. untransformed ordinal variable as the primary endpoint, the adequacy of normality approximation for a non-normal random variable.

Patient Disposition, Demographic and Baseline Characteristics

Male or female subjects, between 18-55 years of age who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV) criteria for a diagnosis of BED of at least moderate severity, were included in this study. A patient's binge eating disorder had to be of at least moderate severity; meaning a subject reported at least 3 binge eating days per week for the 2 weeks prior to the Baseline Visit (Visit 0) as documented in the subject take-home binge diary. A study participant's body mass index (BMI) had to be between 25 and 45. Note

that a person with a BMI of 25 or greater is considered overweight, and a person with a BMI of 30 or greater is considered obese.

Table A1. Subject Disposition [Study 208]

| | Placebo n (%) | SPD489 30mg n (%) | SPD489 50mg n (%) | SPD489 70mg n (%) | SPD489 All Doses n (%) | Total n (%) |
|--|----------------------|-------------------------|-------------------------|-------------------------|------------------------------|-------------------------|
| Screened subjects | | | | | | 511 |
| Randomized Subjects | 67 | 68 | 68 | 68 | 204 | 271 |
| Safety analysis set ^a | 66 (98.5) | 68 (100.0) | 68 (100.0) | 68 (100.0) | 204 (100.0) | 270 ^b (99.6) |
| Full analysis set ^c | 65 (97.0) | 68 (100.0) | 67 (98.5) | 66 (97.1) | 201 (98.5) | 266 (98.2) |
| Completed titration phase ^d | 60 (89.6) | 62 (91.2) | 64 (94.1) | 63 (92.6) | 189 (92.6) | 249 (91.9) |
| Completed study | 50 (74.6) | 53 (77.9) | 55 (80.9) | 55 (80.9) | 163 (79.9) | 213 (78.6) |
| Completer analysis set ^e | 50 (74.6) | 53 (77.9) | 55 (80.9) | 55 (80.9) | 163 (79.9) | 213 (78.6) |
| Did not complete study | 17 (25.4) | 15 (22.1) | 13 (19.1) | 13 (19.1) | 41 (20.1) | 58 (21.4) |
| Primary Reason for Withdrawal (All Randomized Subjects) | | | | | | |
| Adverse event | 0 | 3 (4.4) | 1 (1.5) | 3 (4.4) | 7 (3.4) | 7 (2.6) |
| Protocol violation | 7 (10.4) | 2 (2.9) | 2 (2.9) | 5 (7.4) | 9 (4.4) | 16 (5.9) |
| Withdrawal by subject | 6 (9.0) ^b | 4 (5.9) | 4 (5.9) | 2 (2.9) | 10 (4.9) | 16 (5.9) |
| Lost to follow-up | 4 (6.0) | 6 (8.8) | 3 (4.4) | 2 (2.9) | 11 (5.4) | 15 (5.5) |
| Lack of efficacy | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 3 (4.4) | 1 (1.5) | 4 (2.0) | 4 (1.5) |

^a The Safety Analysis Set includes all randomized subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

^b Subject 012-0018 (placebo) did not have any post-baseline safety assessments and was excluded from the Safety Population.

^c The Full Analysis Set includes all subjects who took at least 1 dose of investigational product and had 1 post-baseline primary efficacy assessment.

^d The Titration Phase was completed at Week 3 when the 70mg treatment arm had completed 1 week of dosing at 70mg.

^e The Completer Analysis Set includes all randomized subjects who completed the study through Visit 8 (Week 11).

Note: Percentages are based on all randomized subjects except where otherwise noted.

Denominators for reasons for withdrawal are detailed in the label in parentheses.

(Source: Study Report p. 59)

Baseline characteristics [Study 208]

The mean age was 38.7 years, with similar proportions of subjects being <40 years (50.7%) and ≥40 years (49.3%). The majority of subjects, regardless of treatment group, were female and white. The overall mean values for weight was 216.9 lbs and the overall mean BMI was 34.9. The majority of subjects, regardless of treatment group, were in a baseline BMI category of obese.

The mean number of binge days per week at baseline was between 4.3 and 4.6 days, and the mean number of binge episodes per week was between 5.3 and 5.8. Based on the CGI-S, the majority of subjects were moderately or markedly ill at baseline. An overview of the baseline characteristics is provided in Table A2.

Table A2. Demographic and Baseline Characteristics [Study 208]

| | Placebo (N=66) | SPD489 30mg (N=68) | SPD489 50mg (N=68) | SPD489 70mg (N=68) | SPD489 All Doses (N=204) | Total (N=270) |
|----------------------------------|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------------|------------------|
| | Safety Analysis Set | | | | | |
| Age (years) ^a | | | | | | |
| n | 66 | 68 | 68 | 68 | 204 | 270 |
| Mean (SD) | 38.3 (10.23) | 38.5 (11.01) | 39.5 (9.45) | 38.6 (10.01) | 38.9 (10.13) | 38.7 (10.14) |
| Median | 37.5 | 39.0 | 41.0 | 39.0 | 39.5 | 39.0 |
| Min, Max | 20, 55 | 20, 55 | 19, 55 | 20, 55 | 19, 55 | 19, 55 |
| Age category (years) n (%) | | | | | | |
| <40 | 35 (53.0) | 35 (51.5) | 31 (45.6) | 36 (52.9) | 102 (50.0) | 137 (50.7) |
| ≥40 | 31 (47.0) | 33 (48.5) | 37 (54.4) | 32 (47.1) | 102 (50.0) | 133 (49.3) |
| Sex n (%) | | | | | | |
| Male | 16 (24.2) | 9 (13.2) | 15 (22.1) | 10 (14.7) | 34 (16.7) | 50 (18.5) |
| Female | 50 (75.8) | 59 (86.8) | 53 (77.9) | 58 (85.3) | 170 (83.3) | 220 (81.5) |
| Ethnicity n (%) | | | | | | |
| Hispanic or Latino | 5 (7.6) | 7 (10.3) | 7 (10.3) | 10 (14.7) | 24 (11.8) | 29 (10.7) |
| Not Hispanic or Latino | 61 (92.4) | 61 (89.7) | 61 (89.7) | 58 (85.3) | 180 (88.2) | 241 (89.3) |
| Race n (%) | | | | | | |
| White | 55 (83.3) | 50 (73.5) | 55 (80.9) | 51 (75.0) | 156 (76.5) | 211 (78.1) |
| Non-White | 11 (16.7) | 18 (26.5) | 13 (19.1) | 17 (25.0) | 48 (23.5) | 59 (21.9) |
| Black or African American | 9 (13.6) | 15 (22.1) | 11 (16.2) | 12 (17.6) | 38 (18.6) | 47 (17.4) |
| Asian | 2 (3.0) | 1 (1.5) | 0 | 1 (1.5) | 2 (1.0) | 4 (1.5) |
| American Indian or Alaska Native | 0 | 0 | 1 (1.5) | 3 (4.4) | 4 (2.0) | 4 (1.5) |
| Other | 0 | 2 (2.9) | 1 (1.5) | 1 (1.5) | 4 (2.0) | 4 (1.5) |

Table A2. Continued

| | Placebo (N=66) | SPD489 30mg (N=68) | SPD489 50mg (N=68) | SPD489 70mg (N=68) | SPD489 All Doses (N=204) | Total (N=270) |
|---|--------------------|--------------------------|--------------------------|--------------------------|--------------------------------|--------------------|
| Weight (lb) | | | | | | |
| n | 66 | 68 | 68 | 68 | 204 | 270 |
| Mean (SD) | 212.89 (37.450) | 216.59 (40.639) | 221.10 (41.246) | 216.77 (38.444) | 218.15 (39.984) | 216.87 (39.376) |
| Median | 212.25 | 213.00 | 221.75 | 217.25 | 216.25 | 214.75 |
| Min, Max | 143.0, 309.0 | 127.6, 333.0 | 143.0, 322.0 | 143.5, 348.5 | 127.6, 348.5 | 127.6, 348.5 |
| Height (in) | | | | | | |
| n | 66 | 68 | 68 | 68 | 204 | 270 |
| Mean (SD) | 66.12 (3.239) | 65.88 (3.663) | 66.28 (3.229) | 65.93 (3.553) | 66.03 (3.474) | 66.05 (3.413) |
| Median | 65.50 | 66.00 | 66.40 | 65.75 | 66.00 | 66.00 |
| Min, Max | 59.5, 74.3 | 59.0, 74.0 | 59.5, 73.5 | 59.5, 75.0 | 59.0, 75.0 | 59.0, 75.0 |
| BMI (703*lb/in²) | | | | | | |
| n | 66 | 68 | 68 | 68 | 204 | 270 |
| Mean (SD) | 34.21 (5.289) | 34.98 (5.320) | 35.31 (5.703) | 34.98 (4.914) | 35.09 (5.298) | 34.87 (5.300) |
| Median | 34.86 | 35.16 | 35.40 | 34.88 | 35.05 | 35.00 |
| Min, Max | 25.9, 44.7 | 25.8, 44.8 | 25.2, 45.3 | 26.0, 45.4 | 25.2, 45.4 | 25.2, 45.4 |
| BMI category n (%) | | | | | | |
| Overweight (25 to <30) | 15 (22.7) | 14 (20.6) | 16 (23.5) | 15 (22.1) | 45 (22.1) | 60 (22.2) |
| Obese (>=30 to <40) | 41 (62.1) | 41 (60.3) | 35 (51.5) | 42 (61.8) | 118 (57.8) | 159 (58.9) |
| Morbidly Obese (>=40) | 10 (15.2) | 13 (19.1) | 17 (25.0) | 11 (16.2) | 41 (20.1) | 51 (18.9) |
| Baseline binge days per week | | | | | | |
| n | 66 | 68 | 68 | 68 | 204 | 270 |
| Mean (SD) | 4.3 (1.35) | 4.6 (1.45) | 4.6 (1.27) | 4.5 (1.26) | 4.5 (1.32) | 4.5 (1.33) |
| Median | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| Min, Max | 2, 7 | 2, 7 | 3, 7 | 3, 7 | 2, 7 | 2, 7 |
| Baseline binge episodes per week | | | | | | |
| n | 66 | 68 | 68 | 68 | 204 | 270 |
| Mean (SD) | 5.3 (2.15) | 5.8 (3.00) | 5.5 (2.71) | 5.5 (2.41) | 5.6 (2.70) | 5.5 (2.58) |
| Median | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| Min, Max | 2, 12 | 3, 14 | 3, 15 | 3, 14 | 3, 15 | 2, 15 |

(Source: Study report p. 61-62)

A summary of major protocol deviations is presented in Table A3. Of the 270 subjects in the Safety Analysis Set, 44 subjects (16.3%) had at least one major deviation from the protocol. The most frequently recorded deviation, regardless of treatment group, was violation of inclusion/exclusion criteria (e.g., 5 subjects had fewer than three binge eating days per week during the two week screening period and 9 subjects had a positive urine drug screen).

Table A3. Summary of Major Protocol Deviations [Study 208]

| | Placebo (N=66) | SPD489 30mg (N=68) | SPD489 50mg (N=68) | SPD489 70mg (N=68) | SPD489 All Doses (N=204) | Total (N=270) |
|--|-------------------|--------------------------|--------------------------|--------------------------|--------------------------------|------------------|
| Subjects With Any Major Protocol Deviation | 14 (21.2) | 10 (14.7) | 11 (16.2) | 9 (13.2) | 30 (14.7) | 44 (16.3) |
| Major Protocol Deviation: ^a | | | | | | |
| Failed to Meet Inclusion or Exclusion Criteria | 10 (15.2) | 6 (8.8) | 5 (7.4) | 7 (10.3) | 18 (8.8) | 28 (10.4) |
| Misuse of Investigational Product | 3 (4.5) | 2 (2.9) | 3 (4.4) | 0 | 5 (2.5) | 8 (3.0) |
| Took Prohibited Medication | 1 (1.5) | 1 (1.5) | 2 (2.9) | 1 (1.5) | 4 (2.0) | 5 (1.9) |
| Overall Compliance of <80% or >120% | 0 | 1 (1.5) | 0 | 1 (1.5) | 2 (1.0) | 2 (0.7) |
| Other | 0 | 0 | 1 (1.5) | 1 (1.5) | 2 (1.0) | 2 (0.7) |

^a Major protocol deviations are presented in decreasing frequency based on the "Total" column.

Note: Percentages are based on the number of subjects in each treatment group and total.

(For Safety Analysis Set; Source: Study report p. 70)

Results and Conclusions

Study 208 is a Phase 2 study evaluating three doses of SPD489: 30, 50, and 70 mg.

Primary endpoint

The primary endpoint is the change in log transformed number of binge days per week. A few notes on the log transformation:

- Log “=” ln “=” natural logarithm “=” log base e
- Log transformation: $\ln(\text{binge days per week} + 1)$
- $\ln(0+1) = 0$ [avoids $\ln(0) = -\infty$]
- $\ln(\text{change_binge_days}) = \ln(\text{binge_days_at_visit_i} + 1) - \ln(\text{binge_days_at_BL} + 1)$

Mean decreases from baseline in the log transformed number of binge days per week, which were noted for all treatment groups at all post-baseline assessment time points (Visits 1-8), were consistently numerically superior for the SPD489 groups (30, 50, 70 mg) compared to placebo.

The differences at Visit 8 (Week 11) for the least square mean changes from baseline in the log transformed number of binge days per week were statistically significant between SPD489 50 mg and placebo (-0.33, $p < 0.001$) and between SPD489 70 mg and placebo (-0.41, $p < 0.001$) [Table A4]. Although SPD489 30 mg was numerically superior to placebo for having fewer mean binge days per week at Visit 8 (Week 11), the difference between these groups was not statistically significant (-0.09, $p=0.347$) (208 Study Report p. 72).

Table A4. Primary Endpoint: Change from Baseline in Log Transformed Binge Eating Days per Week at Week 11 - FAS [Study 208]

| | Placebo (N=65) | LDX 30 mg (N=68) | LDX 50 mg (N=67) | LDX 70 mg (N=66) |
|---|---------------------------|---------------------------------|---------------------------------|---------------------------------|
| Baseline Mean | 1.64 | 1.68 | 1.69 | 1.68 |
| LS Mean Change from Baseline | -1.17 | -1.26 | -1.50 | -1.58 |
| LS Mean Diff.* (95% CI) | | -0.09 (-0.28, 0.10) | -0.33 (-0.51, -0.14) | -0.41 (-0.59, -0.22) |

(Source: 208 Study report p. 73, 74; results replicated by reviewer; *Diff = LDX – Placebo; negative value indicates greater improvement for LDX patients compared to Placebo patients; 95% CI is confidence interval without adjusting for multiplicity.)

Exploratory Analysis on Nontransformed Data

The differences at Visit 8 (Week 11) for the least square mean changes from baseline in the nontransformed number of binge days per week (Table A5) were statistically significant between SPD489 50 mg and placebo (-0.76, $p < 0.001$) and between SPD489 70 mg and placebo (-0.89, $p < 0.001$). The mean difference between SPD489 30 mg and placebo at Visit 8 (Week 11) was -0.15, which was not statistically significant ($p=0.51$).

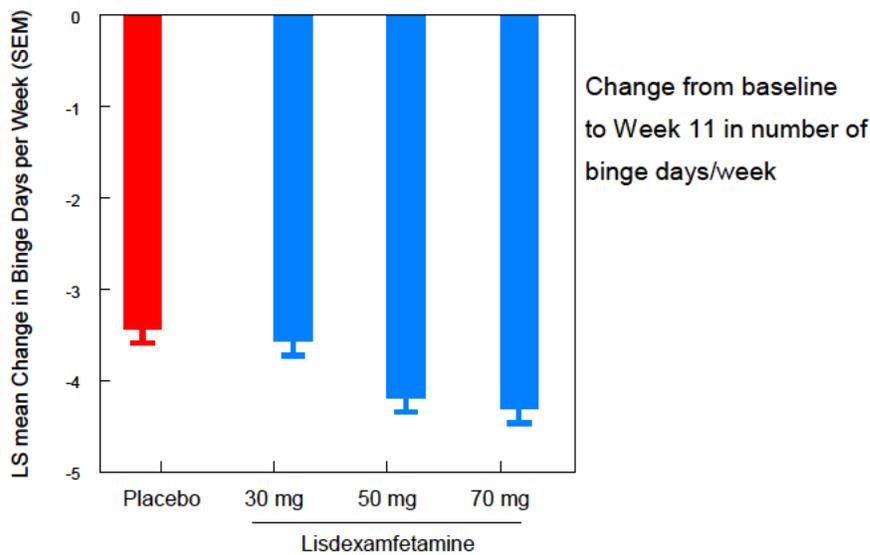
Table A5. Primary Endpoint (Exploratory Analysis): Change from Baseline in Nontransformed Binge Eating Days per Week at Week 11 - FAS [Study 208]

| | Placebo (N=65) | LDX 30 mg (N=68) | LDX 50 mg (N=67) | LDX 70 mg (N=66) |
|---|---------------------------|---------------------------------|---------------------------------|---------------------------------|
| Baseline Mean | 4.33 | 4.57 | 4.58 | 4.50 |
| LS Mean Change from Baseline | -3.43 | -3.57 | -4.19 | -4.31 |

| | | | | |
|--------------------------------|--|------------------------|-------------------------|-------------------------|
| LS Mean Diff.* (95% CI) | | -0.15 (-0.58, 0.29) | -0.76 (-1.20, -0.33) | -0.89 (-1.32, -0.46) |
|--------------------------------|--|------------------------|-------------------------|-------------------------|

(Source: 208 Study report p. 76, 77; results replicated by reviewer; *Diff = LDX – Placebo; negative value indicates greater improvement for LDX patients compared to Placebo patients; 95% CI is confidence interval without adjusting for multiplicity)

Figure A2. Exploration of Dose Response - FAS [Study 208]



(Source: Reviewers; estimates from an MMRM model with fixed factors for treatment and visit, the interaction of treatment and visit, the baseline number of binge days per week as a covariate, and the interaction of the baseline covariate and visit)

Secondary endpoints:

The following selected secondary endpoints achieved nominal statistical significance for the 50 and 70 mg SPD 489 groups compared to placebo:

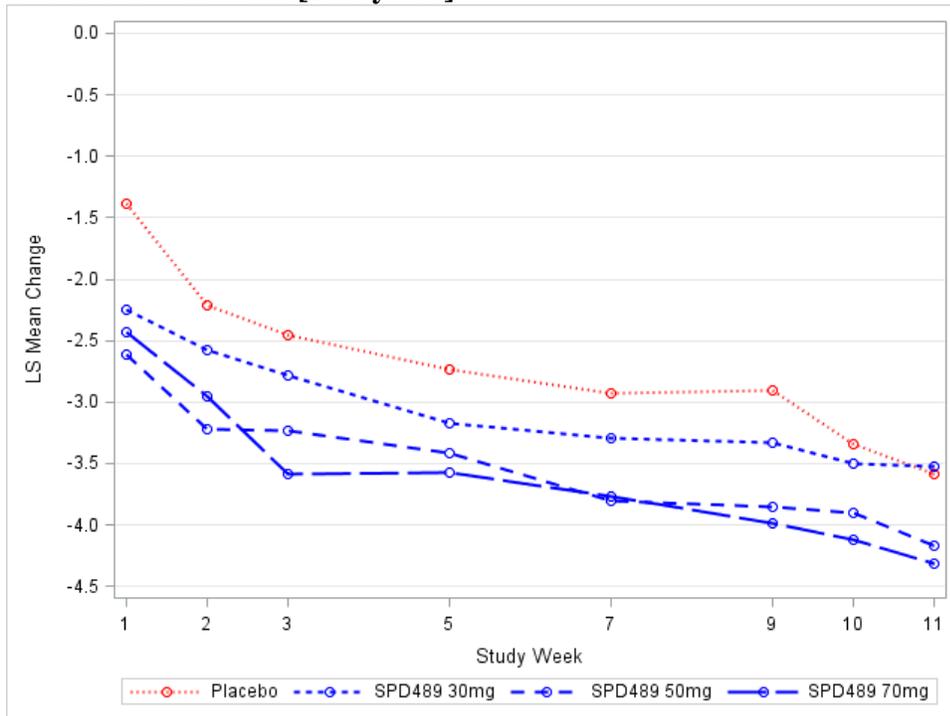
- Change in number of binge episodes per week from baseline
- 4-week remission
- Dichotomized Clinical Global Impression – Improvement (CGI-I)

Reviewer's analysis

Recall the exploratory analysis by the sponsor on the untransformed primary endpoint data (208 study report p. 76). The estimated differences are somewhat smaller in Study 208 (-0.8 to -0.9 days) compared to Studies 343 and 344 (-1.3 to -1.7 days). A possible explanation is the larger placebo response in Study 208 (i.e., about one additional binge day less in the Placebo group at the end of study compared to the Phase 3 studies).

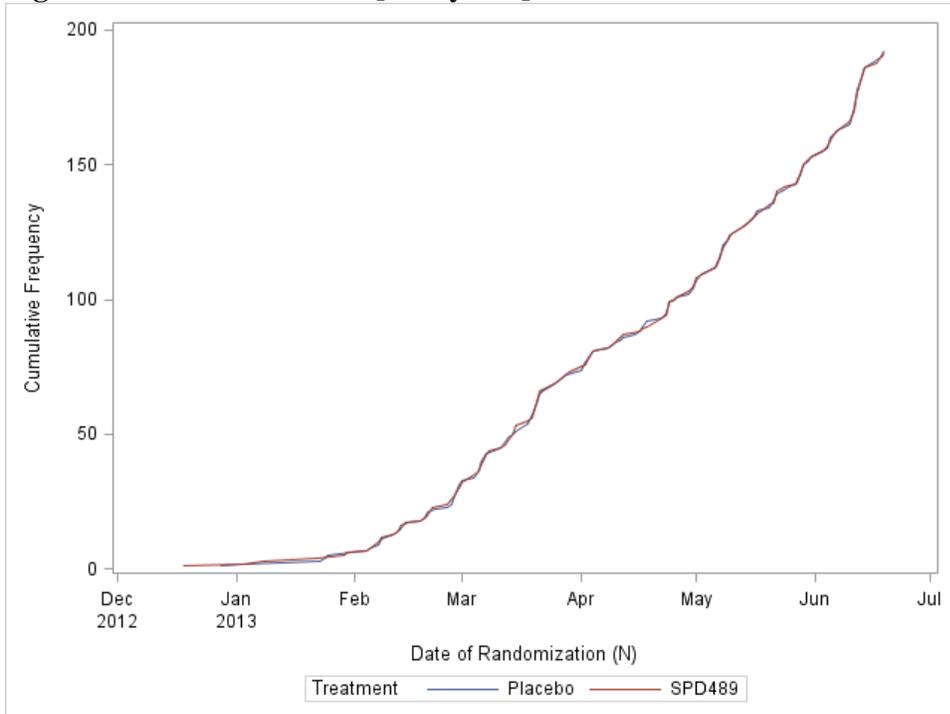
Figure A3 displays the LS mean change in binge days (untransformed) over the course of Study 208 by treatment group. Note that a large proportion of the reduction in binge days occurs early, in fact that the largest decrease happens between baseline and week 1.

Figure A3. LS Mean Changes in Primary Endpoint over Course of Study for Untransformed Data [Study 208]



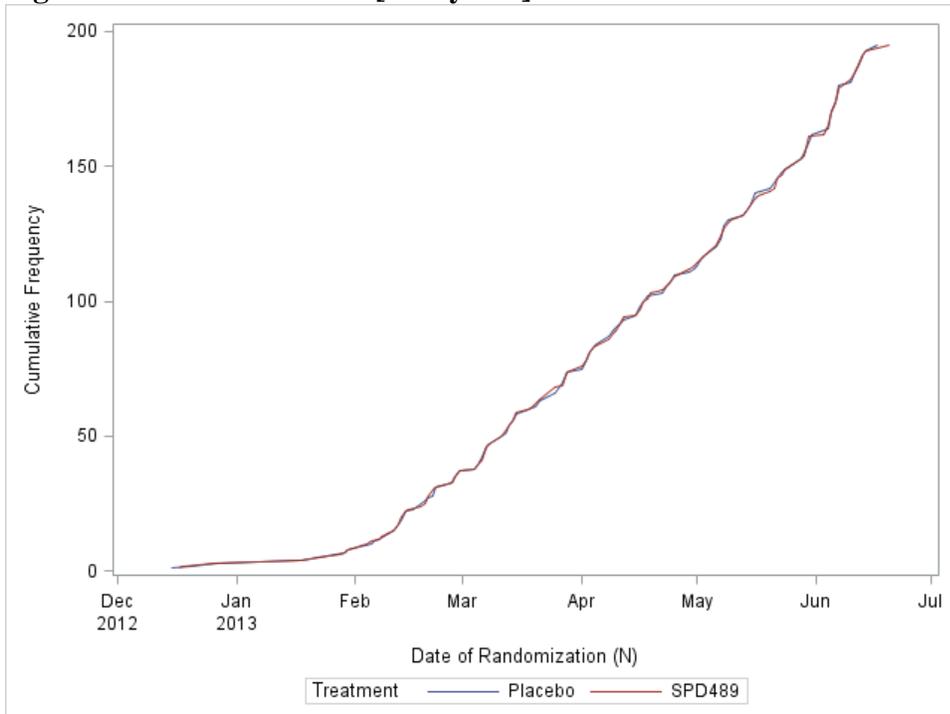
(Source: Reviewer; data from Table 3.1.2.7 in addendum to study report [MMRM])

Figure A4. Randomization [Study 343]



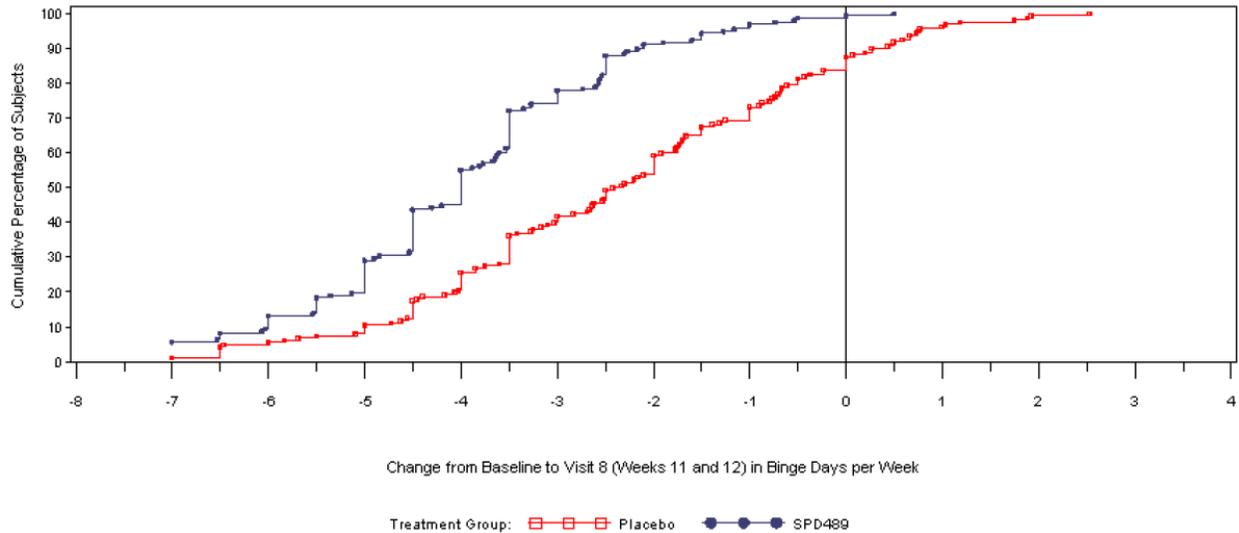
(Source: Reviewer)

Figure A5. Randomization [Study 344]



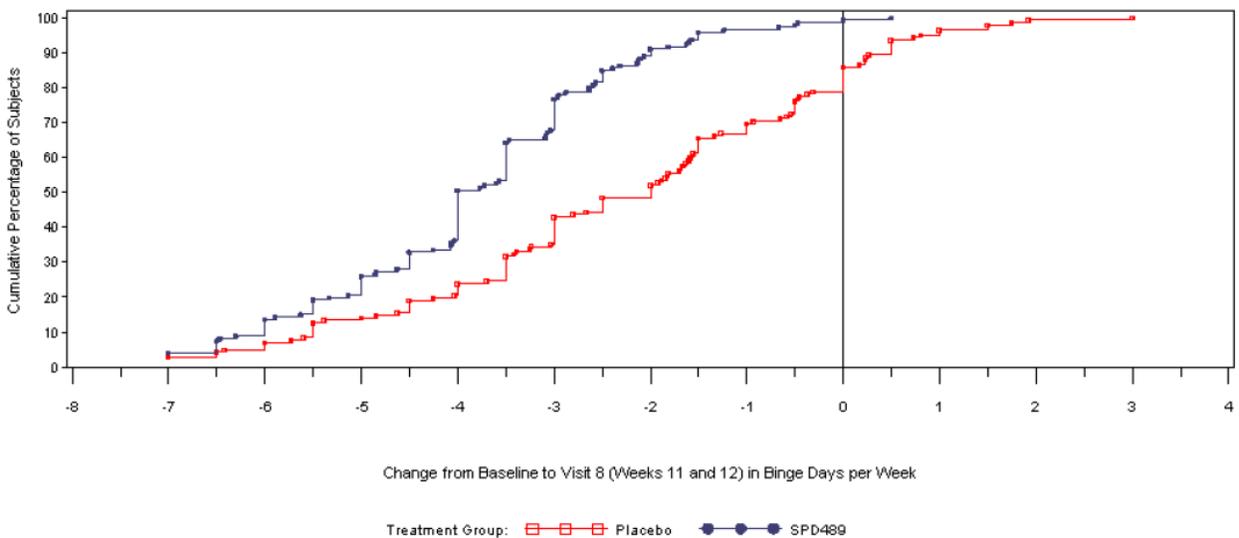
(Source: Reviewer)

Figure A6. Cumulative Distribution Function (CDF) for the Change from Baseline in the Number of Binge Days per Week to Visit 8 (Weeks 11 and 12) by Treatment Group – FAS [Study 343]



(Source: 343 Study Report p. 914)

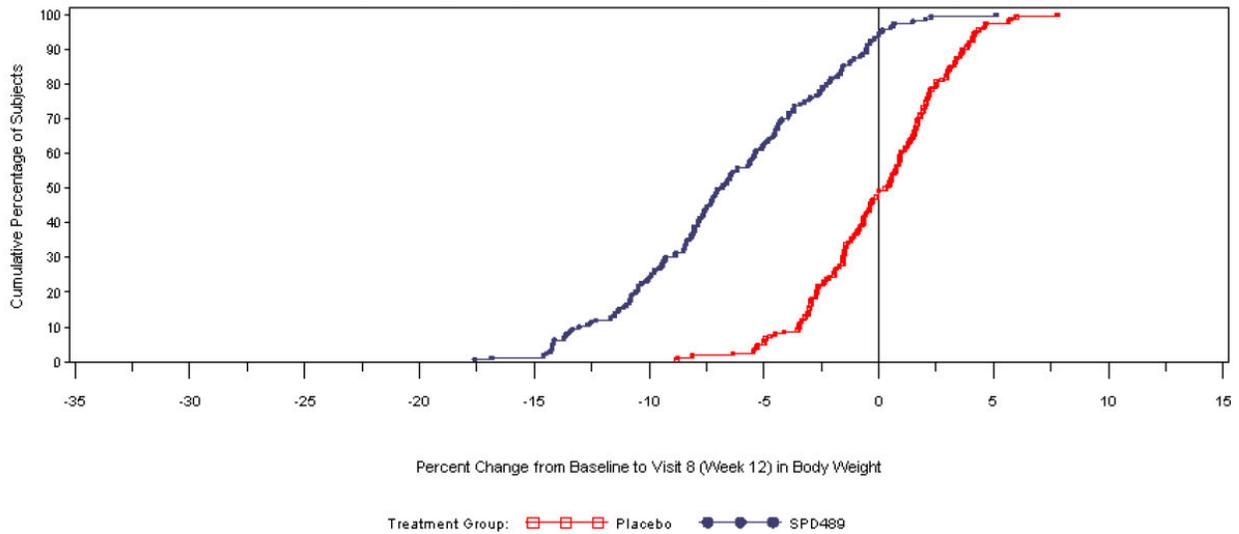
Figure A7. Cumulative Distribution Function (CDF) for the Change from Baseline in the Number of Binge Days per Week to Visit 8 (Weeks 11 and 12) by Treatment Group – FAS [Study 344]



(Source: 344 Study Report p. 1218)

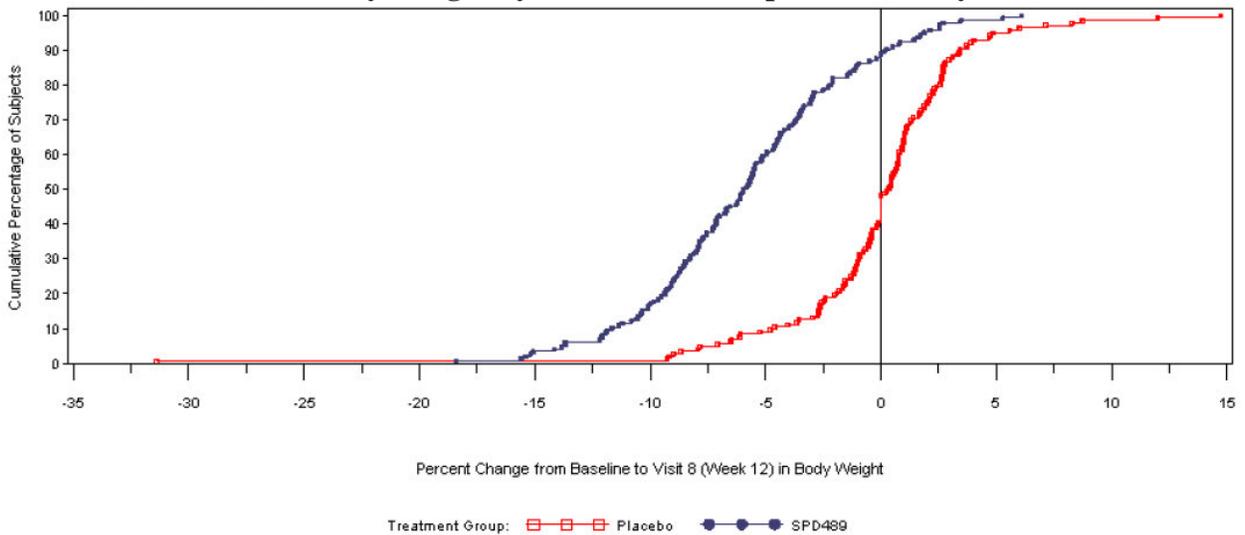
Reviewer's Comment: It appears that the CDFs submitted by the sponsor are based on data for completers.

Figure A8. Cumulative Distribution Function (CDF) for the Percent Change from Baseline to Visit 8 (Week 12) in Body Weight by Treatment Group – FAS [Study 343]



(Source: 343 Study Report p. 918)

Figure A9. Cumulative Distribution Function (CDF) for the Percent Change from Baseline to Visit 8 (Week 12) in Body Weight by Treatment Group – FAS [Study 344]



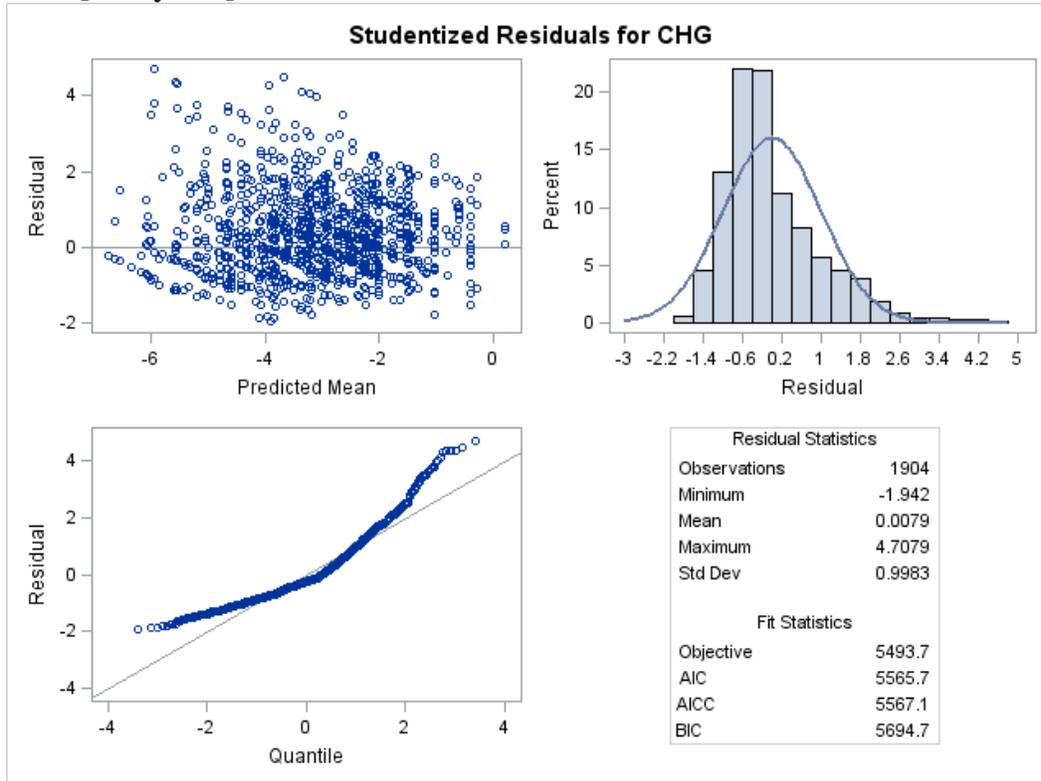
(Source: 344 Study Report p. 1222)

Reviewer's Comment: It appears that roughly 50% of placebo subjects had some weight loss and close to 90% of actively treated patients had some weight loss.

Change in Log Transformed Binge Days vs. Change in Binge Days

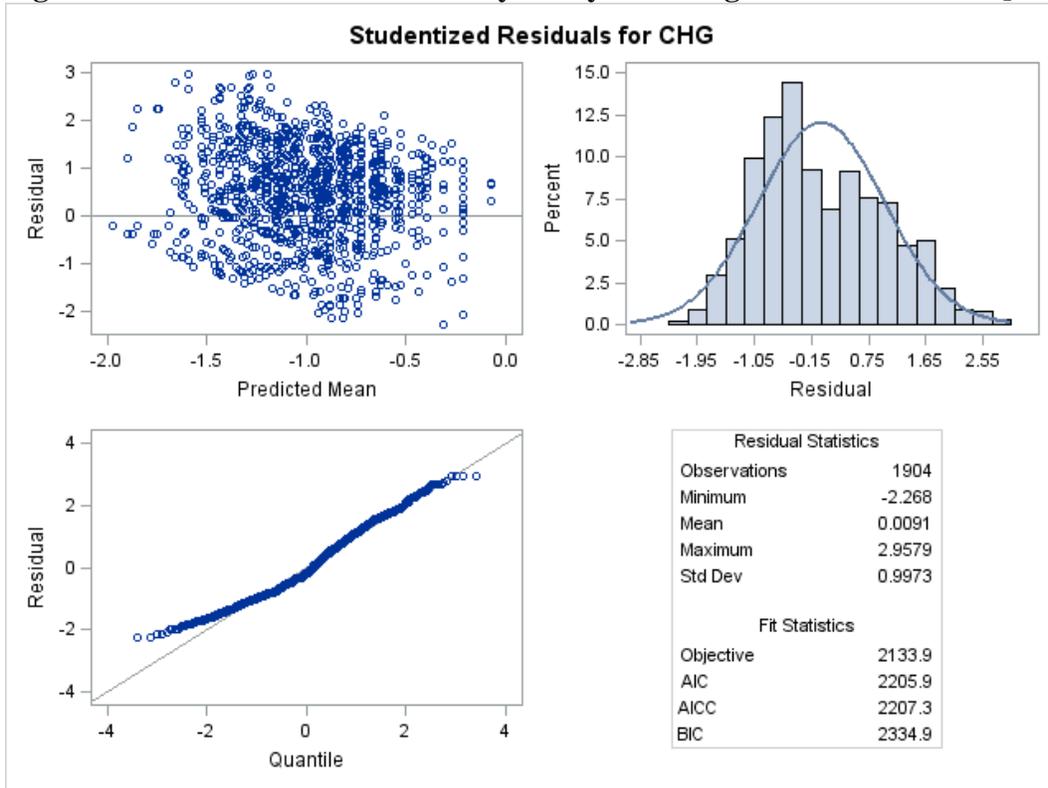
Study 208

Figure A10. Fit Statistics for Exploratory Analysis of Primary Endpoint on Untransformed Data [Study 208]



(Source: Reviewer, program: Eff_prim_208)

Figure A11. Fit Statistics for Primary Analysis on Log-transformed Data [Study 208]



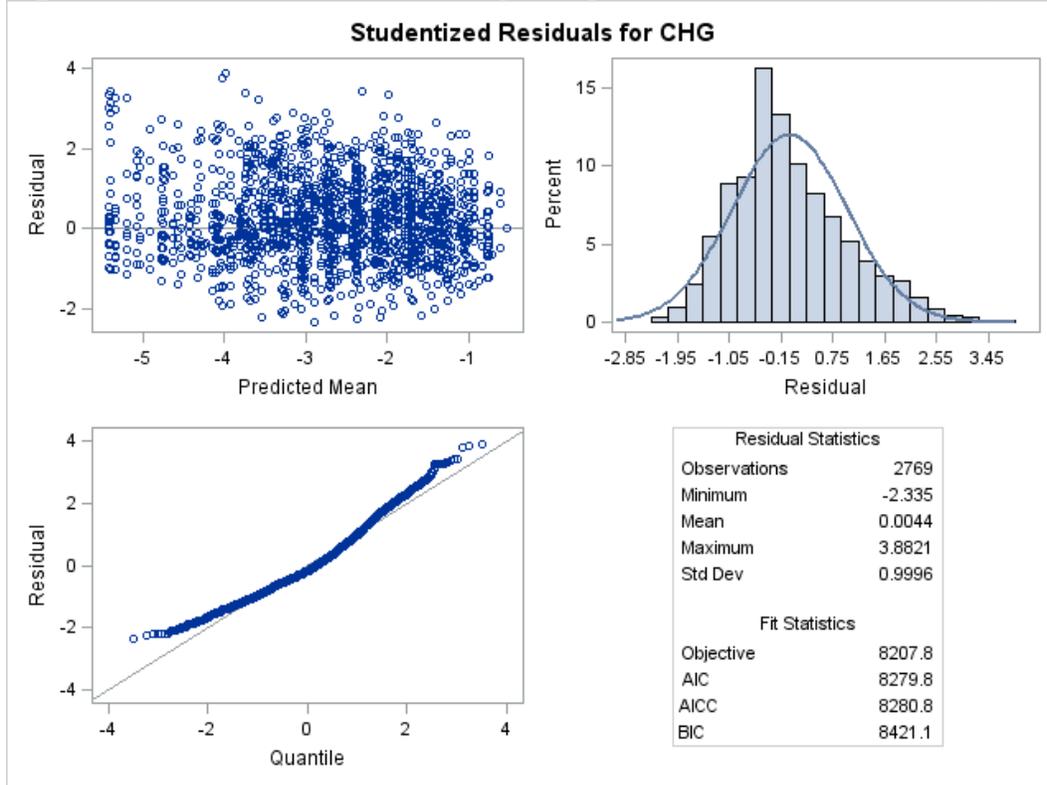
(Source: Reviewer)

Reviewer's Comment: Fit appears better after log transformation.

Study 343 (N=374)

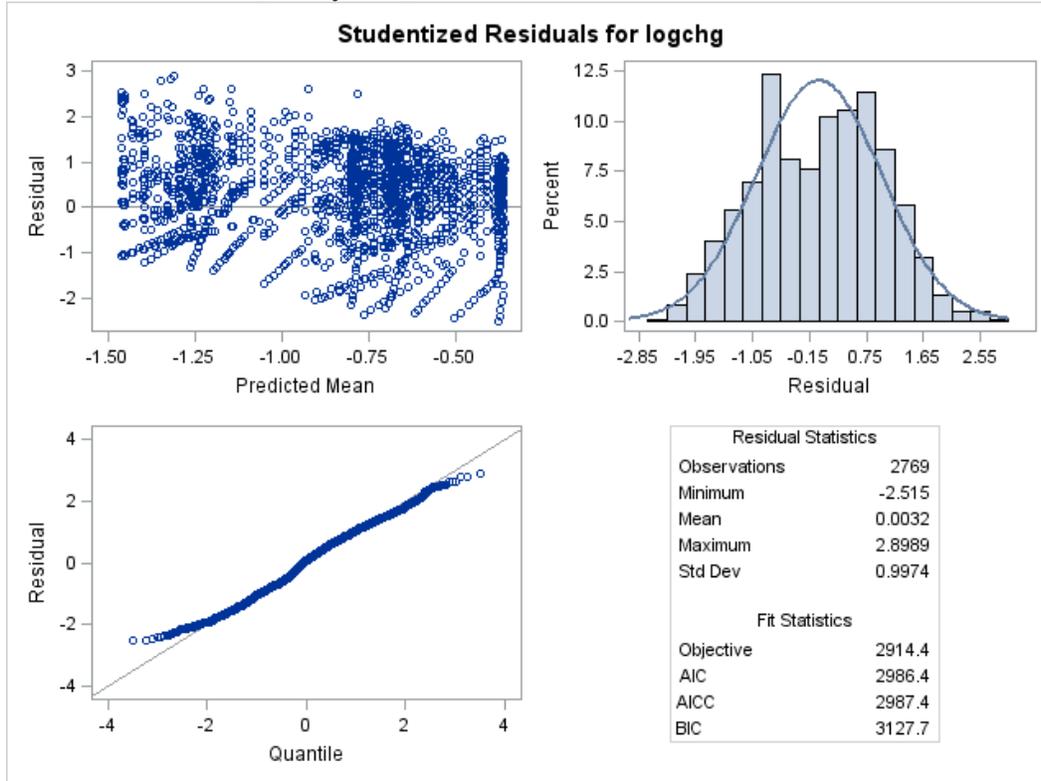
(MMRM model with ln_base replacing base and ln_chg replacing chg)

Figure A12. Fit Statistics for Primary Analysis on Untransformed Data [Study 343]



(Source: Reviewer)

Figure A13. Fit Statistics for Exploratory Analysis of Primary Endpoint on Log-transformed Data [Study 343]

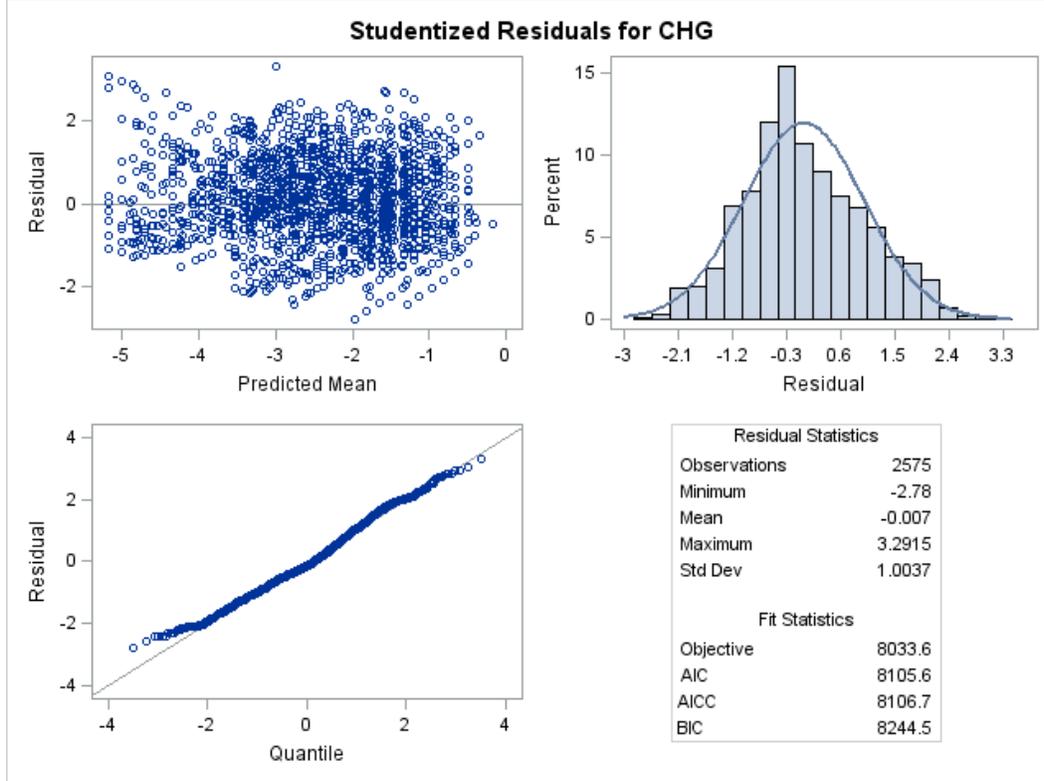


(Source: Reviewer; program: Eff_prim_343)

Reviewer’s Comments: For Study 343 the fit appears slightly better for log transformed data (pre-specified primary analysis was on untransformed data). However, hypothesis testing conclusions are the same ($p < 0.001$). Estimate of difference in log (change) = -0.5266, (95% CI: -0.6547, -0.3984) favoring SPD489.

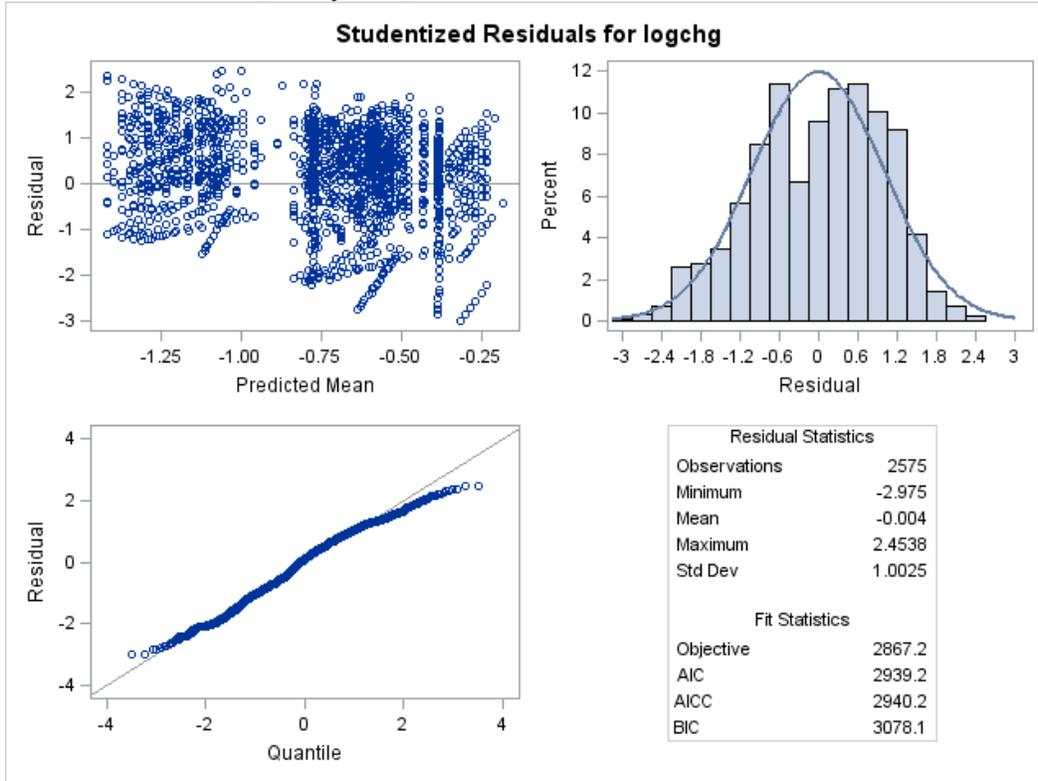
Study 344 (N=350)

Figure A14. Fit Statistics for Primary Analysis on Untransformed Data [Study 344]



(Source: Reviewer)

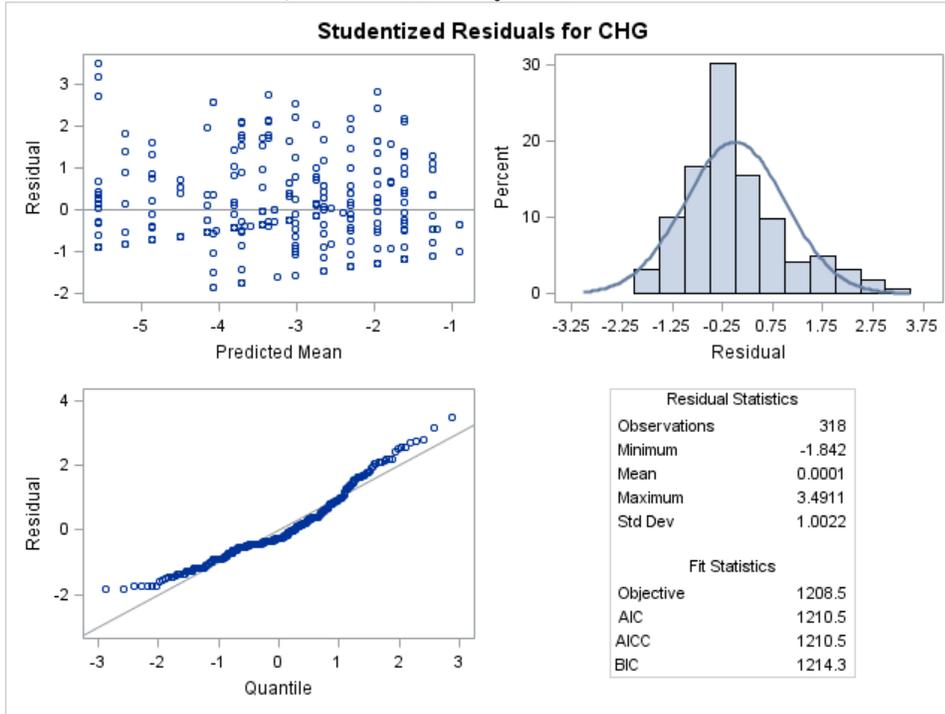
Figure A15. Fit Statistics for Exploratory Analysis of Primary Endpoint on Log-transformed Data [Study 344]



(Source: Reviewer)

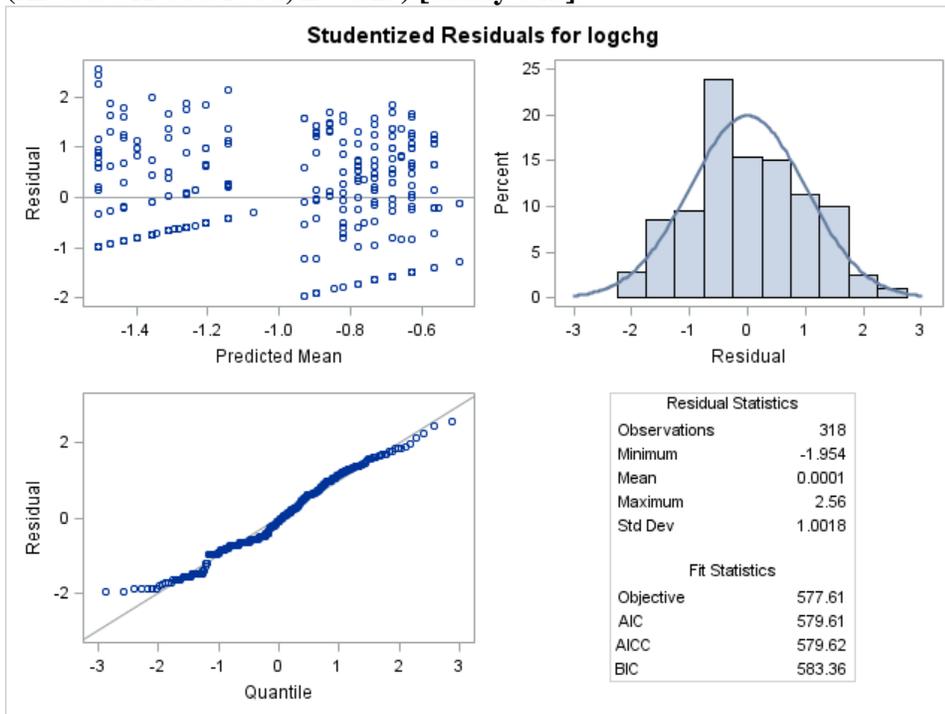
Reviewer’s Comments: For Study 344 the fit does not appear better when using log transformed data. However, hypothesis testing conclusions are the same ($p < 0.001$). Estimate of difference in $\log(\text{change}) = -0.5836$ (95% CI: -0.7190, -0.4482) favoring SPD489.

Figure A16. Residual Plots for Change in Number of Binge Days per Week at Week 12 (ANCOVA observed, n = 319) [Study 343]



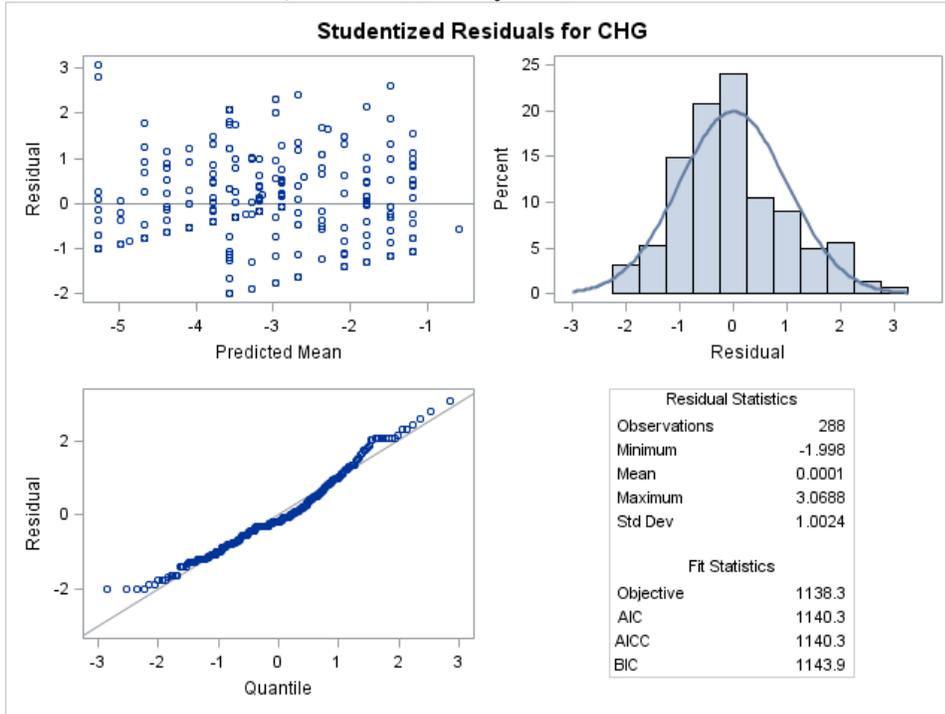
(Source: Reviewer, program: Eff_prim_343)

Figure A17. Residual Plots for Change in Log Number of Binge Days per Week at Week 12 (ANCOVA observed, n = 319) [Study 343]



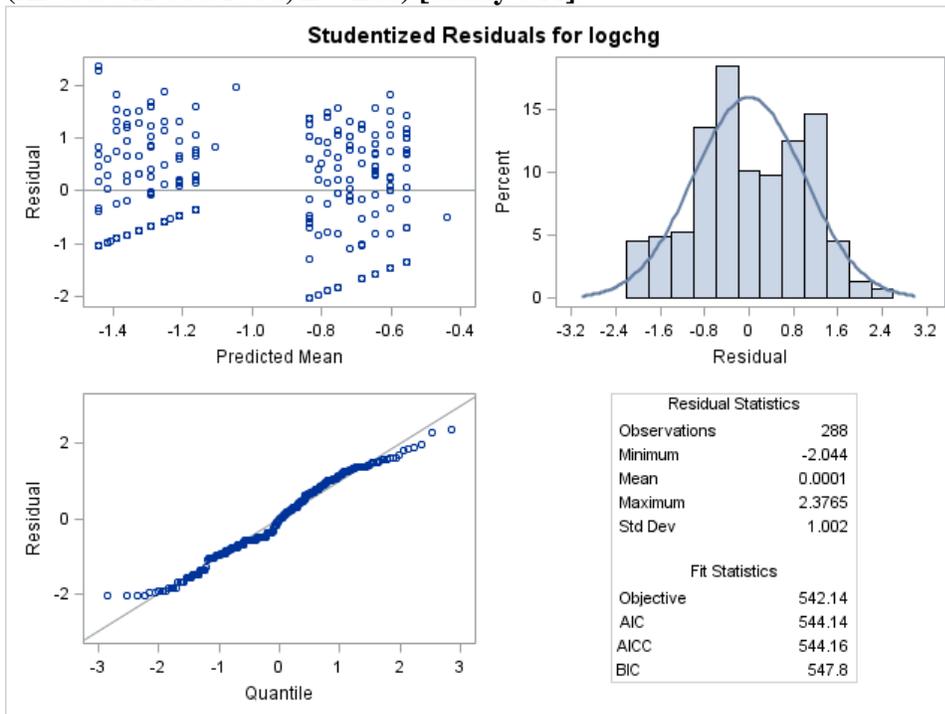
(Source: Reviewer, program: Eff_prim_343)

Figure A18. Residual Plots for Change in Number of Binge Days per Week at Week 12 (ANCOVA observed, n = 288) [Study 344]



(Source: Reviewer, program: Eff_prim_344)

Figure A19. Residual Plots for Change in Number of Log Binge Days per Week at Week 12 (ANCOVA observed, n = 288) [Study 344]



(Source: Reviewer, program: Eff_prim_344)

Exploration of the impact of dropouts on the efficacy results

Primary Endpoint: Change in Binge Days

Subsequent tables and figures are based on the Full Analysis Set (any subjects dropping out in first week of study [before Week 1 visit] are not included).

Study 343

Table A6. Last Study Visits - FAS [Study 343]

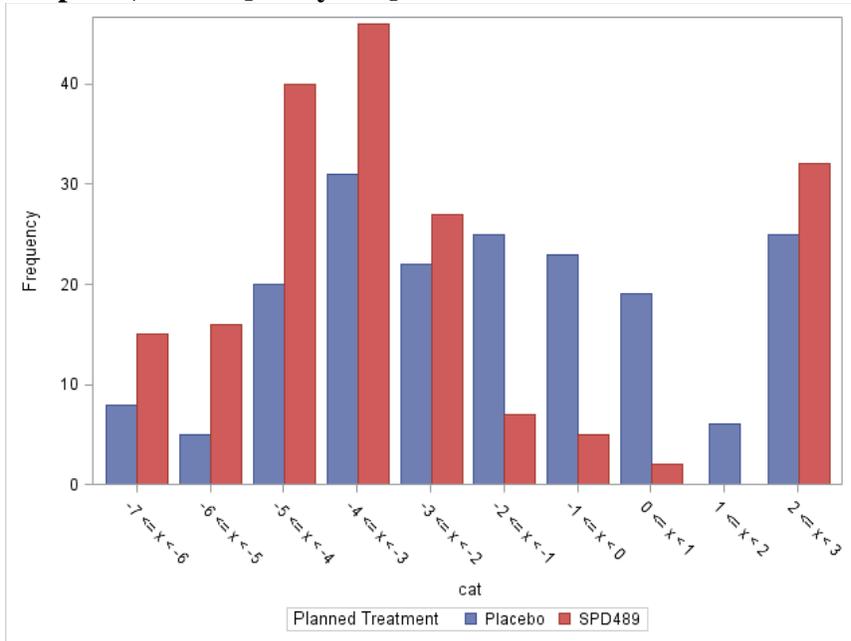
| AVISIT | Analysis Visit | | | |
|-------------------|----------------|---------|----------------------|--------------------|
| | Frequency | Percent | Cumulative Frequency | Cumulative Percent |
| Visit 1 (Week 1) | 6 | 1.60 | 6 | 1.60 |
| Visit 2 (Week 2) | 6 | 1.60 | 12 | 3.21 |
| Visit 3 (Week 3) | 12 | 3.21 | 24 | 6.42 |
| Visit 4 (Week 4) | 7 | 1.87 | 31 | 8.29 |
| Visit 5 (Week 6) | 10 | 2.67 | 41 | 10.96 |
| Visit 6 (Week 8) | 7 | 1.87 | 48 | 12.83 |
| Visit 7 (Week 10) | 7 | 1.87 | 55 | 14.71 |
| Visit 8 (Week 12) | 319 | 85.29 | 374 | 100.00 |

Reviewer's Comment: For FAS: 14.7% dropped out before final visit; 85.3% had final visit.

The figures on the next page are descriptive only (display of frequencies by category after imputation).

Imputation of worst observed change (+2.53 for all subjects without week 12 binge day value)

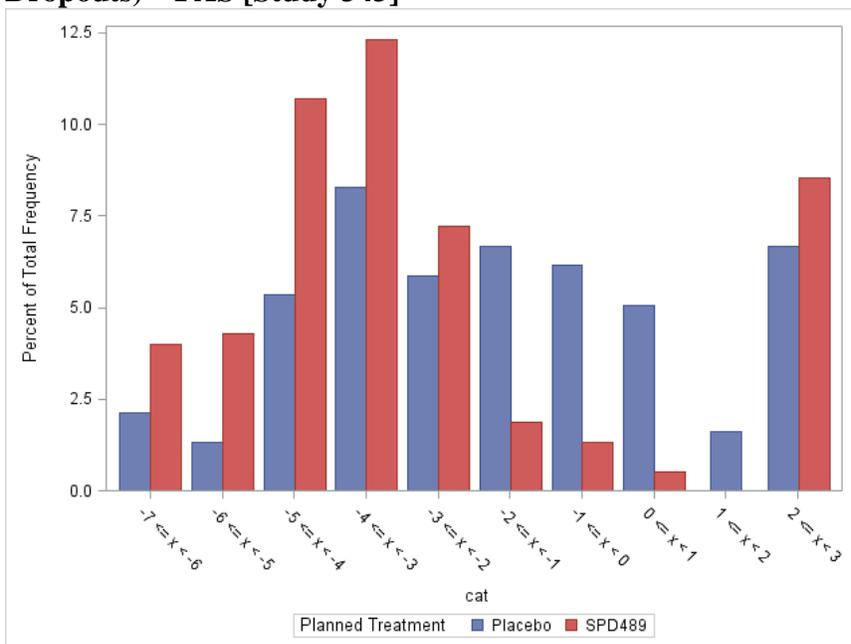
Figure A20. Week 12 Change in Binge Day Distribution (Worst Case Imputation for Dropouts) – FAS [Study 343]



(Source: Reviewer)

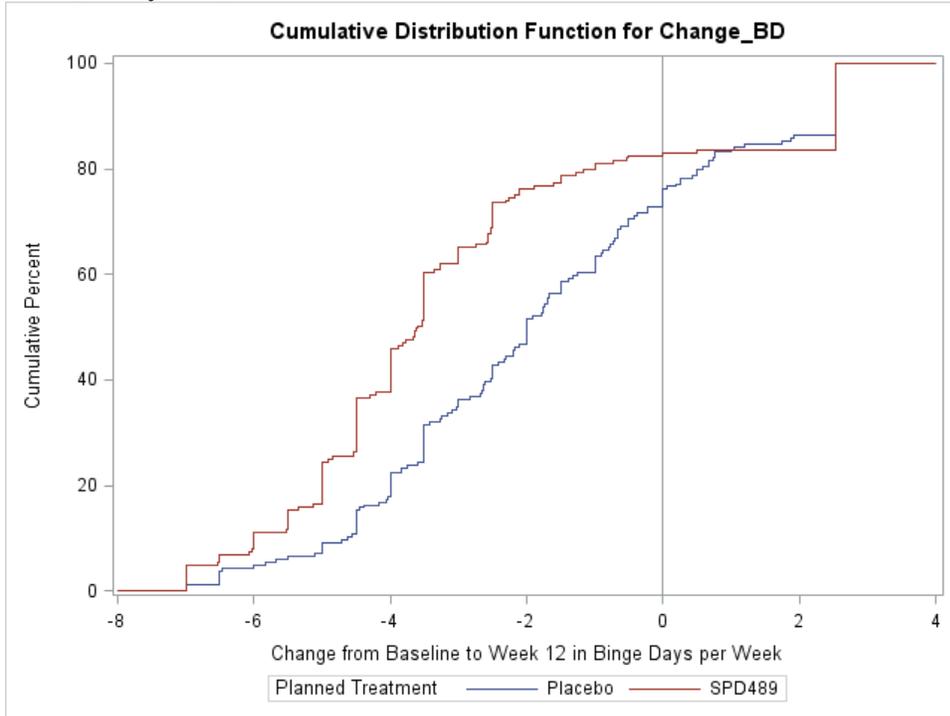
Alternatively: With Percent of Total Frequency vs. Frequency along y-axis

Figure A21. Week 12 Change in Binge Day Distribution (Worst Case Imputation for Dropouts) – FAS [Study 343]



(Source: Reviewer)

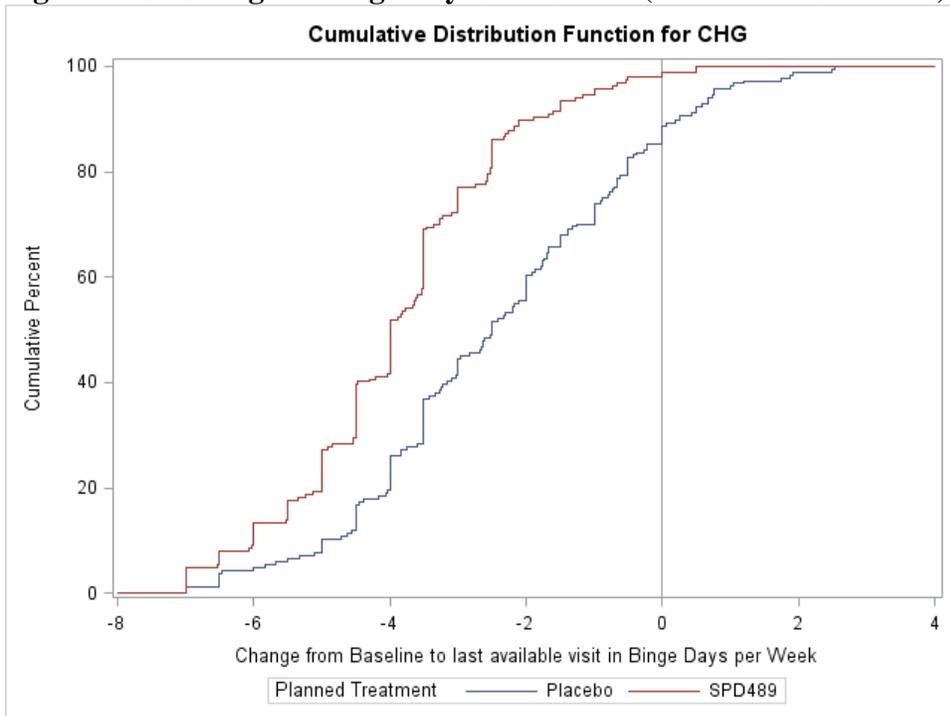
Figure A22. Change in Binge Days at Week 12 (Worst Case Imputation for Dropouts) – FAS [Study 343]



(Source: Reviewer)

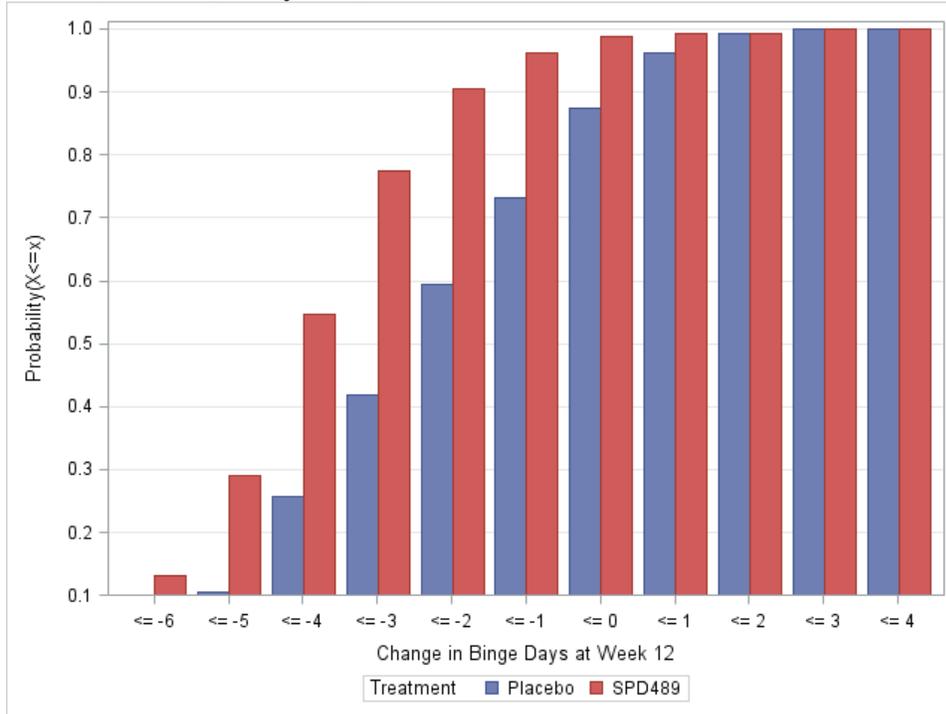
Figure below for comparison only:

Figure A23. Change in Binge Days at Week 12 (Last Available Value) – FAS [Study 343]



(Source: Reviewer)

Figure A24. Week 12 Change in Binge Days Worst Case (Imputed +2.53 for Missing Values) – FAS [Study 343]



(Source: Reviewer)

Study 344

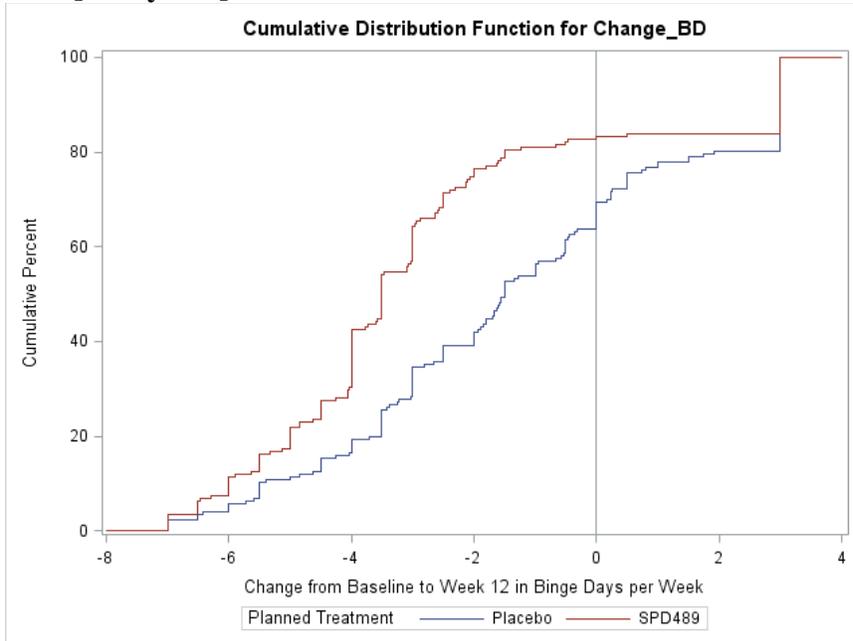
Table A7. Last Study Visits - FAS [Study 344]

| AVISIT | Analysis Visit | | | |
|-------------------|----------------|---------|----------------------|--------------------|
| | Frequency | Percent | Cumulative Frequency | Cumulative Percent |
| Visit 1 (Week 1) | 6 | 1.71 | 6 | 1.71 |
| Visit 2 (Week 2) | 7 | 2.00 | 13 | 3.71 |
| Visit 3 (Week 3) | 6 | 1.71 | 19 | 5.43 |
| Visit 4 (Week 4) | 9 | 2.57 | 28 | 8.00 |
| Visit 5 (Week 6) | 15 | 4.29 | 43 | 12.29 |
| Visit 6 (Week 8) | 8 | 2.29 | 51 | 14.57 |
| Visit 7 (Week 10) | 11 | 3.14 | 62 | 17.71 |
| Visit 8 (Week 12) | 288 | 82.29 | 350 | 100.00 |

Reviewer’s Comment: For FAS: 17.7% dropped out before final visit; 82.3% had final visit.

Imputation of worst observed change (+3.0 for all subjects without week 12 binge day value)

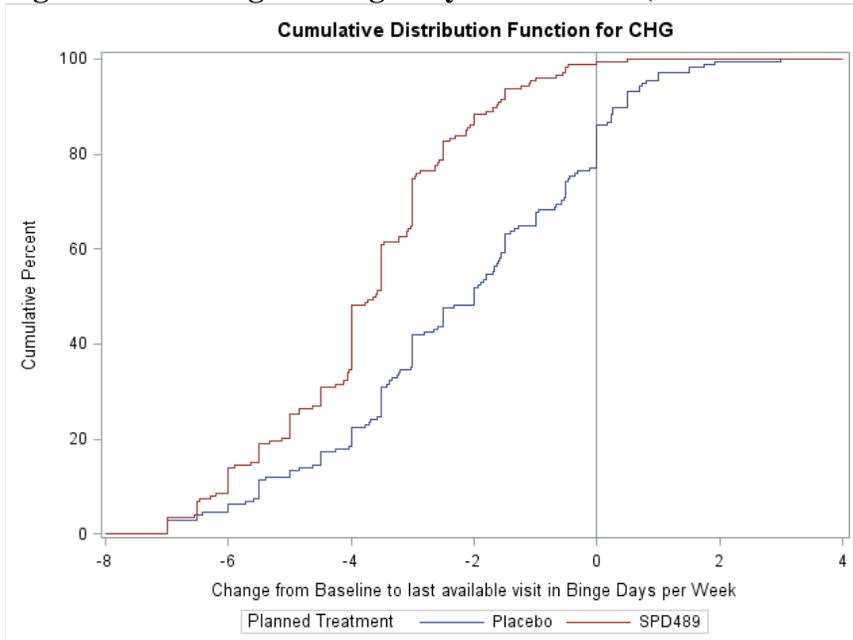
Figure A25. Change in Binge Days at Week 12 (Worst Case Imputation for Dropouts) – FAS [Study 344]



(Source: Reviewer)

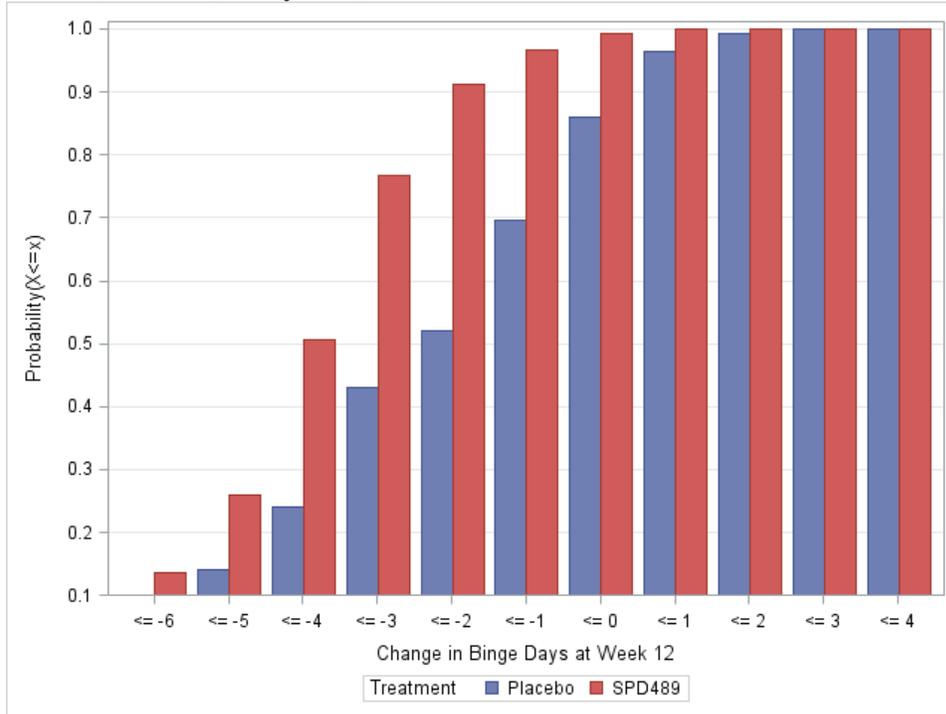
Figure below for comparison only:

Figure A26. Change in Binge Days at Week 12 (Last Available Value) – FAS [Study 344]



(Source: Reviewer)

Figure A27. Change in Binge Days at Week 12 Worst Case (Imputed +3.0 for Missing Values) – FAS [Study 344]



(Source: Reviewer)

Table A8. Maximum Observed Increase in Binge Days by Visit [Studies 343 and 344]

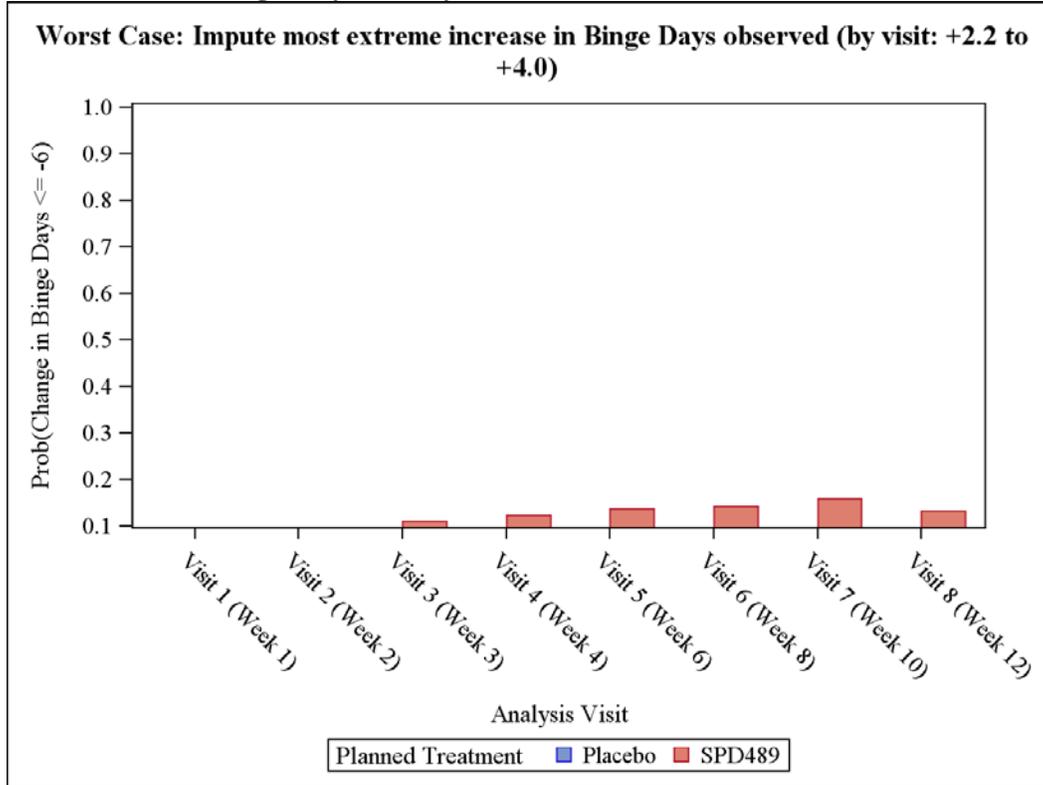
| Visit | Worst Increase in Binge Days | |
|-------|------------------------------|-----------|
| | Study 343 | Study 344 |
| 1 | 4 | 3 |
| 2 | 4 | 3 |
| 3 | 3.23 | 3.5 |
| 4 | 3 | 3.5 |
| 5 | 2.15 | 2.6 |
| 6 | 2.15 | 2.33 |
| 7 | 2.15 | 3.06 |
| 8 | 2.53 | 3 |

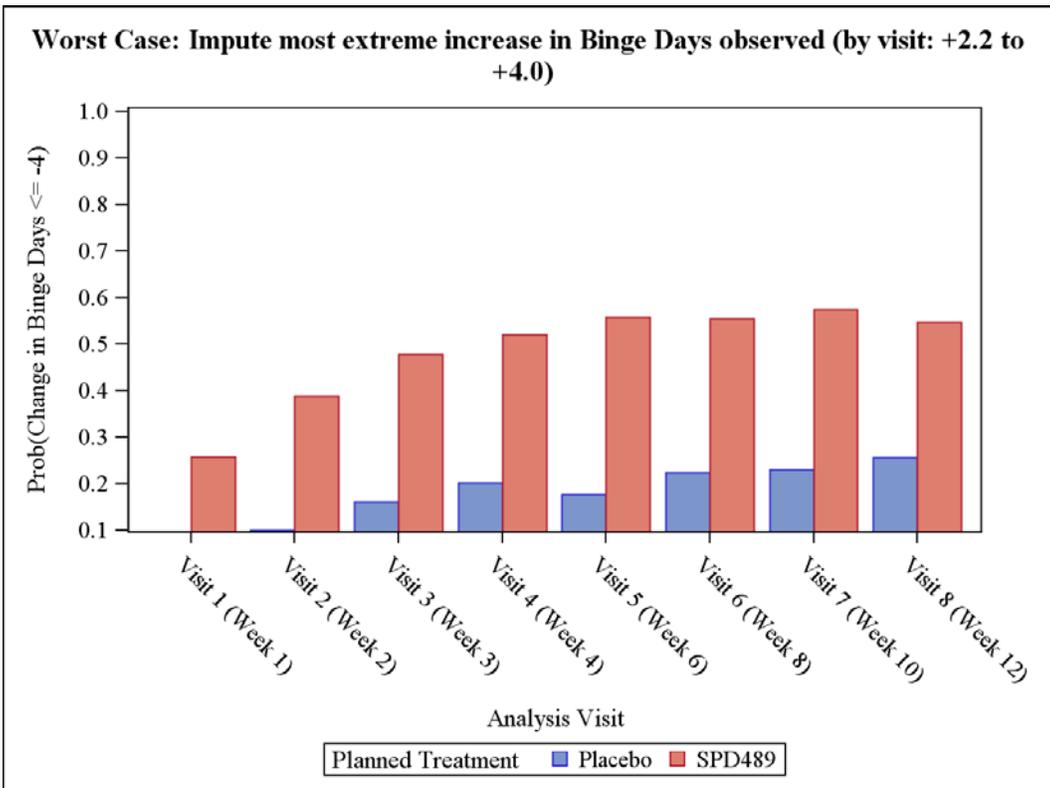
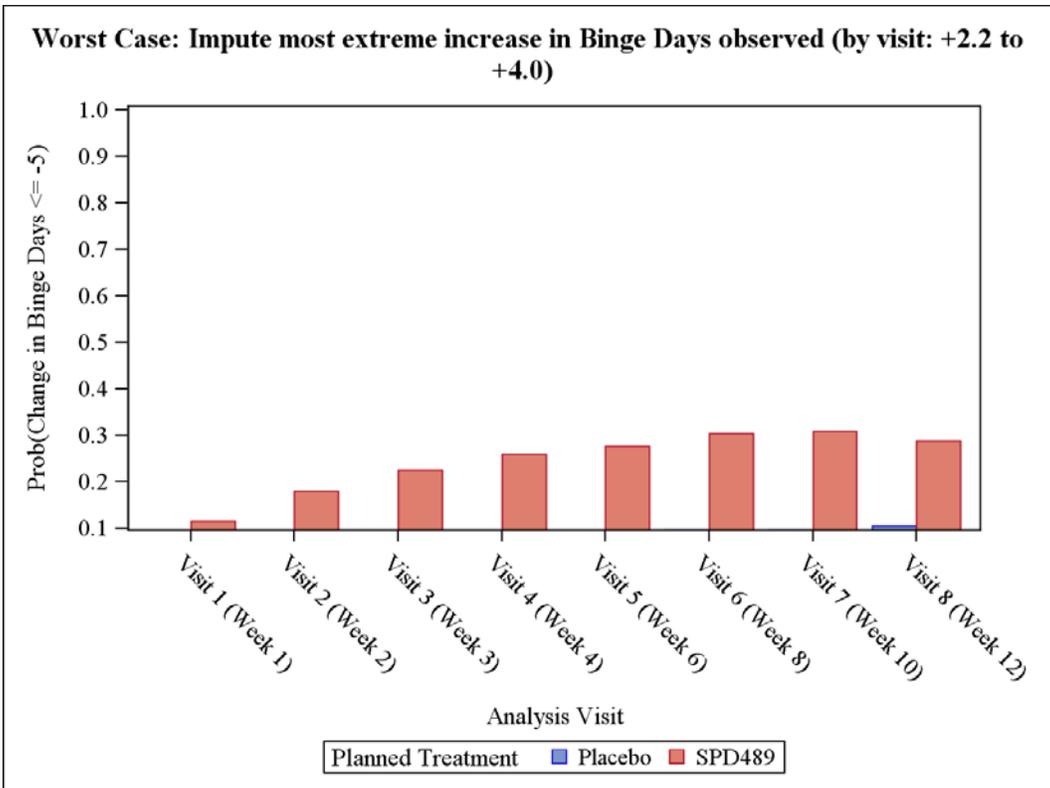
(Source: Reviewer)

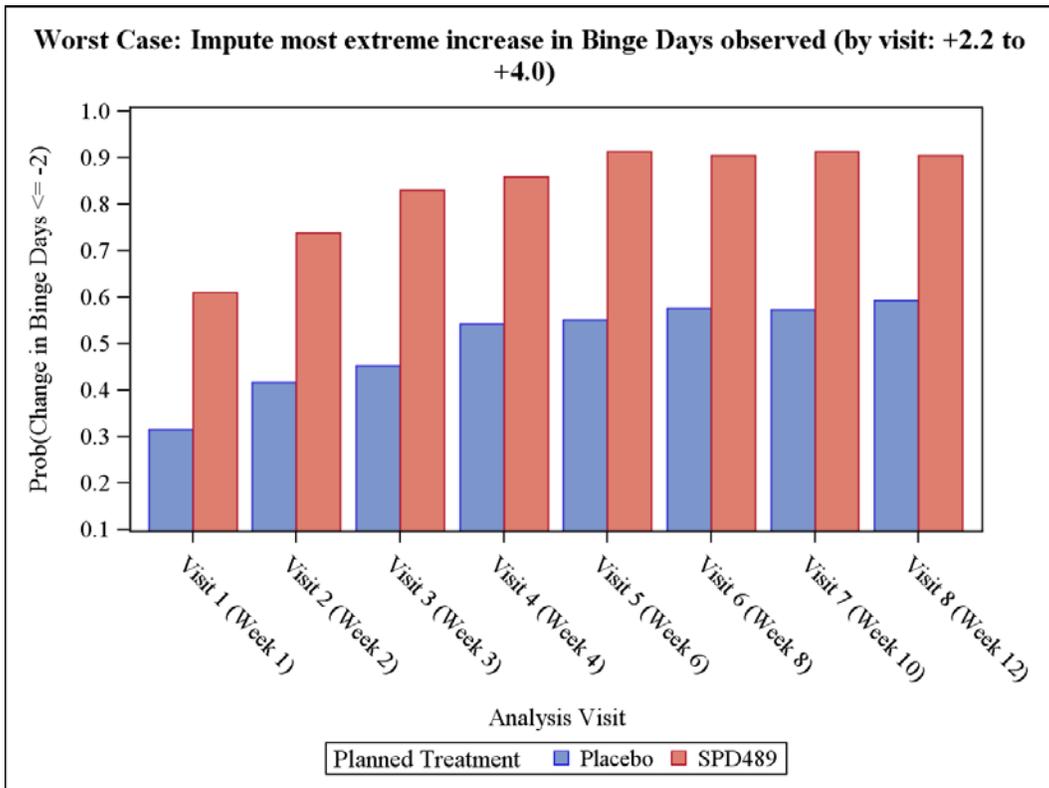
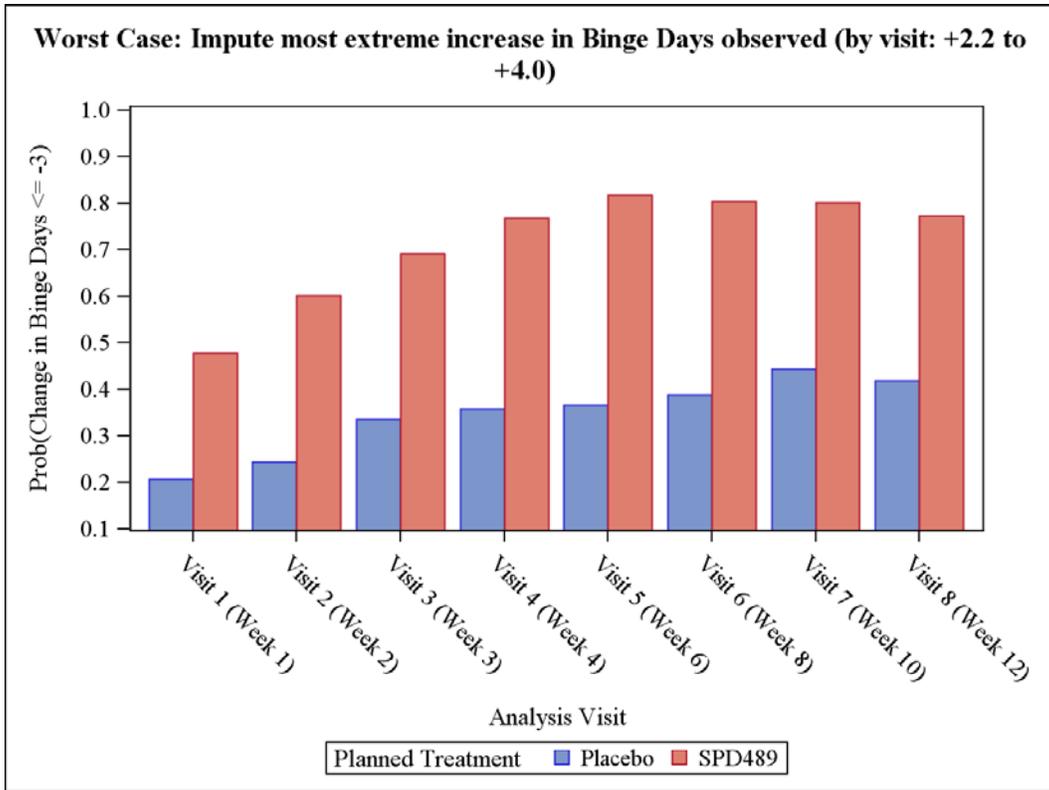
For the figures depicting probabilities by visit below the following approach was used: Imputation of worst observed outcome (increase) in Binge Days at that particular visit for all missing change values at that visit (i.e., imputation value can differ from visit to visit).

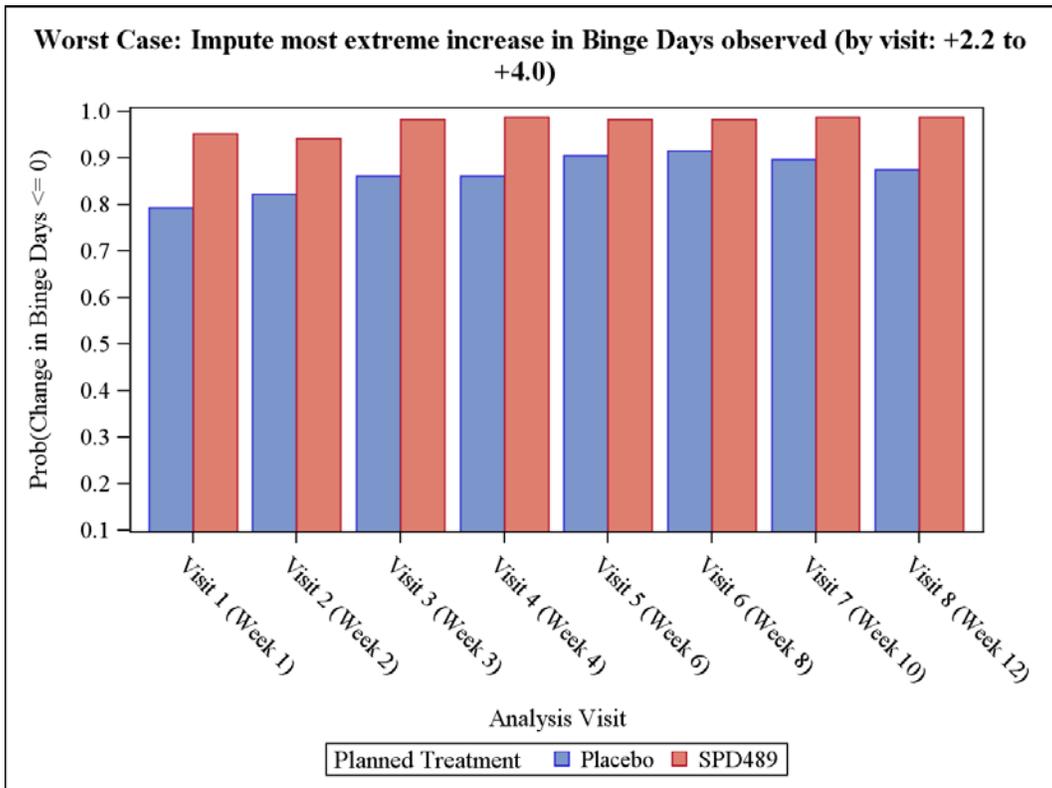
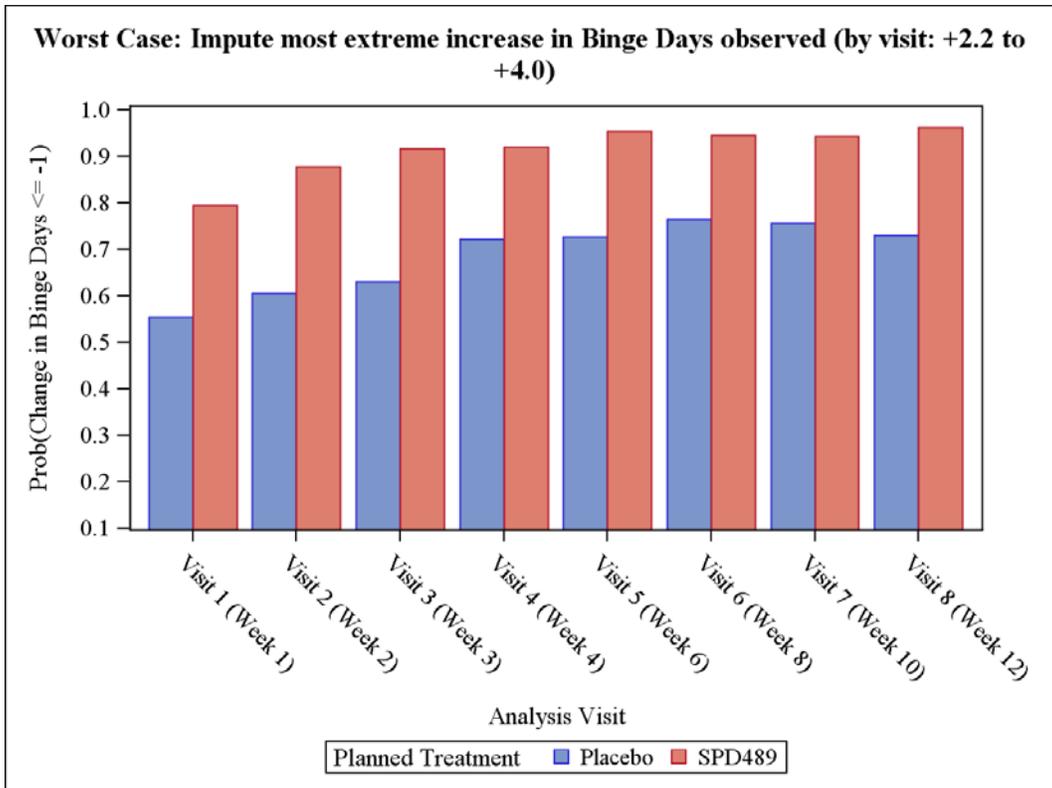
Study 343

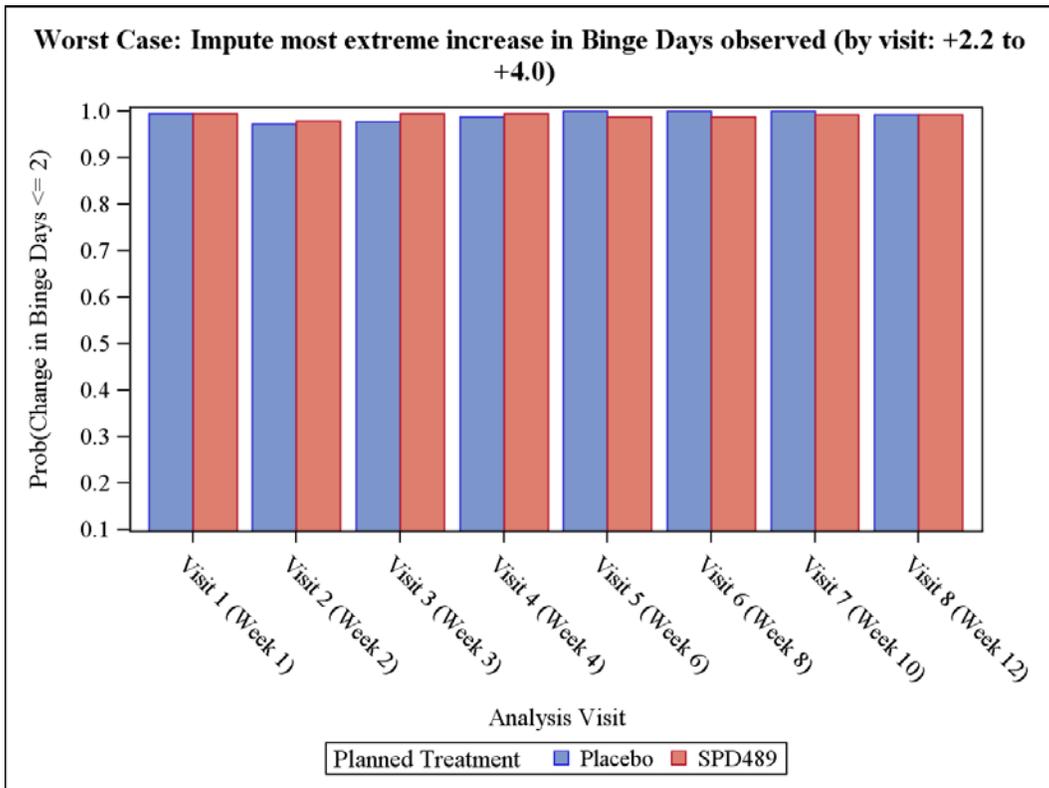
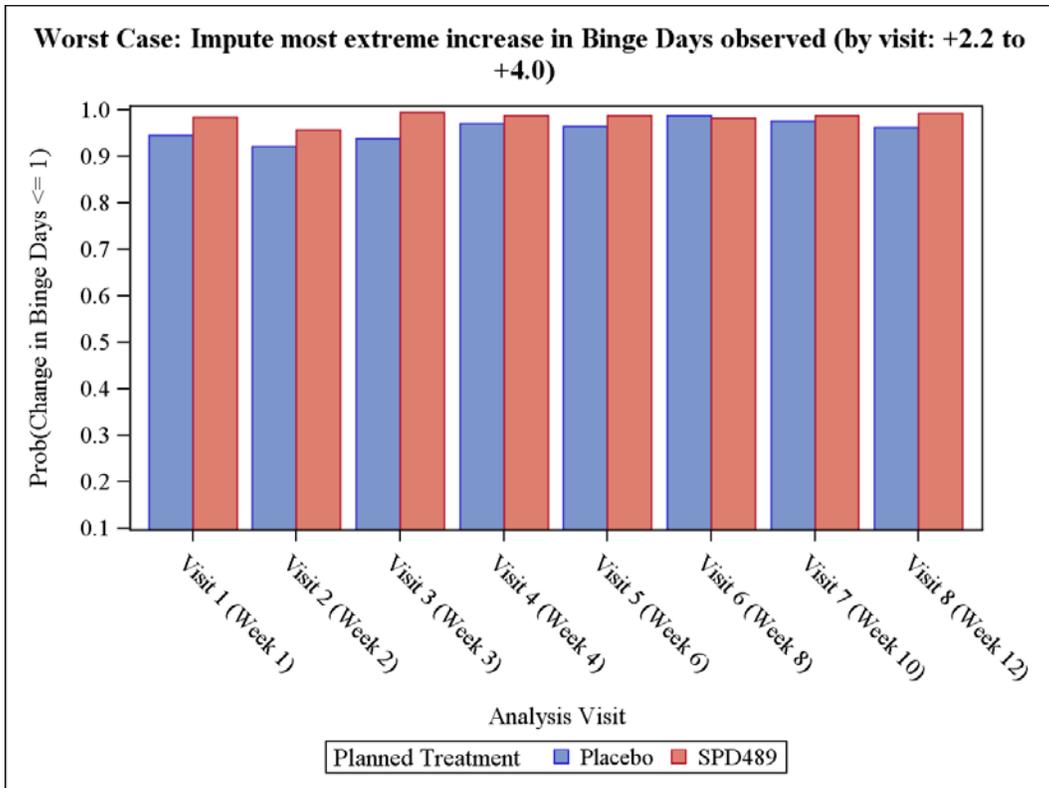
Figure A28. Probability (Change in Binge Days $\leq x$) by Visit - Imputation of Largest Observed Increase in Binge Days [Study 343]

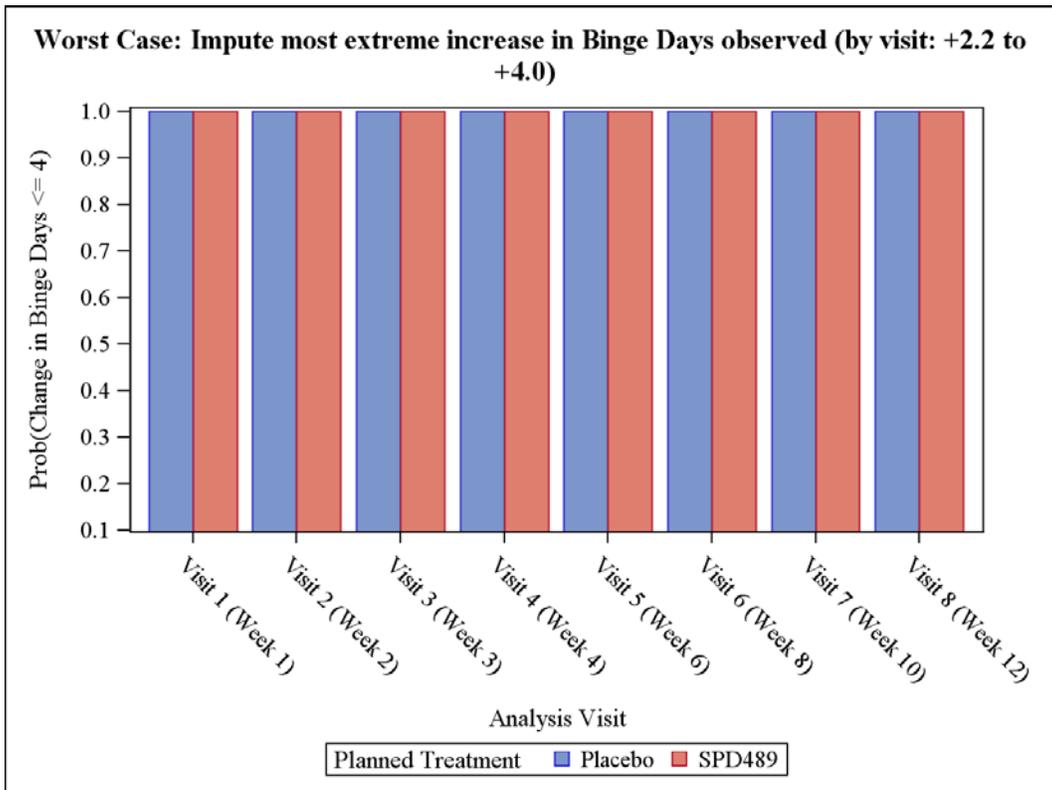
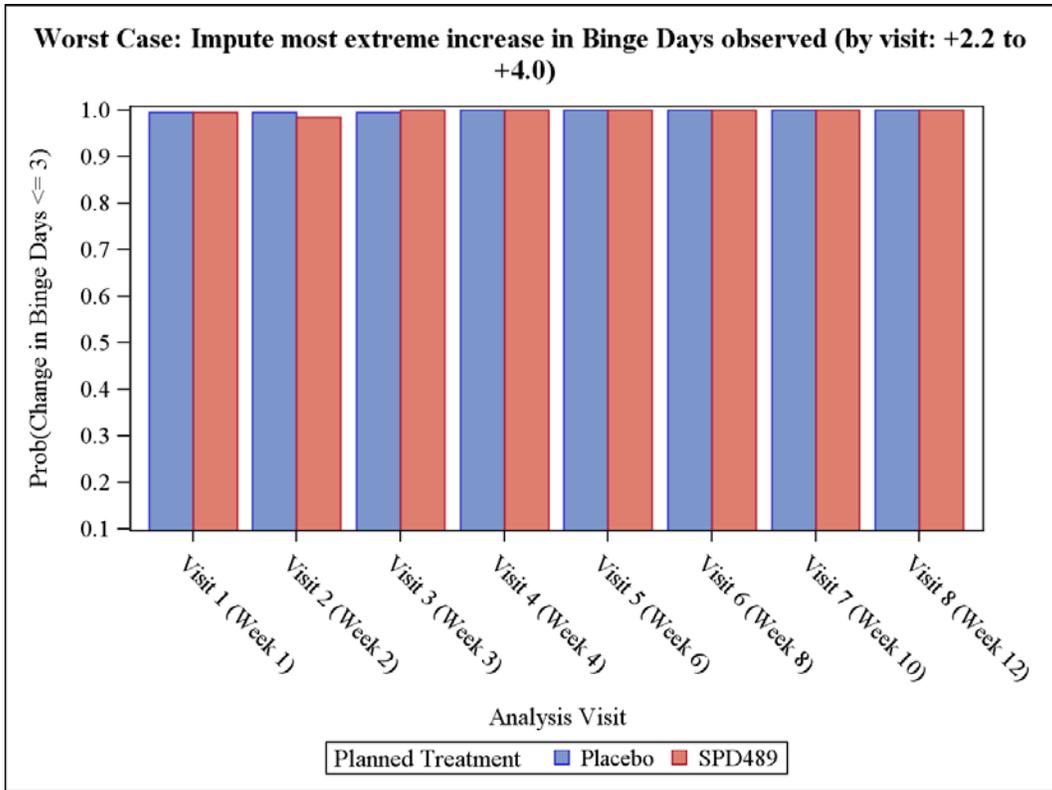








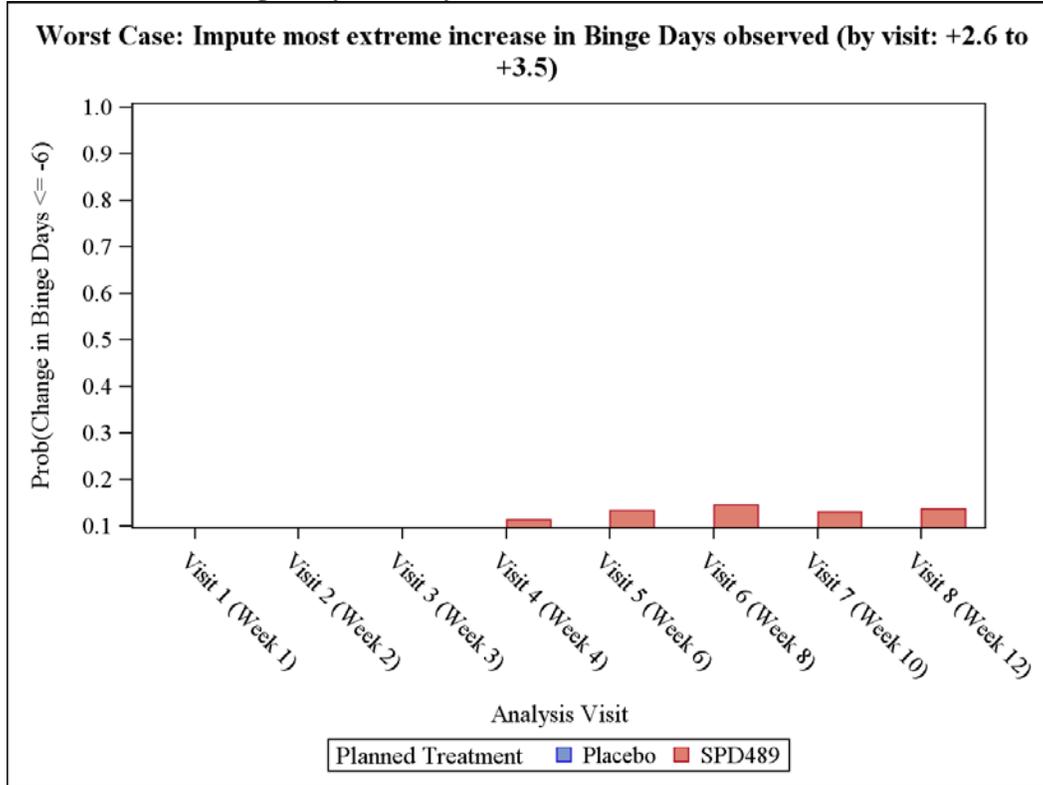


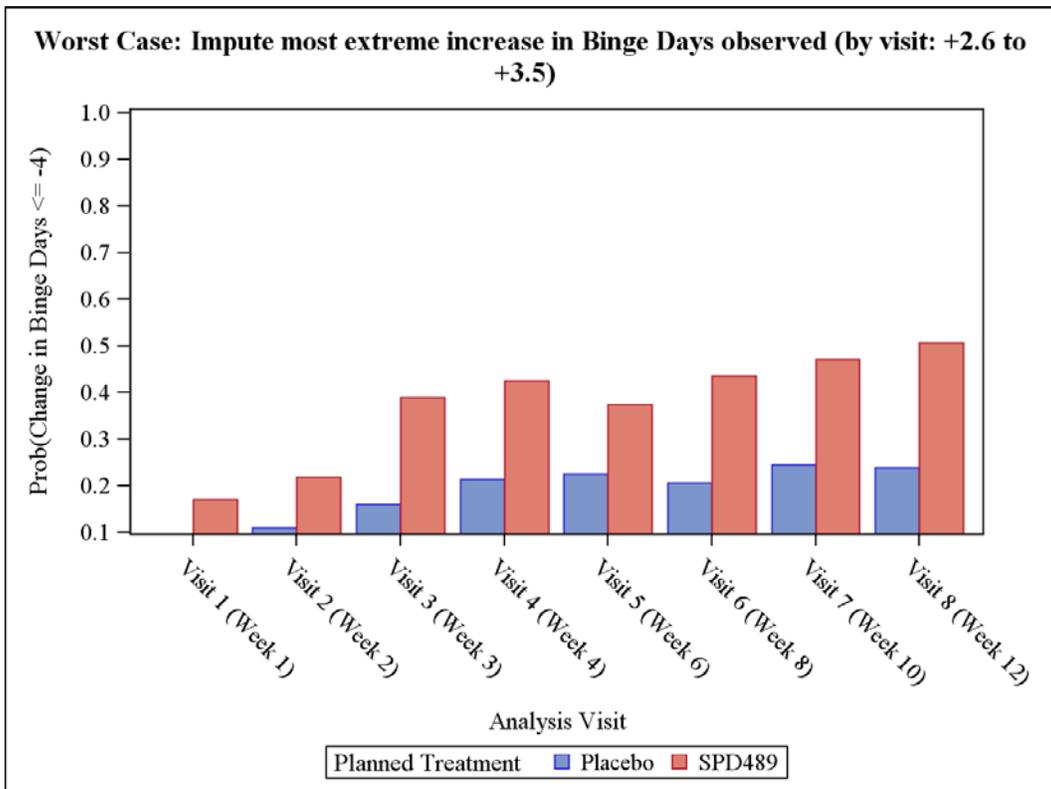
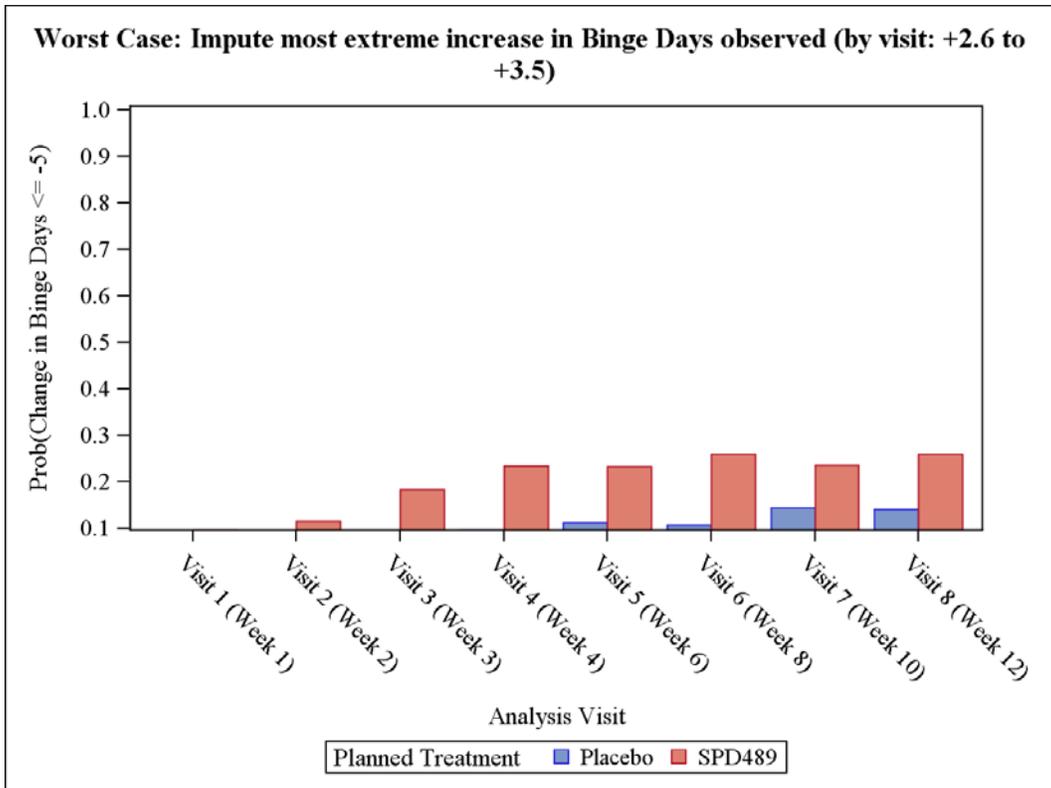


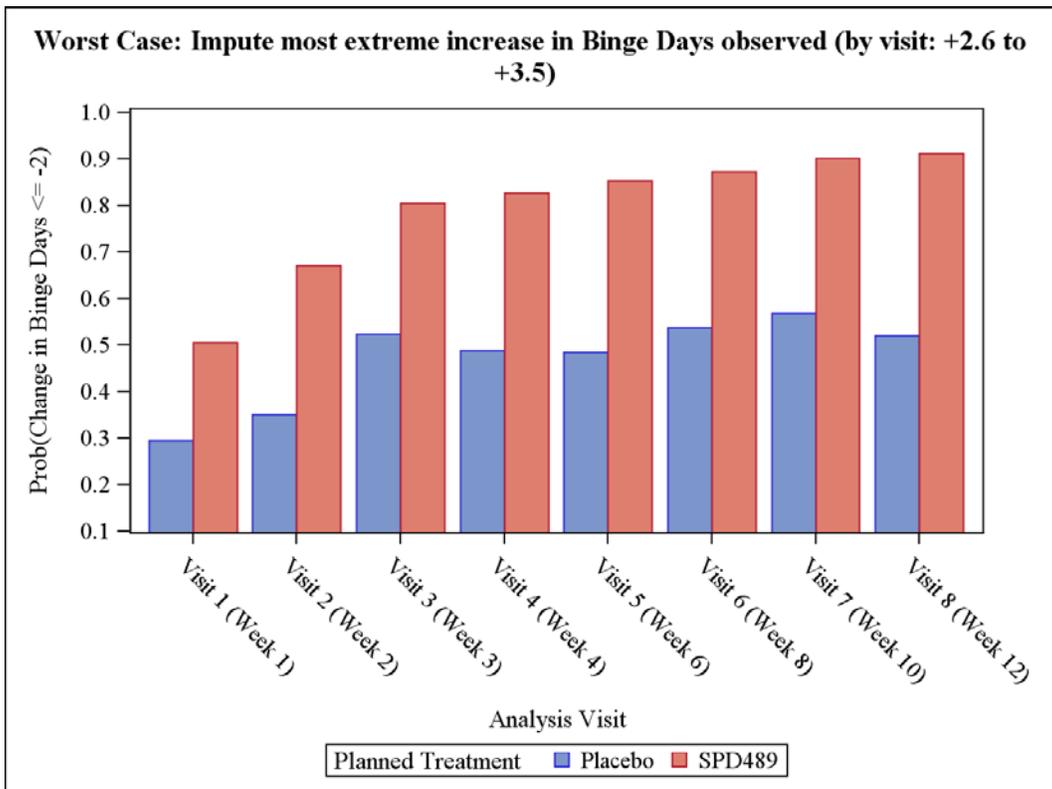
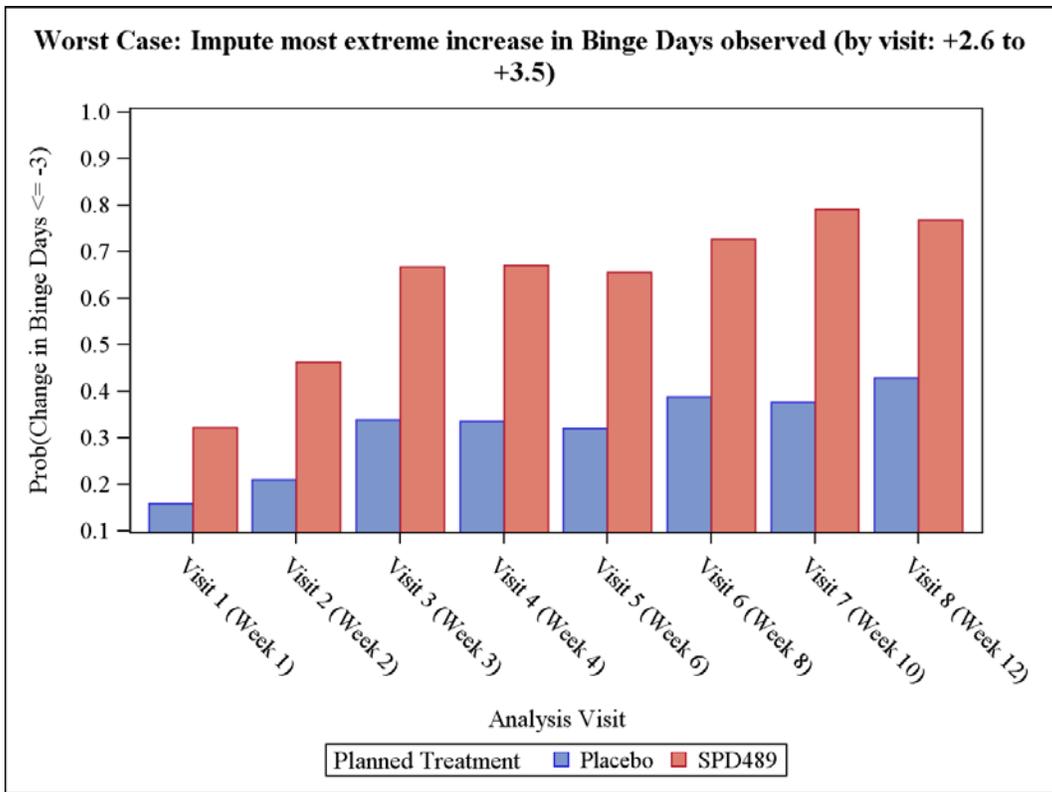
(Source: Reviewer)

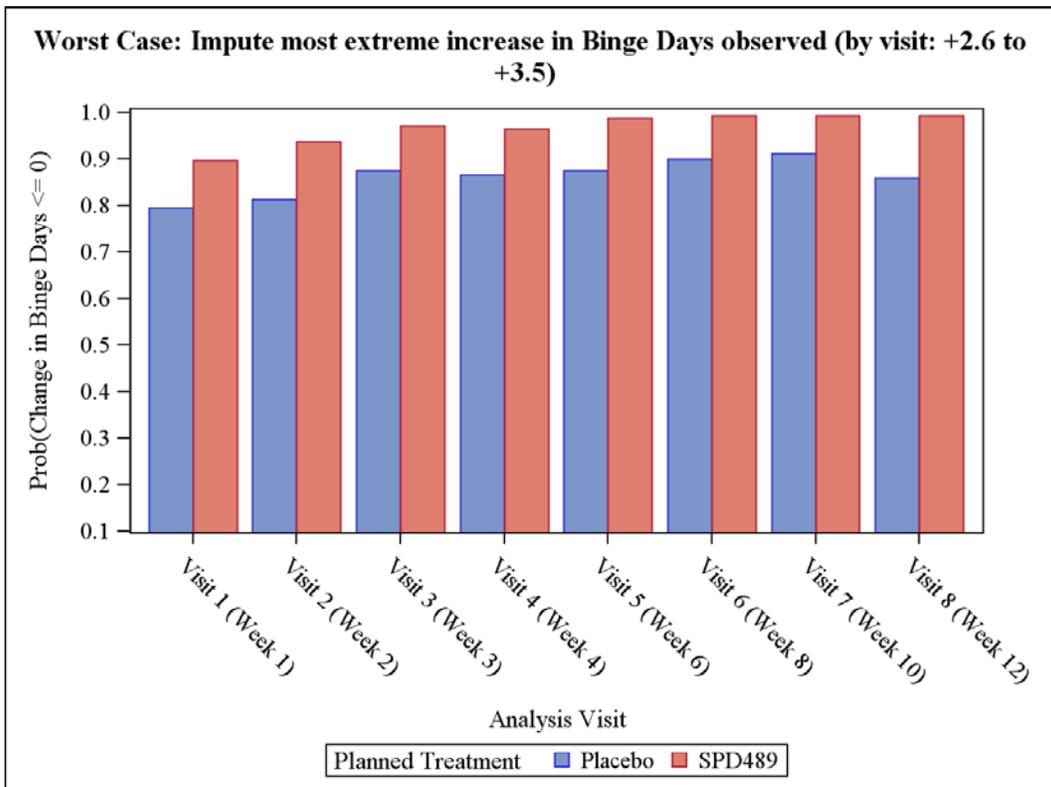
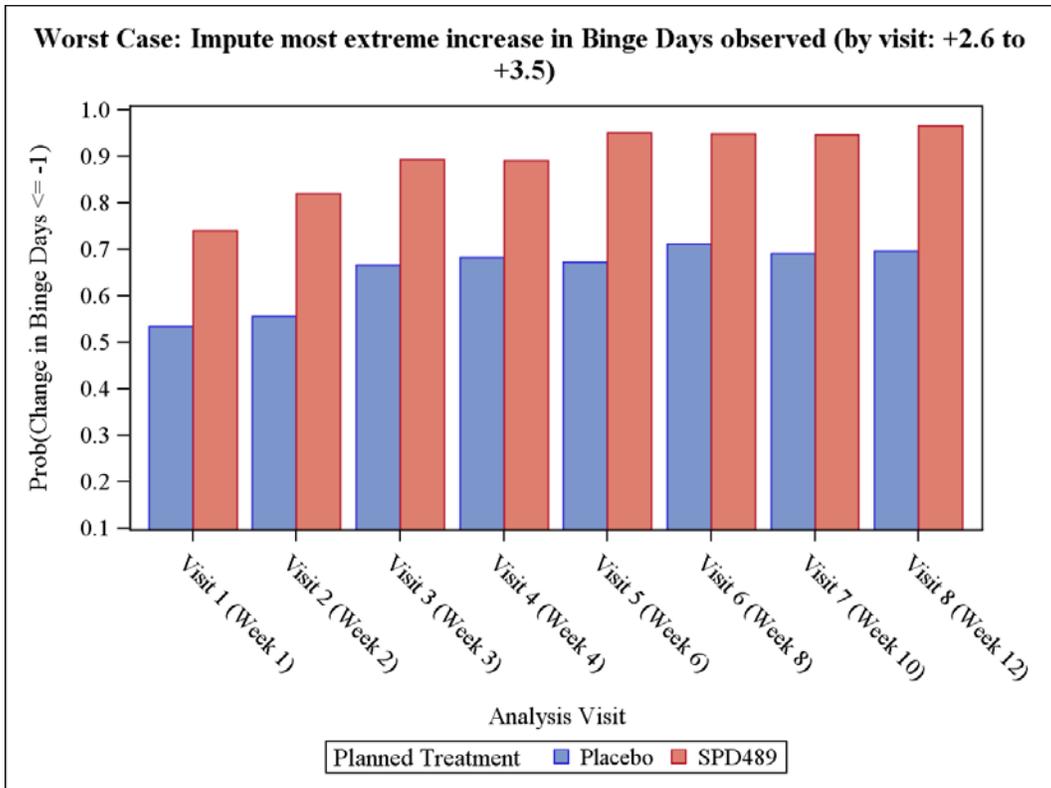
Study 344

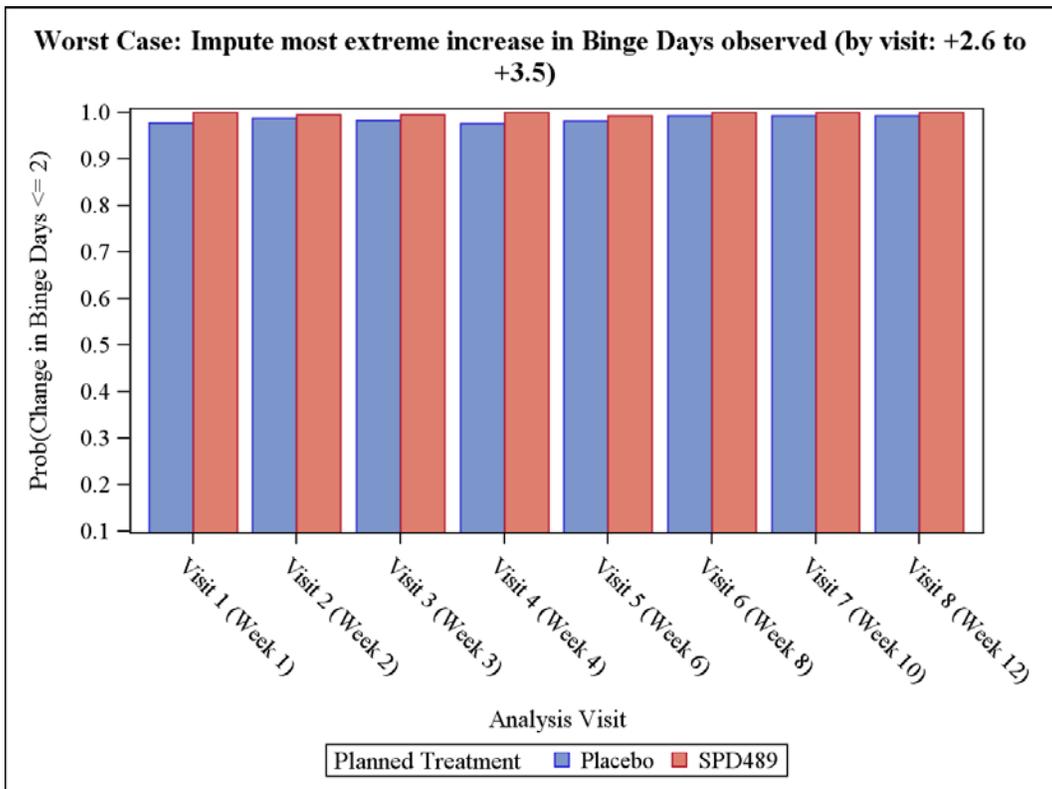
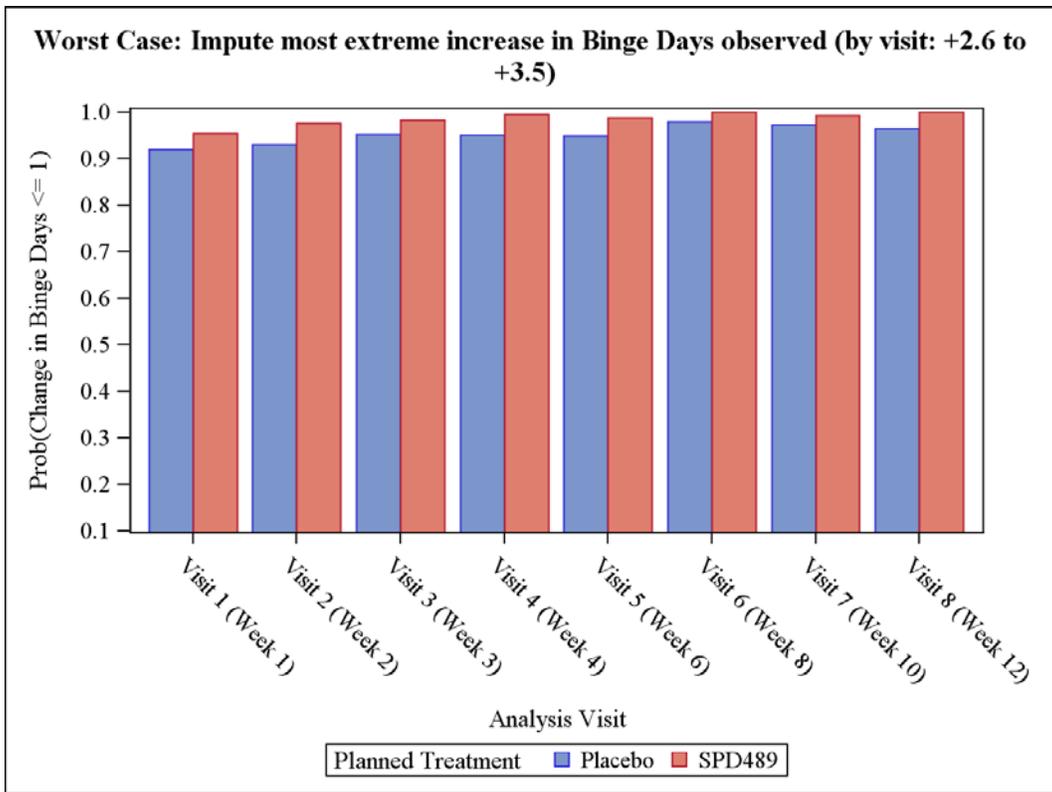
Figure A29. Probability (Change in Binge Days $\leq x$) by Visit - Imputation of Largest Observed Increase in Binge Days [Study 344]

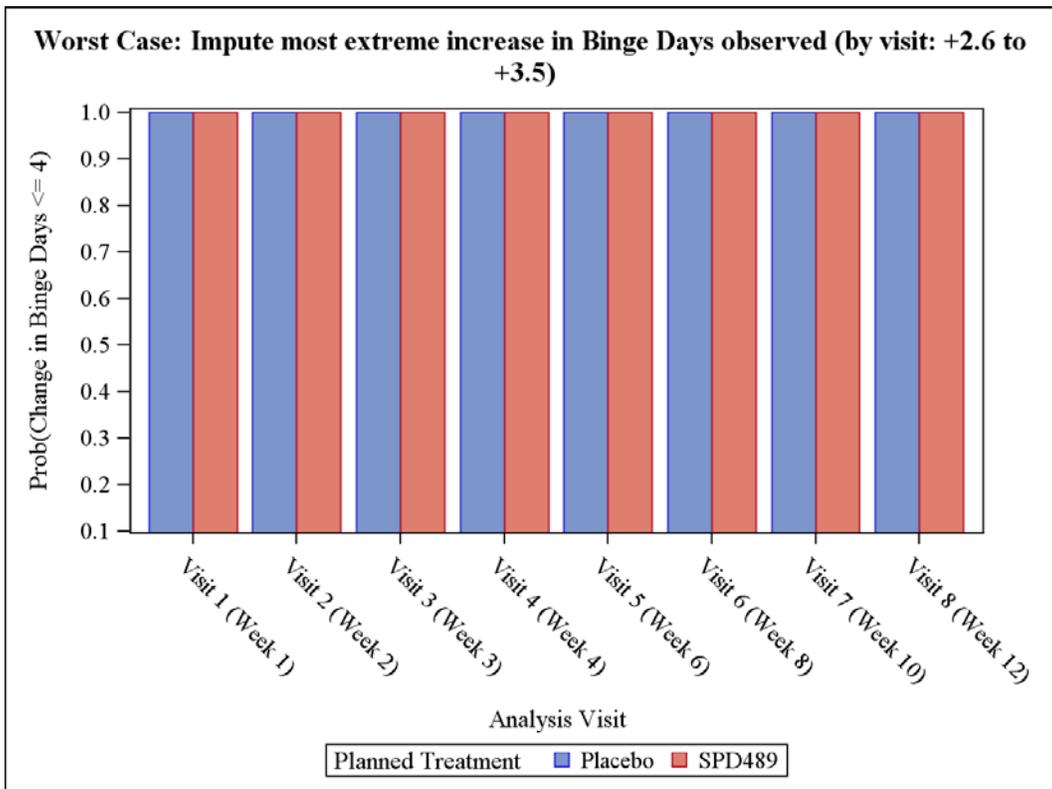
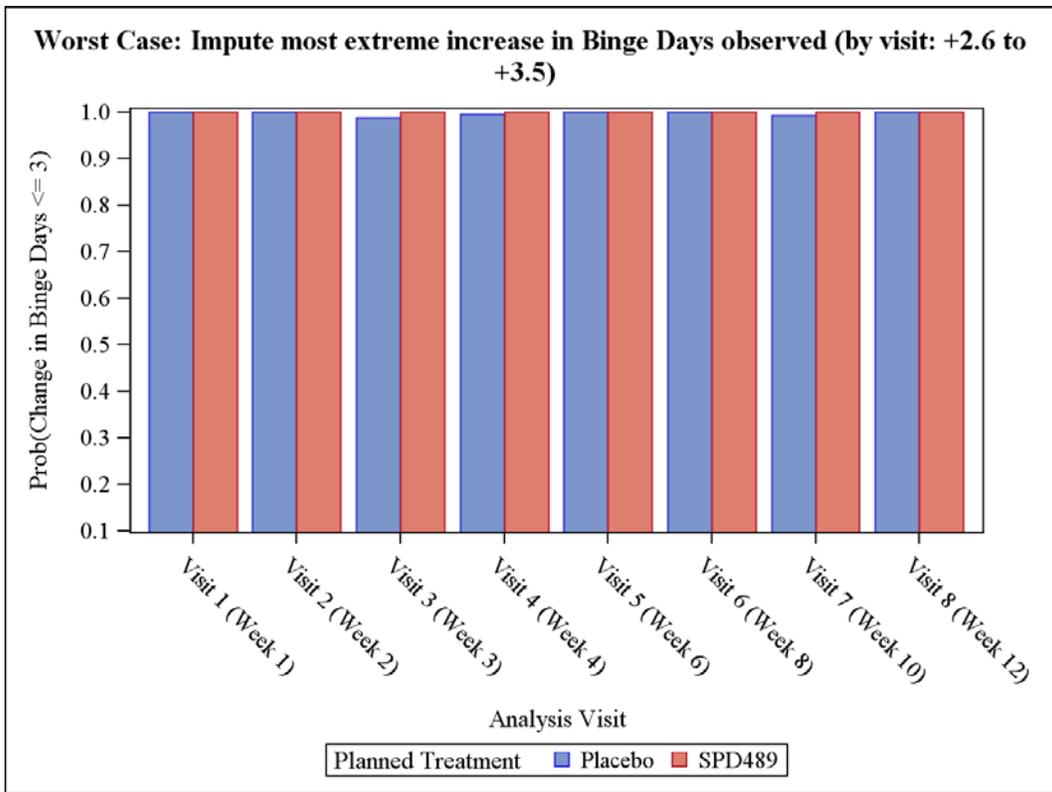












(Source: Reviewer)

Weight

Correlation BMI at baseline and BMI at endpoint:

Figure A30. BMI Baseline vs. BMI Week 12 for Completers, SPD489 Group [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343)

Figure A31. BMI Baseline vs. BMI Week 12 for Completers, Placebo Group [Study 343]

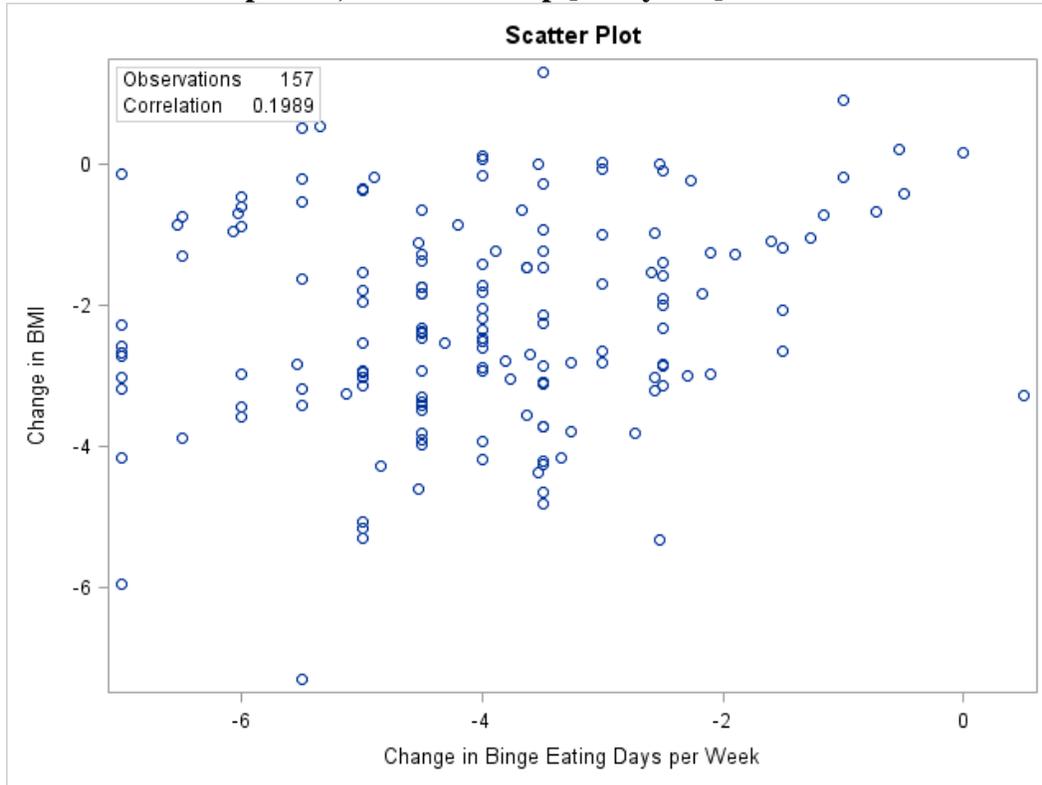


(Source: Reviewer, program: Eff_key_sec_wgtm_343)

Reviewer's Comment: Based on the scatter plots, it appears that BMI measures are highly correlated over the whole observed range.

Correlation/Association between change in number of binge days and weight loss (in terms of percent change, absolute difference, or BMI)

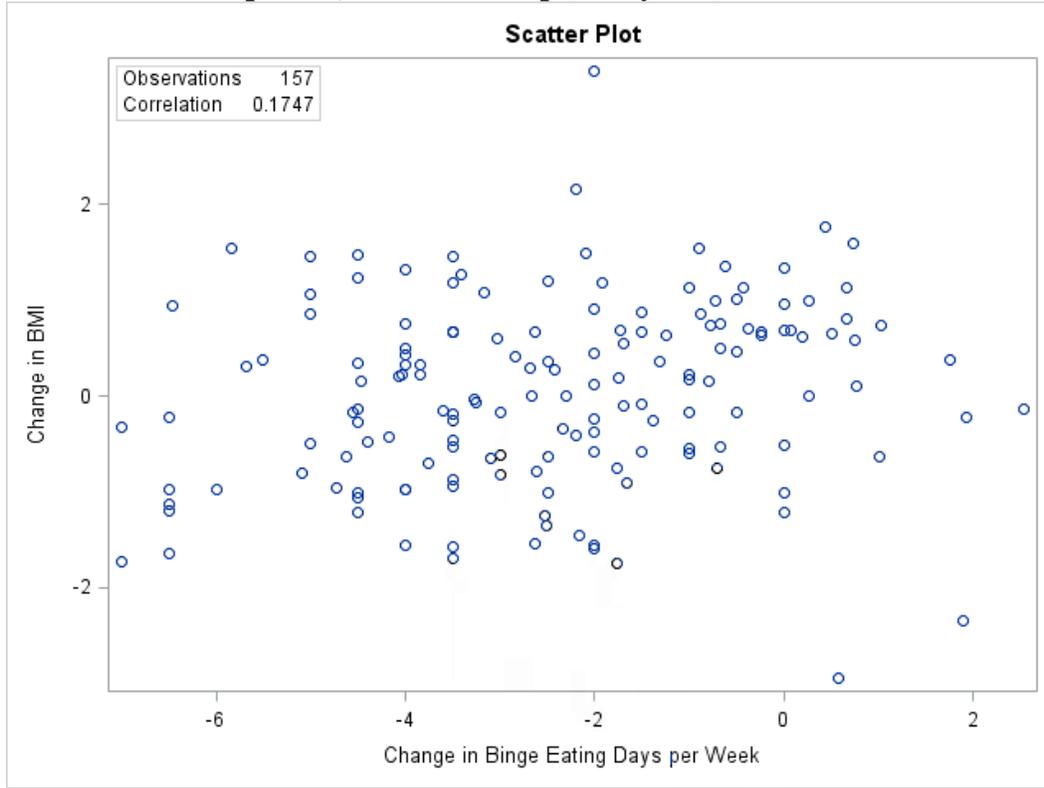
Figure A32. Change in Number of Binge Eating Days per Week vs. Change in BMI at Week 12 for Completers, SPD489 Group [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343)

Reviewer's Comments: Notice the decreases in both measures (BMI and BED) for SPD489 subjects, but decreases are hardly correlated; range of decreases in BMI appears to be larger compared to placebo subjects.

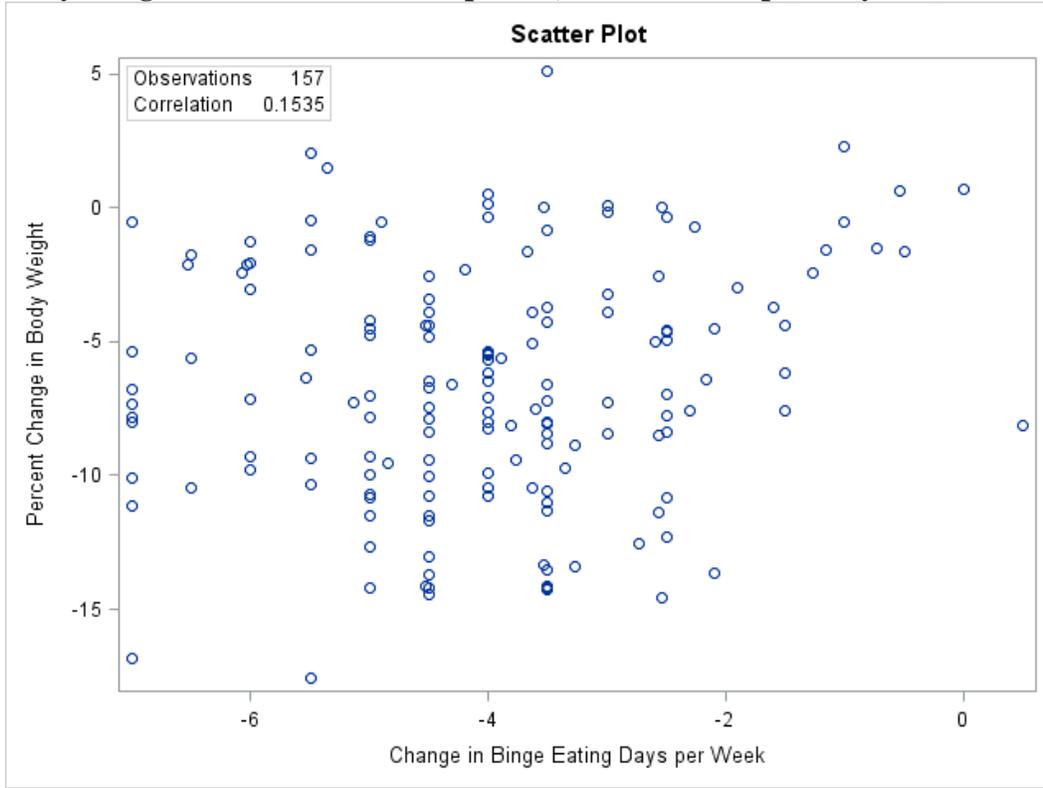
Figure A33. Change in Number of Binge Eating Days per Week vs. Change in BMI at Week 12 for Completers, Placebo Group [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343)

Reviewer's Comments: Observation: Natural (not treatment related) variability in BMI change at Week 12 of about plus/minus 2, uncorrelated to Change in Binge Eating Days; Change in Binge Eating Days for Placebo patients ranges from plus 2 to minus 7 (range [not mean change] is similar to SPD489 subjects).

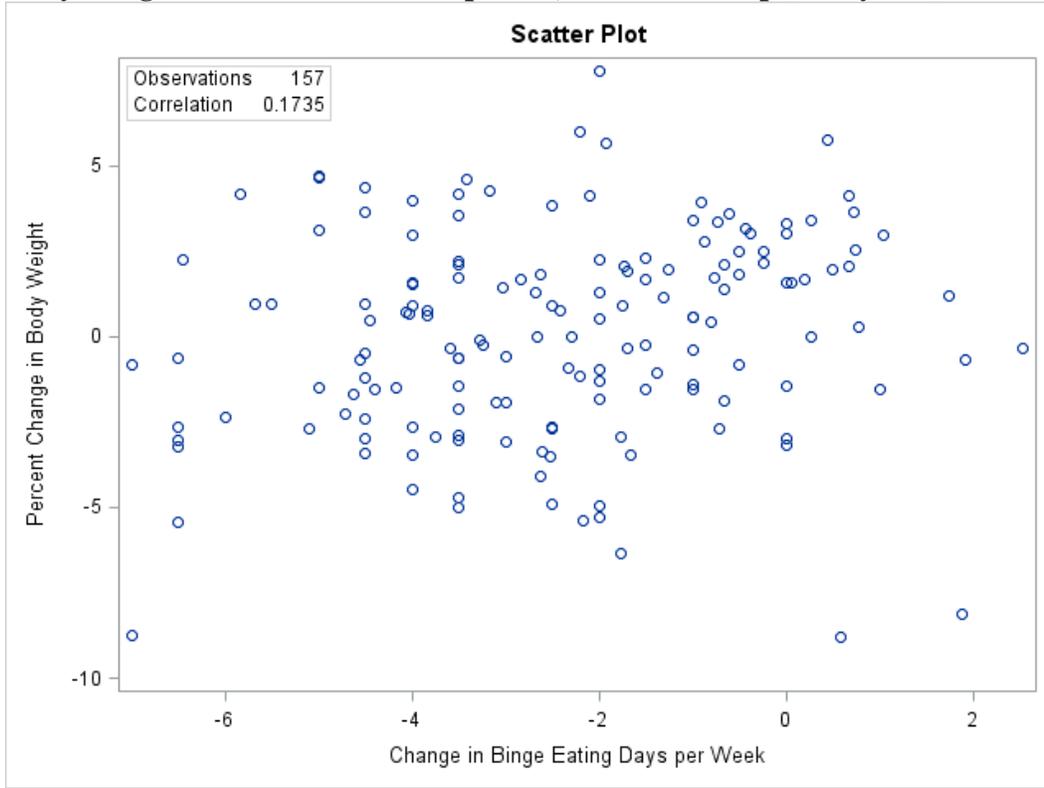
Figure A34. Change in Number of Binge Eating Days per Week vs. Percent Change in Body Weight at Week 12 for Completers, SPD489 Group [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343)

Reviewer's Comment: Not much correlation, but range (i.e., 0 to -15%) for Percent change in body weight differs from placebo group in figure below (range from 5 to -5%).

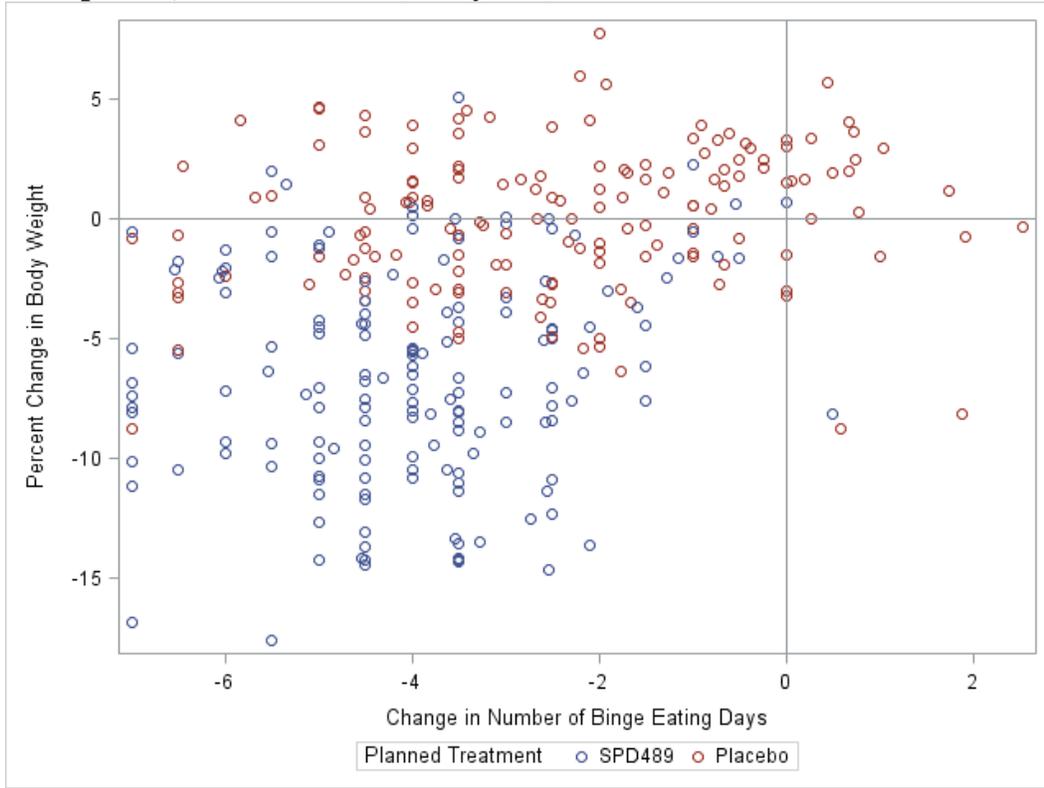
Figure A35. Change in Number of Binge Eating Days per Week vs. Percent Change in Body Weight at Week 12 for Completers, Placebo Group [Study 343]



(Source: Reviewer, program: Eff_key_sec_wgtm_343)

Reviewer's Comment: Not much of a correlation; Placebo patients had a decrease in Binge Eating Days per Week, but this did not translate into weight loss on average.

Figure A36. Change in Binge Days versus Percent Change in Weight at Week 12 (Completers, observed data) [Study 343]



(Source: Reviewer)

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/s/

THOMAS BIRKNER
01/15/2015

PEILING YANG
01/15/2015
I concur with the review.

HSIEN MING J HUNG
01/15/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 21,977 S-37 **Applicant:** Shire

Stamp Date: 08/01/2014

Drug Name: Vyvanse **NDA Type:** Supplement

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter | Yes | No | NA | Comments |
|---|---|------------|-----------|-----------|---|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc. | X | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable). | X | | | Efficacy by subgroup for primary endpoint |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | X | | | |

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|------------|-----------|-----------|----------------|
| Designs utilized are appropriate for the indications requested. | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | X | | | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | X | | | |

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| | |
|------------------------|------------|
| Thomas Birkner | 08/26/2014 |
| Reviewing Statistician | Date |
| Peiling Yang | 08/26/2014 |
| Supervisor/Team Leader | Date |

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/s/

THOMAS BIRKNER
08/26/2014

PEILING YANG
08/28/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

| | Information | | Information |
|----------------------------------|---------------|-------------------------|---|
| NDA/BLA Number | 21977 | Brand Name | Lisdexamfetamine dimesylate, |
| OCP Division (I, II, III, IV, V) | I | Generic Name | Vyvanse |
| Medical Division | DPP | Drug Class | Stimulant |
| OCP Reviewer | Andre Jackson | Indication(s) | Binge eating disorder in adults 18-55 years of age |
| OCP Team Leader | Hao Zhu | Dosage Form | IR tablet |
| Pharmacometrics Reviewer | n/a | Dosing Regimen | Dosage strengths: 20mg, 30mg, 40mg, 50mg, 60 mg and 70 mg |
| Date of Submission | 8/1/2014 | Route of Administration | Oral |
| Estimated Due Date of OCP Review | 11/30//2014 | Sponsor | Shire |
| Medical Division Due Date | 12/30/2014 | Priority Classification | Standard- PREA |
| PDUFA Due Date | 1/30/2015 | | |

Summary

Shire conducted two identically designed pivotal studies (SPD489-343 and SPD489-344), to support the safety and efficacy of SPD489 for the treatment of binge eating disorder (BED) in adults 18-55 years of age. The aim of the two pivotal studies is to demonstrate that SPD489 is more effective than placebo in treating moderate to severe BED. Efficacy of SPD489 for the treatment of BED has been investigated based upon the primary endpoint of number of binge days per week in subjects treated with SPD489 as compared to placebo. The effect of SPD489 was also investigated on secondary binge-related endpoints: CGI-I (a global BED-related measure of symptoms, function and distress), 4-week cessation of bingeing behavior, and binge-related psychopathology (change from baseline in Y-BOCS-BE total score).

In addition to Study SPD489-343 and Study SPD489-344, this sNDA included the data from the Phase 2 study (SPD489-208), and the interim data from the long-term open-label safety study (SPD489-345). The sponsor also provided population PK and PK/PD reports based on the clinical trial data.

DPP has granted priority review for this application.

Clin. Pharm. and Biopharm. Information

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|--|--|-----------------------------|----------------------------|--|
| STUDY TYPE | Efficacy supplement (PREA and elderly patients for GAD) | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | | | | |
| Tabular Listing of All Human Studies | | | | |
| Human PK Summary | | | | |
| Labeling | | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD - | | | | |
| Phase 2: | x | 1 | 0 | The objective of this study was to build population pharmacokinetic (PK)/ pharmacodynamic (PD) models to describe d-amphetamine plasma concentrations and their effect on ambulatory blood pressure measures following administration of SPD489 (lisdexamfetamine dimesylate, LDX, Vyvanse [®]) using data from Shire clinical study SPD489-116. |
| Phase 3: | | | | |
| PK/PD - | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|--|---|---|---|---|
| Data rich: | x | 1 | 0 | The objective of this analyses was to build a population pharmacokinetic model to describe <i>d</i> -amphetamine plasma concentrations following administration of Vyvanse® (SPD489, lisdexamfetamine dimesylate, LDX). |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies | | | | |
| Bio-waiver request based on BCS | | | | |
| BCS class | | | | |
| Dissolution study to evaluate alcohol induced dose-dumping | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 2 | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|-----|----|-----|---------|
| Criteria for Refusal to File (RTF) | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | x | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | x | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | x | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | | x | |
| 5 | Has a rationale for dose selection been submitted? | | | x | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | | | x | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | | | x | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | | | x | |
| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
| Data | | | | | |

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|-----------------------------|--|---|--|---|---------------------|
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | x | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | x | |
| Studies and Analyses | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | x | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | x | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | x | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | x | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | x | Requesting a waiver |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | x | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | x | |
| General | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | | | x | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | x | |

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No comments for the sponsor.

| | | |
|--------------------------------|----------------------|------|
| Clinical Pharmacology Reviewer | Andre Jackson, Ph.D. | Date |
| Team Leader/Supervisor | Hao Zhu, Ph.D. | Date |

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/s/

ANDRE J JACKSON
09/16/2014

HAO ZHU
09/16/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

OTHER REVIEW(S)

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: *{See appended electronic signature page}*

DRUG/NDA: Vyvanse (lisdexamfetamine dimesylate) 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg Capsules / NDA 021977

Sponsor: Shire Development, Inc.

Indication: ADHD

Supplements:

| NDA | Supplement | Dated | Action |
|------------|-------------------|--------------|----------------------------|
| 21977 | SLR-033 | 05/16/2014 | AP Letter dated 11/14/2014 |
| (b) (4) | | | |
| 21977 | SLR-036 | 7/24/2014 | Open |
| 21977 | SLR-037 | 8/1/2014 | Open |
| | | | |

NOTES

- The last approved labeling, for comparison purposes, was the labeling attached to the 11/14/2014 approval letter for NDA 021977/S-033.
- The scope of this RPM labeling review will be the Prior Approval Supplement S-037 and the Changes Being Effected Supplement 036.

- [REDACTED] (b) (4)

REVIEW

021977/S-037

Dated: 8/1/2014

CBE: No

Reviewed by Medical Officer: Yes (see review dated 1/11/2015)

The sponsor proposed adding Binge Eating Disorder as an indication based on two identically designed pivotal studies in adults 18-55 years of age. The review team agrees that substantial evidence of safety and effective have been provided and therefore has recommended approval.

021977/S-036

Dated: 7/24/2014

CBE: Yes

Reviewed by Medical Officer: Yes (see review dated 12/15/2014)

The sponsor proposed adding “constipation” to the Postmarketing Experience, Section 6.2, of the Full Prescribing Information. The clinical reviewer agrees with the proposed change and has recommended approval.

CONCLUSIONS

1. These labeling supplements found no changes other than those described above when compared to the last approved labeling (approval letter dated 11/14/2014).
2. I recommend that an approval letter issue for these pending supplemental applications.

{See appended electronic signature page}

Hiren Patel, PharmD, RAC

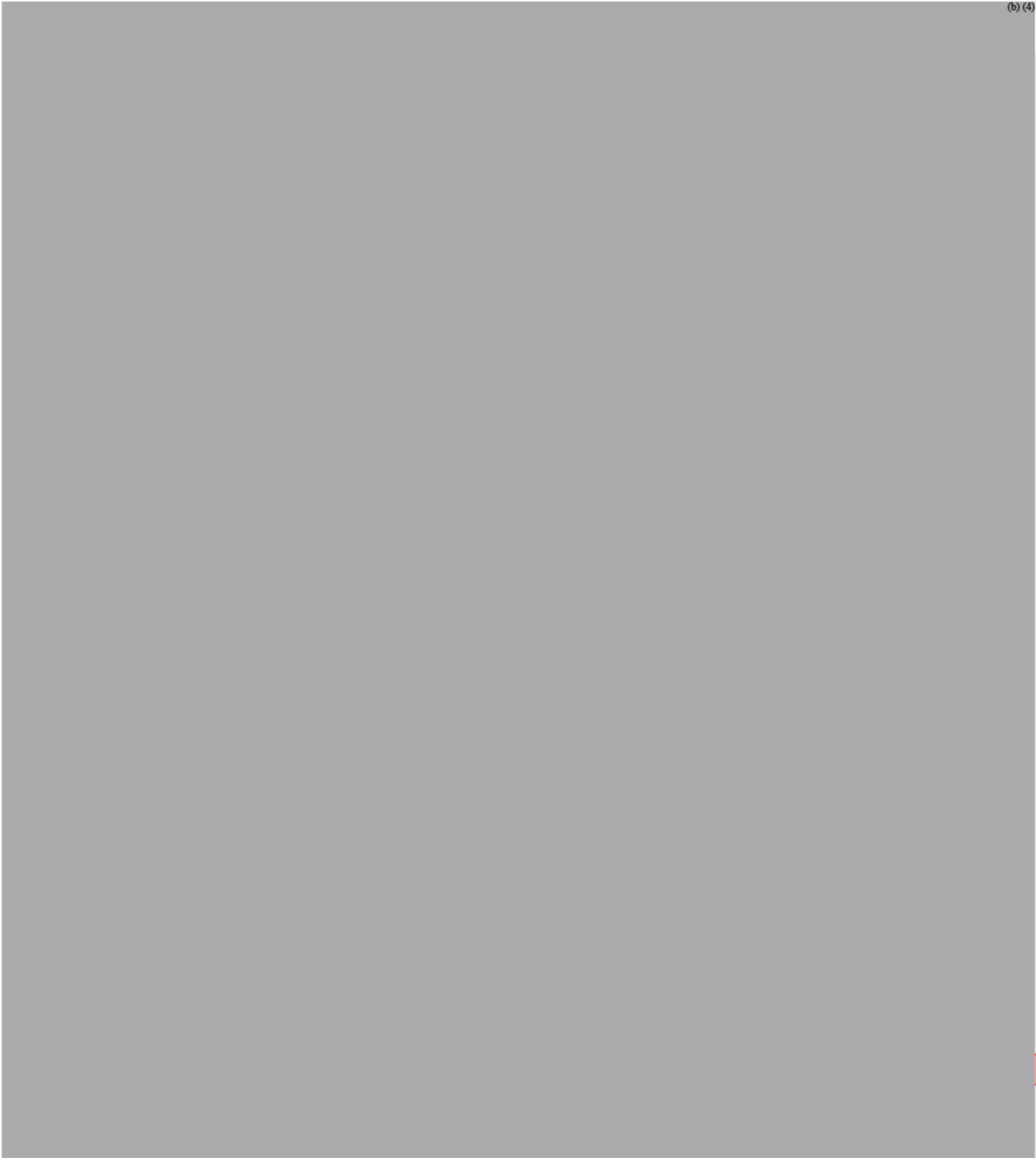
Senior Regulatory Project Manager

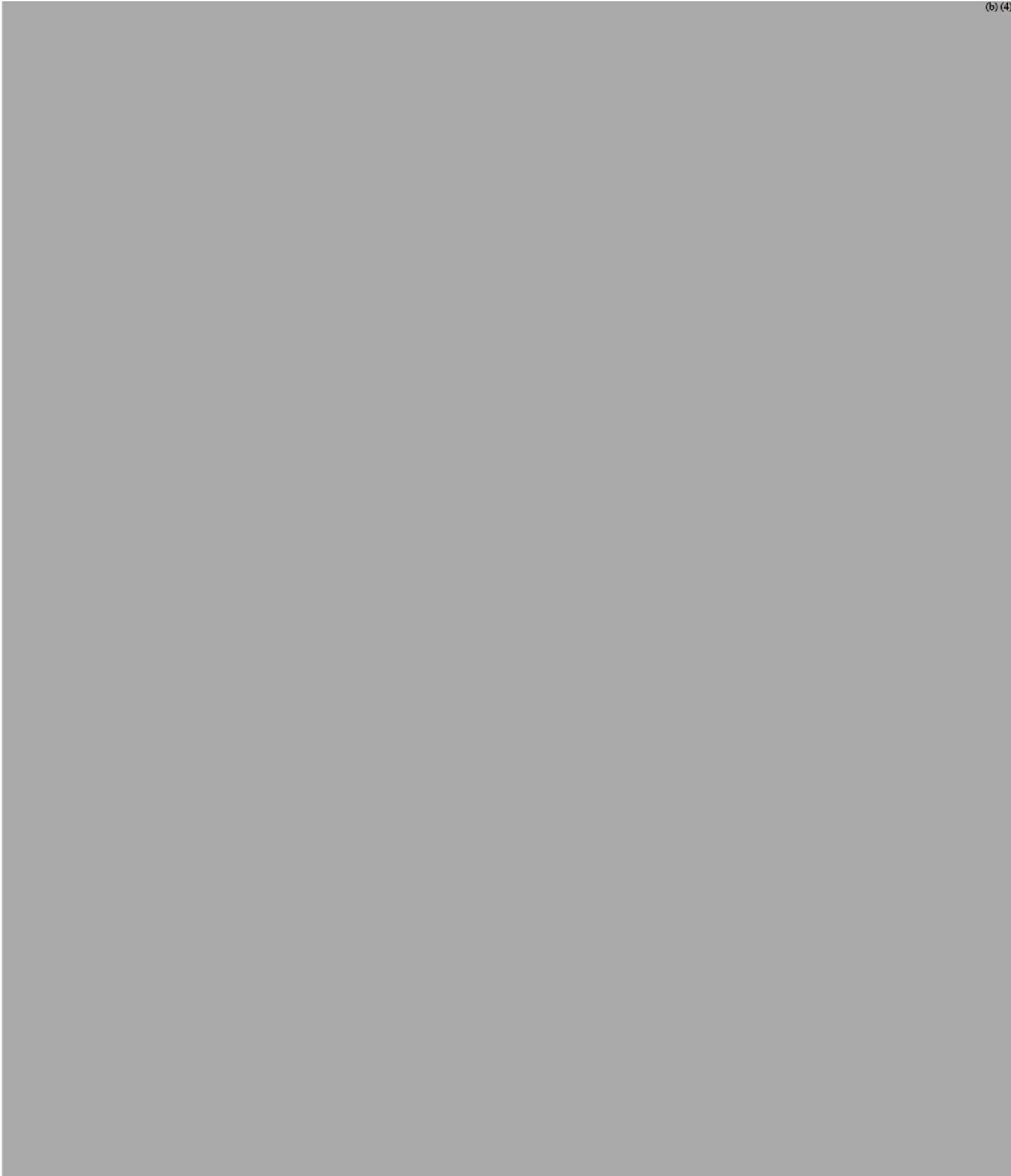
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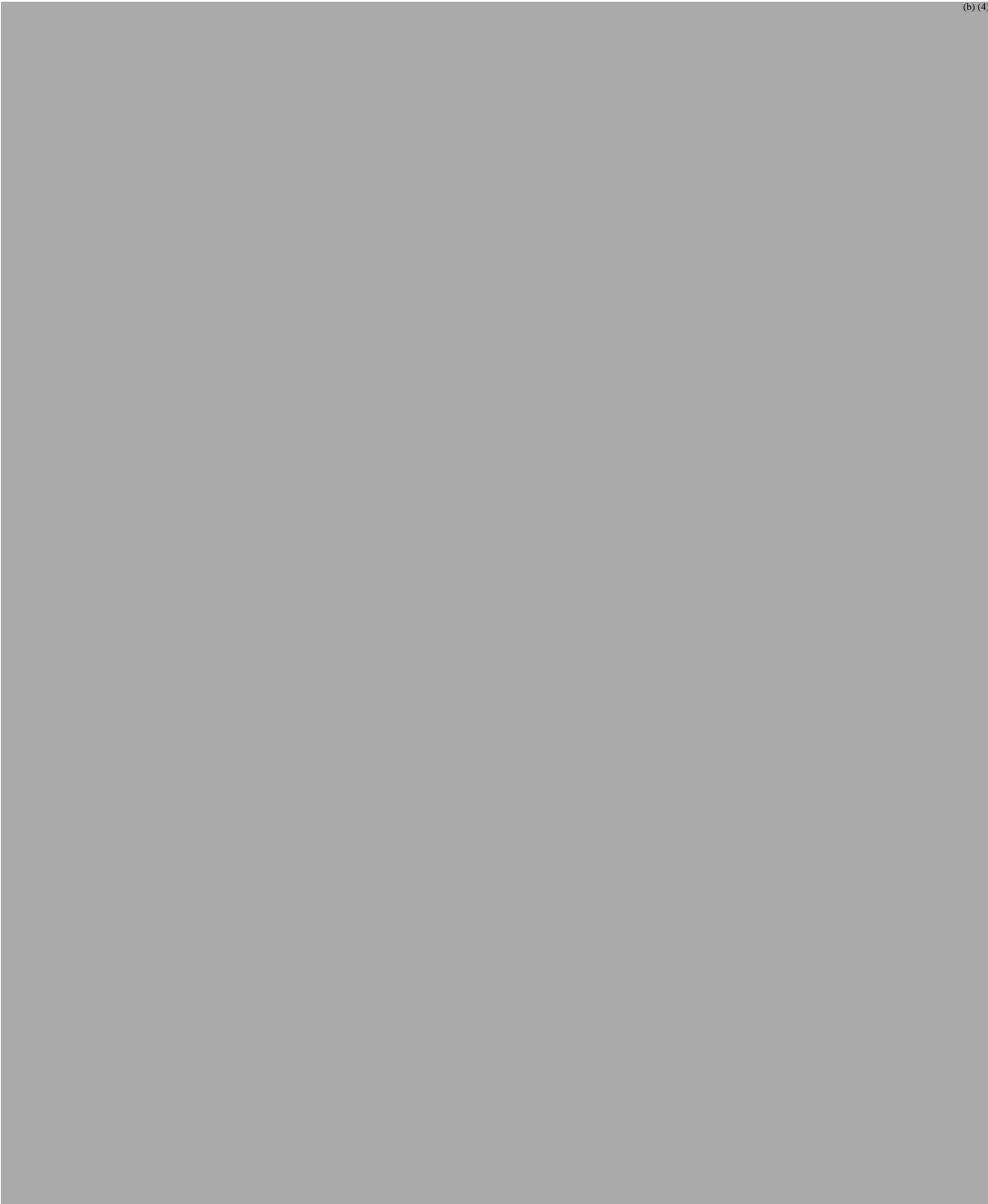
CAPT Paul David, RPh

Chief, Project Management Staff

Enclosure: Annotated labeling changes – Full Prescribing Information and Medication Guide



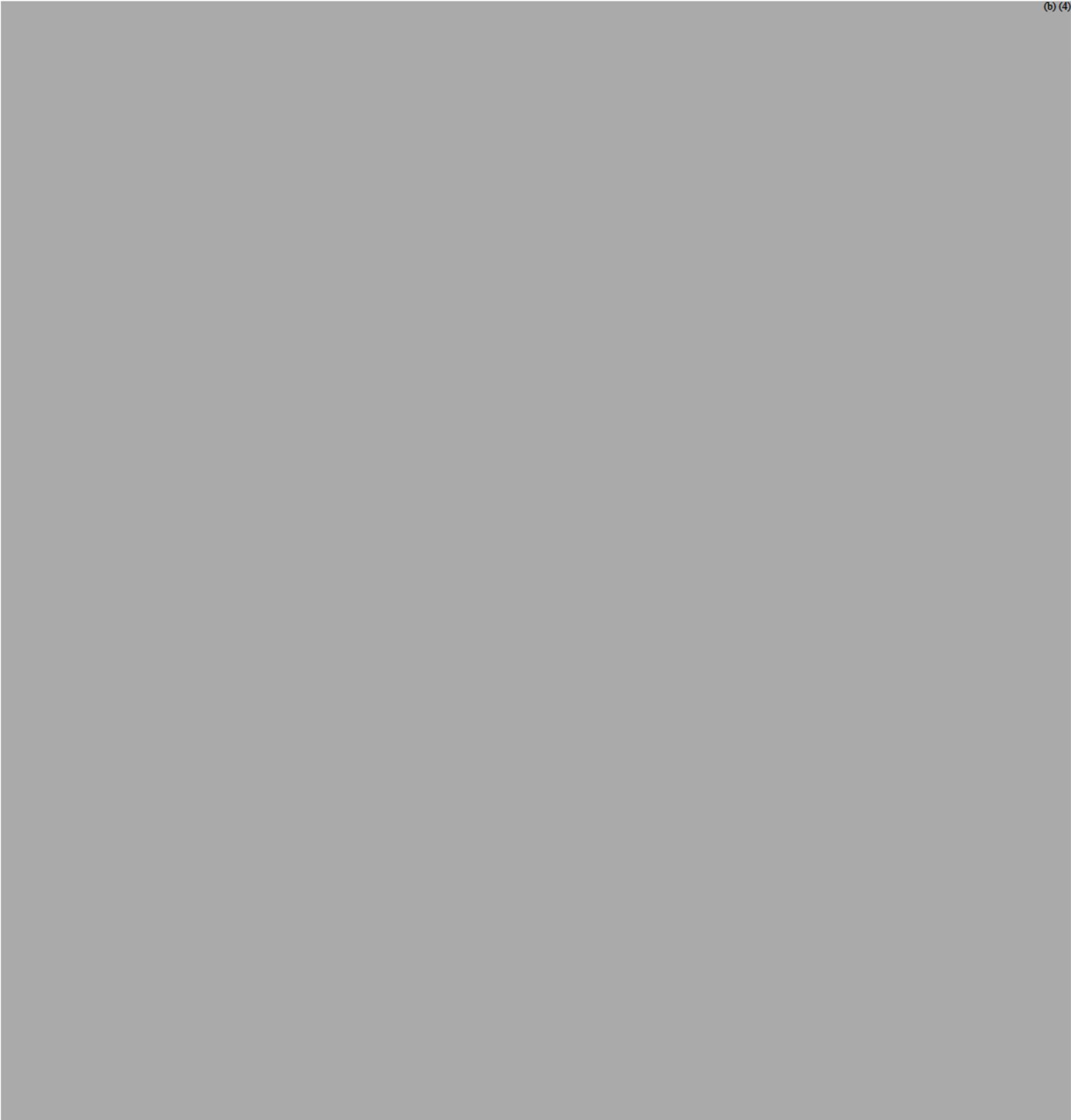






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/s/

HIREN PATEL
01/30/2015

PAUL A DAVID
01/30/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 20, 2015

To: Hiren Patel, PharmD, MS, RAC
Senior Regulatory Health Project Manager
Division of Psychiatry Products (DPP)

From: Susannah O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

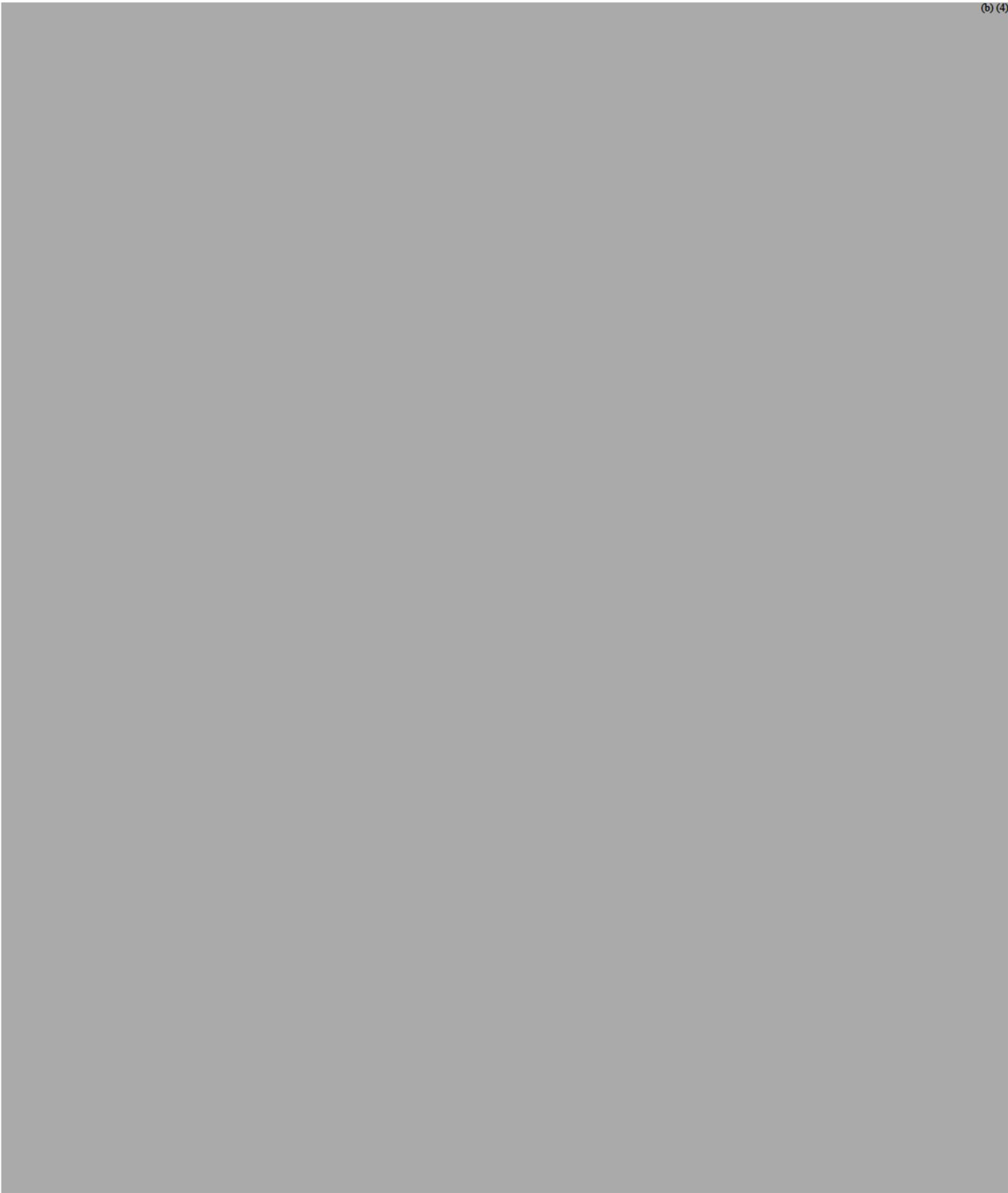
Subject: **NDA 021977 S-037**
VYVANSE (lisdexamfetamine dimesylate) capsules, for oral use, CII

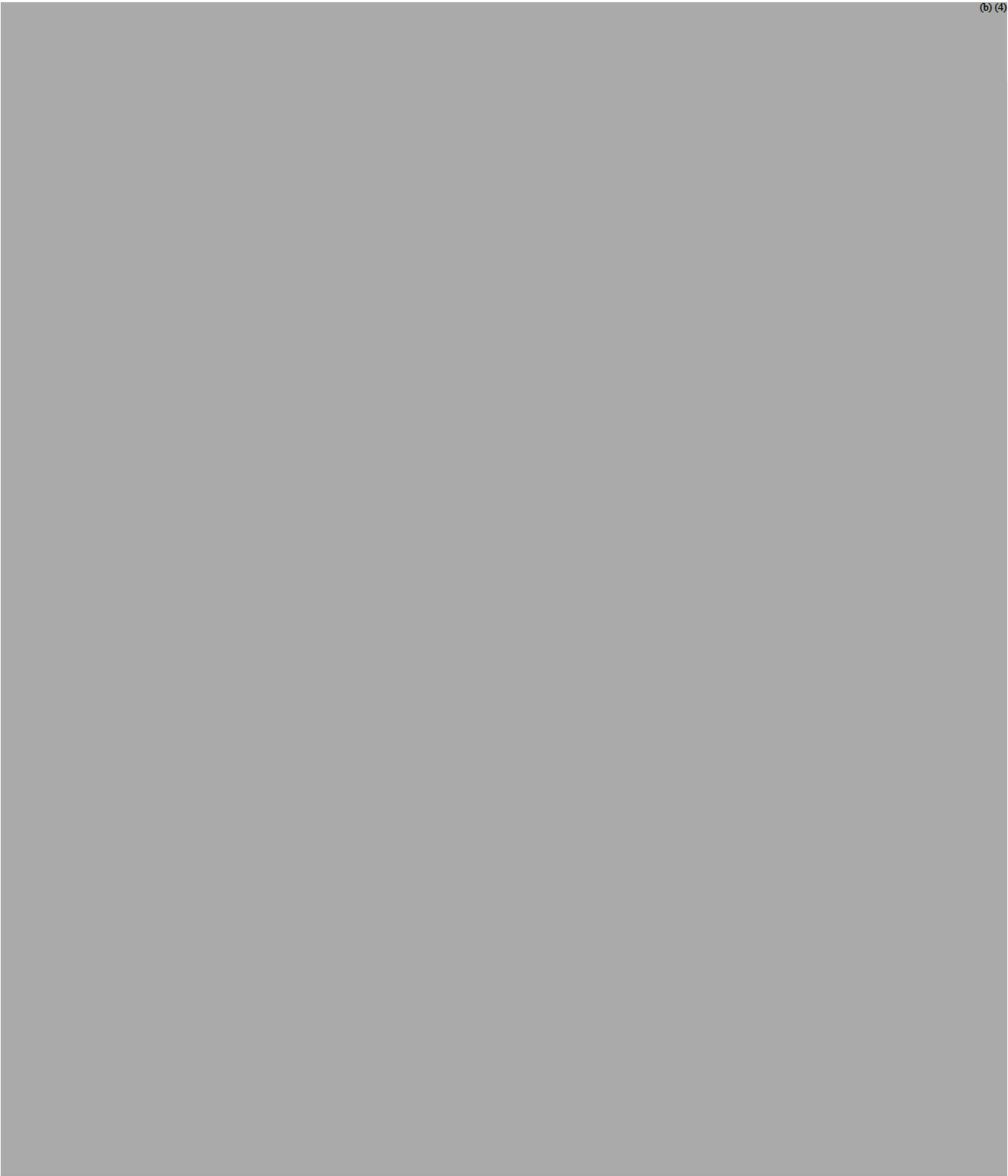
OPDP has reviewed the draft product labeling (PI) and Medication Guide (MG) for VYVANSE (lisdexamfetamine dimesylate) capsules, for oral use, CII (Vyvanse) as requested in the consult from DPP dated August 7, 2014.

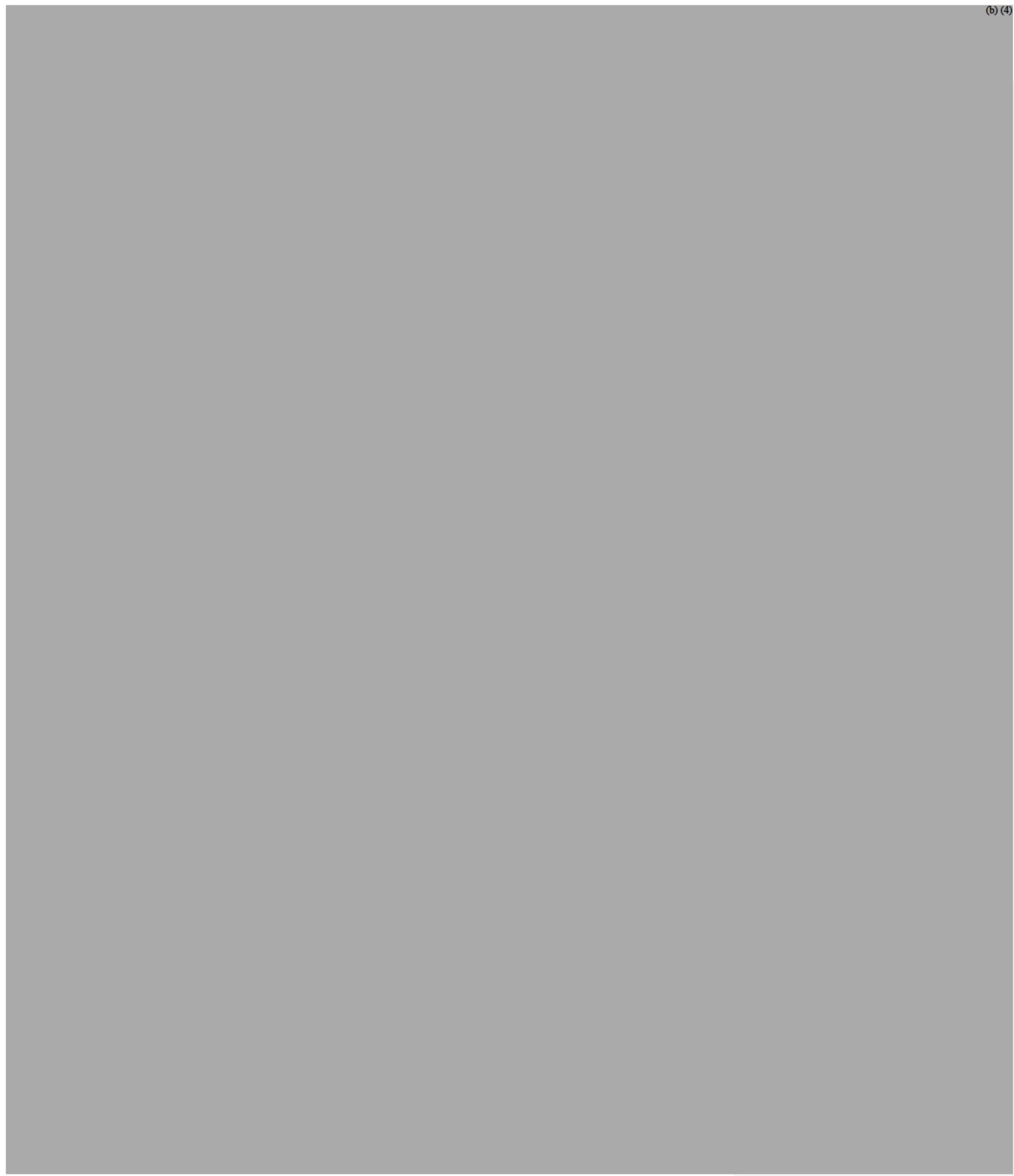
OPDP's comments on the draft PI for Kapvay are based on the version located in Sharepoint dated January 14, 2015 ([Vyvanse BED Documents](#)).

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

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/s/

SUSANNAH O'DONNELL
01/20/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: January 15, 2015

To: Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Focused Review of Patient Labeling: Medication Guide
(MG)

Drug Name (established name): Vyvanse (lisdexamfetamine dimesylate) CII

Dosage Form and Route: Capsules, for oral use

Application Type/Number: NDA 21977

Supplement Number: S-037

Applicant: Shire Development LLC

1 INTRODUCTION

On August 1, 2014, Shire Development LLC submitted for the Agency's review a prior approval labeling supplement for Vyvanse (lisdexamfetamine dimesylate) CII capsules for oral use. The purpose of this submission is for the treatment of Binge Eating Disorder (BED). Vyvanse (lisdexamfetamine dimesylate) CII capsules were approved on February 23, 2007, and is indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Psychiatry Products (DPP) on August 7, 2014, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for Vyvanse (lisdexamfetamine dimesylate) CII capsules for oral use.

2 MATERIAL REVIEWED

- Draft Vyvanse (lisdexamfetamine dimesylate) CII capsules MG received on August 1, 2014, and received by DMPP on January 14, 2015.
- Draft Vyvanse (lisdexamfetamine dimesylate) CII capsules Prescribing Information (PI) received on August 1, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on January 14, 2015.

3 REVIEW METHODS

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
01/15/2015

MELISSA I HULETT
01/15/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: October 24, 2014

TO: Hiren Patel, Pharm.D., Regulatory Project Manager
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Division of Psychiatry Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
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Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 21977 S-37

APPLICANT: Shire Development, LLC

DRUG: Lisdexamfetamine dimesylate (Vyvanse[®])

NME: No

INDICATION: Treatment of binge eating disorder (BED)

THERAPEUTIC CLASSIFICATION: Priority

CONSULTATION REQUEST DATE: September 9, 2014

INSPECTION SUMMARY GOAL DATE: October 31, 2014

REGULATORY ACTION GOAL DATE: January 30, 2015

PDUFA DUE DATE: February 1, 2015

I. BACKGROUND

Shire Development, LLC (**Shire**) sponsored Study SPD489-343 (**Study 343**) and Study SPD489-344 (**Study 344**) as pivotal studies to demonstrate the safety and efficacy of Vyvanse® (lisdexamfetamine dimesylate) in managing binge eating disorder (**BED**) in adults. At approval of this NDA 21977 S-37, Shire expects to be granted three additional years of Vyvanse® marketing exclusivity.

BED is characterized by recurrent distressing episodes of uncontrolled eating without compensatory behavior (e.g., of bulimia nervosa). As the most common eating disorder in the United States (**US**) affecting up to 3% of the population, BED is often comorbid with other psychopathology, obesity, and general disability. Growing evidence suggests: (1) dopamine (**DA**) and norepinephrine (**NE**) are important in regulating eating and reward behavior, (2) binge eating may be mediated by dopaminergic and/or noradrenergic hypofunction, and (3) stimulants that increase DA and NE levels in the brain may be effective in managing BED.

In animal models, the use of the stimulant methylphenidate has been shown to reduce sucrose intake. Clinically, BED is often comorbid with attention deficit hyperactivity disorder (**ADHD**), for which methylphenidate is effective. In fact, Shire originally developed Vyvanse® for ADHD (initial approval in children, 2007). Vyvanse® may be effective also for BED, by normalizing DA and/or NE hypofunction and reducing impulsivity (impulsive eating). Lisdexamfetamine dimesylate (Vyvanse®) is metabolized to d-amphetamine, which blocks DA and NE reuptake to increase their availability, and presumably, to normalize DA and/or NE hypofunction. Currently there is no approved pharmacological agent for BED.

In this NDA supplement, Shire claims that Studies 343 and 344 demonstrate the safety and efficacy of Vyvanse® in managing BED in adults 18-55 years of age. These two studies were audited at good clinical practice (**GCP**) inspections to support this NDA review. The two studies are identical in title and study design and are described together below, with emphasis on study features important to inspectional findings. During product development, Vyvanse® was called SPD489.

Studies 343 and 344

A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder

- Study 343: This randomized, double-blind, placebo-controlled study was conducted between November 2012 and September 2013 in 383 subjects randomized at 50 study sites in the United States (**US**), Germany, Sweden, and Spain.
- Study 344: This study (identical to Study 344 in study title, objective, and design) was conducted concurrently with Study 343 in 390 subjects randomized at 43 study sites, 41 in US and 2 in Germany.
- Both studies: The primary study objective was to demonstrate the efficacy of SPD489 relative to placebo in managing moderate to severe BED, as measured by the number of binge eating days per week according to clinical interview and subject diary. The study consisted of four periods: (1) screening; (2) dose-optimization, four weeks; (3) dose-maintenance, eight weeks; and (4) follow-up.

Inclusion Criteria

- Adults (age 18-55 years) with moderate to severe BED per criteria in *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – Text Revision (DSM-IV-TR)*, BED diagnosis confirmed by Structural Clinical Interview for DSM-IV-TR disorders (**SCID-I**) and Eating Disorder Examination Questionnaire (**EDE-Q**)
- Three or more binge eating days per week for 14 days prior to the baseline Visit 0 per subject report and documented in subject diary

- Recurrent episodes of binge eating: An episode of binge eating characterized by eating within a discrete period an amount of food much greater than most people would eat under similar circumstances, along with a sense of lack of control (cannot stop or control what/how much)
- Episodes associated with at least three of the following: (1) eating much more rapidly than normal, (2) eating until uncomfortably full, (3) eating large amounts of food when not feeling hungry, (4) eating alone because of being embarrassed by how much one is eating, or (5) feeling disgusted with oneself, depressed, or guilty after overeating
- The binge eating occurs, on average, at least two days per week for six months, and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa
- CGI-S score ≥ 4 at screening and baseline; body mass index (**BMI**) between 18 and 45 (inclusive) at screening and at baseline; for female subjects, negative serum pregnancy test at screening and negative urine pregnancy test at baseline

Exclusion Criteria

- Exclusion for current diagnoses of: bulimia nervosa or anorexia nervosa (as defined in SCID-I), or any comorbid Axis I or Axis II psychiatric disorder, either uncontrolled or controlled with medications prohibited in this study
- 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
- 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
- Receiving psychotherapy or weight loss support for BED initiated within three months of screening (earlier initiation permitted unchanged); psychostimulants that facilitate fasting or dieting within six months; lifetime history of psychosis, mania, hypomania, dementia, or ADHD
- Symptomatic manifestations (such as agitated states) that contraindicate treatment with SPD489 or confound efficacy or safety assessments in the opinion of the investigator
- Montgomery-Asberg Depression Rating Scale (**MADRS**) total score ≥ 18 at screening; suicide risk in the opinion of the investigator (intermittent passive suicidal ideation not necessarily excluded)
- Concurrent chronic or acute illness, disability, or other condition that might confound the results of safety assessments administered in the study or that might increase risk to the subject
- Family history of sudden cardiac death or ventricular arrhythmia; any significant ECG abnormality; any clinically significant laboratory abnormality, including hypokalemia
- Current abnormal thyroid function (abnormal thyroid stimulating hormone and thyroxine, stable treatment with thyroid medication for at least three months permitted)
- Initiation of treatment with a lipid lowering medication within three months (stable treatment for at least 3 months permitted); history of moderate or severe hypertension; any medication that is excluded (complete list in study protocol)
- History (within six months) of suspected substance abuse or dependence disorder in accordance with DSM-IV-TR criteria; lifetime history of amphetamine, cocaine, or other stimulant abuse and/or dependence (nicotine dependence not exclusionary)

- Positive drug testing at screening unless due to medication (verified); use of medications that have central nervous system effects or affect performance, such as chronic use of sedating antihistamines and decongestant sympathomimetic agents within seven days
- History of bariatric surgery, lap bands, duodenal stents, or other procedures for weight loss; glaucoma; pregnant or nursing; intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients
- Participation in an investigational or observational study within 30 days, or any prior clinical study involving SPD489; previously completed, discontinued, or withdrawn from this study

Treatment Groups and Regimen

- Randomization in equal ratio to SPD489 or placebo (oral, once daily during blinded treatment), treatment discontinued for unacceptable efficacy or tolerability
- Initial daily dose of 30mg, titrated upward for optimal efficacy and tolerability (50 or 70mg), then fixed during dose-maintenance, one downward titration permitted ; follow-up visit one week after last dose for safety evaluation (including AEs or concomitant medications)

Major Study Endpoints and Analyses

- Primary Efficacy Endpoint: Change from baseline to Visit 8 (Weeks 11 and 12) in the number of binge eating days per week using diary data for Weeks 11 and 12.
 - Baseline was defined as the weekly average of the number of binge eating days per week for the 14 days prior to the baseline Visit 0. Binge eating information was captured daily by subject self-reporting in paper diary (collected at each study visit).
 - Diary information: number of binges per day, total hours per day spent bingeing, type of binge (at mealtime or not), and a description of the binge (amount and type of food). The clinical investigator (CI) reviewed the diary during subject interview to confirm or reject each episode as a binge episode.
 - Analysis by mixed-effects model for repeated measures (MMRM): change from baseline 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 covariate; and its interaction with visit included in the model
- Other endpoints: Clinical Global Impressions of Severity (CGI-S), Clinical Global Impressions of Improvement (CGI-I), body weight, and safety monitoring by AEs, vital signs, body weight, waist circumference, BMI, laboratory testing, and electrocardiogram (ECG)

Major Sponsor-Reported Study Findings

- Study 343: 383 subjects were randomized (191 placebo, 192 SPD489) and 315 completed the study (157 placebo, 158 SPD489). Two subjects incorrectly randomized were excluded from safety analyses. Relative to placebo, the reduction in binge days per week (primary endpoint) was greater for SPD489, with least square (LS) means of 3.9 and 2.5 days ($p < 0.001$, effect size 0.83).
- Study 344: 390 subjects were randomized (195 each for placebo and SPD489) and 294 completed the study (147 each). No subjects were incorrectly randomized. Relative to placebo, the reduction in binge days per week (primary endpoint) was greater for SPD489, with LS means of 3.9 and 2.3 days ($p < 0.001$, effect size 0.97).
- For both studies, greater for SPD489 (relative to placebo) were: (1) subject proportion with improved CGI-I; (2) subject proportion attaining a 4-week binge eating cessation; and (3) percent reduction of body weight from baseline. SPD489 appeared to be well-tolerated in this population of adult subjects with moderate to severe BED. The observed safety profile was consistent with that known for SPD489 when used for ADHD.

II. INSPECTIONS

Studies 343 and 344 were audited at GCP inspections of two study sites, one site per study. Site 83 in Study 343 was selected for large subject enrollment. Site 32 in Study 344 was selected for large subject enrollment and additionally for GCP deficiencies leading to site closure by the sponsor. The inspection outcomes are shown below.

| Clinical Investigator Site | | Study, Site Enrollment | Inspection Outcome |
|----------------------------|--|---|---|
| 1 | Alexander E. Horwitz, M.D. Oregon Center for Clinical Investigations 702 Church Street NE Salem, Oregon | SPD489-343, Site 83 24 subjects | September 22 – October 2, 2014 Pending, Preliminary NAI |
| 2 | H. Mikel Thomas, M.D. Clinical Trials Technology 8340 Mission Road, Suite 205 Prairie Village, Kansas | SPD489-344, Site 32 25 subjects | September 25 – 30, 2014 Pending, Preliminary NAI |

NAI = no action indicated (no significant GCP violations)

Pending: preliminary results based on communication with field investigator

1. Alexander E. Horwitz, M.D.

a. What was inspected:

- Records review: local institutional review board (**IRB**) oversight and sponsor monitoring, clinical investigator (**CI**) financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

For Study 343, at Site 83: 31 subjects were screened, 24 were enrolled, and 21 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 10 subjects.

No significant deficiencies were seen and a Form FDA 483 was not issued. The following major observations were verbally discussed:

- Subject 3025 took the last dose of oxycodone within five days of screening, in violation of the exclusion criterion which prohibits the use of sedatives and narcotics within 30 days of subject screening. This protocol violation was not reported in the NDA.

Reviewer Comment: At screening, the subject tested negative for opiates, and the protocol allows the use of prescribed narcotics. Although inadequate for the exclusion criterion as specifically worded, the five-day oxycodone washout appears adequate for the intent of the criterion given the oxycodone half-life of 3-4 hours relative to the five-day washout (30 half-lives).

- For five subjects, Visit 8 was held one day earlier than as specified in the study protocol (15 days after Visit 7 and 85±1 day from Visit 0).

- [REDACTED] (b) (6)

The conduct of Study 343 at this Site 83 appeared adequate, including informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The Establishment Inspection Report (EIR) has not been received from the field office. The observations noted above are based on preliminary communication with the field investigator.

2. H. Mikel Thomas, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use
- For-cause audit: In the NDA, the sponsor reported that this site was terminated “due to concerns regarding signs of investigational drug tampering” in [REDACTED] (b) (4) without a detailed discussion, including no discussion about relevance to Study 344. All study data from this Site 32 are included in the sponsor’s analyses of the results of Study 344.

b. General observations and comments:

Study 344, Site 32: 41 subjects were screened, 25 were enrolled, and 21 completed the study. Records were reviewed in detail for all enrolled subjects.

No significant deficiencies were seen and a Form FDA 483 was not issued. Minor isolated deficiency observations were verbally discussed (not cited):

- The standard operating procedures (SOP) for obtaining informed consent (IC) does not specify who is authorized to obtain IC and sign the IC document.
- Adequate training of study personnel in performing delegated study procedures is not consistently documented as part of study records.

For-cause audit findings: Shire closed this site in February 2014 after an anonymous allegation about product tampering in [REDACTED] (b) (4)

[REDACTED] At that time, Study 344 had been completed at this site.

- The sponsor’s audit revealed limited evidence of product tampering in [REDACTED] (b) (4) (broken bottle seals and broken/punctured capsules, product residue on capsule surface). Most bottles/capsules were intact. There was no evidence of product tampering in any [REDACTED] (b) (4) study. The study medication was quarantined and returned to Shire.
- Contents of the tampered capsules were analyzed by infrared spectroscopy and gas chromatography. Capsule content varied from [REDACTED] (b) (4) [REDACTED] (b) (4). Non- [REDACTED] (b) (4) substance was identified as [REDACTED] (b) (4). The AEs reported at this site in [REDACTED] (b) (4) appeared consistent with the known [REDACTED] (b) (4) safety profile.

- The audit could not determine who tampered with the study medication or why. For (b) (4), subject safety and study data integrity appeared not to be impacted. There was no evidence that (b) (4) (b) (4) studies were affected, including Study 344 and other BED studies.
- Previous for-cause FDA inspection: FDA's findings were consistent with the sponsor's findings. Minor deficiencies in drug accountability were also observed. The CI signed a Form 463a (affidavit) certifying that he has no knowledge of product tampering. The outcome of this for-cause FDA inspection has not been finalized (discussion on-going) as of this Clinical Inspection Summary (CIS).
- Current FDA inspection for NDA 21977 S-37: The CI was not aware of any new information about product tampering. Evidence of product tampering was not observed for Study 344. SPD489 was stored double-locked, video-monitored, and temperature-controlled with key card recording of all access. Drug accountability was well tracked and documented.

The conduct of Study 344 at this Site 32 appeared adequate, including informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The EIR has not been received from the field office. The observations noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Shire submitted this NDA 21977 S-37 to support the use of Vyvanse® to treat BED based on two identical studies conducted concurrently between 2012 and 2013 in US and Europe, Study 343 (383 subjects, 50 sites) and Study 344 (390 subjects, 43 sites). In support of this NDA review, both studies were audited at GCP inspections of two study sites, one site per study. Site 83 in Study 343 (Horwitz) was selected for large subject enrollment. Site 32 in Study 344 (Thomas) was selected for large subject enrollment and additionally for GCP deficiencies leading to site closure by the sponsor. At the two inspections combined, records for 49 subjects (6%) were reviewed, including detailed review for 35 subjects (5%).

At both study sites, no significant deficiencies were observed and a Form FDA 483 was not issued. The study conduct at both sites appeared adequate, including IRB oversight and sponsor monitoring of study conduct. Study 344 at Site 32 (Thomas) appears not to be impacted by the concern that led to site closure. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the two inspected study sites appear reliable as reported in the NDA.

Note: For both inspections, the EIR has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communication with the field investigator. An addendum to this CIS will be forwarded to the review division if the inspection outcome classification changes or if additional concerns of clinical or regulatory significance are identified upon receipt and review of the EIR.

{See appended electronic signature page}

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/s/

JONG HOON LEE
10/24/2014

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KASSA AYALEW
10/27/2014

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 21977/S-037

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Vyvanse (lisdexamfetamine dimesylate) 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg capsules

Applicant: Shire Development LLC

Receipt Date: August 1, 2014

Goal Date: February 1, 2015

1. Regulatory History and Applicant's Main Proposals

Shire's is proposing to add Binge Eating Disorder as an indication.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

A SRPI format deficiency was identified in the review of this PI (See the Appendix).

The SRPI format deficiency of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 30, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

| Section | Required/Optional |
|-----------------------------------|-------------------|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |

Selected Requirements of Prescribing Information

| | |
|---|---|
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a BOXED WARNING is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state “None.”) |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|--|
| BOXED WARNING |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- YES** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HIREN PATEL
09/08/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | | |
|--|--|---|
| NDA # 21977 BLA# | NDA Supplement #:S-037 BLA Supplement # | Efficacy Supplement Type SE- 1 |
| Proprietary Name: Vyvanse Established/Proper Name: lisdexamfetamine dimesylate Dosage Form: Capsule Strengths: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg | | |
| Applicant: Shire Development LLC Agent for Applicant (if applicable): | | |
| Date of Application: August 1, 2014 Date of Receipt: August 1, 2014 Date clock started after UN: | | |
| PDUFA Goal Date: February 1, 2015 | | Action Goal Date (if different): January 30, 2015 |
| Filing Date: September 30, 2014 | | Date of Filing Meeting: August 28, 2014 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) | | |
| Proposed indication(s)/Proposed change(s): Binge Eating Disorder | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 . | | |
| Type of BLA | <input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k) | |
| <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i> | | |
| Review Classification: | <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted | |
| <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i> | | |
| Resubmission after withdrawal? <input type="checkbox"/> | | Resubmission after refuse to file? <input type="checkbox"/> |
| Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products | |

| |
|---|
| <input type="checkbox"/> Other (drug/device/biological product) |
|---|

| | | | | |
|---|--|-------------------------------------|--------------------------|----------------|
| <input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | | | |
| Collaborative Review Division (if OTC product): | | | | |
| List referenced IND Number(s): 110503; (b) (4); 67482; (b) (4) | | | | |
| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If yes, explain in comment column. | | | | |
| If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified: | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

| <p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p> | <p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p> | | | | | | | | | | | | | | | | | | | |
|--|--|--|--|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|---------------------------------|---------------------------------|--|--|
| <p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p> | <p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p> | | | | | | | | | | | | | | | | | | | |
| <p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> | <p><input type="checkbox"/></p> | <p><input type="checkbox"/></p> | <p><input checked="" type="checkbox"/></p> | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p> | <p><input type="checkbox"/></p> | <p><input type="checkbox"/></p> | <p><input checked="" type="checkbox"/></p> | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p> | <p><input type="checkbox"/></p> | <p><input type="checkbox"/></p> | <p><input checked="" type="checkbox"/></p> | | | | | | | | | | | | | | | | | |
| <p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | <p><input type="checkbox"/></p> | <p><input type="checkbox"/></p> | <p><input checked="" type="checkbox"/></p> | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | |
| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | | | |
| <p>Exclusivity</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p> | <p><input type="checkbox"/></p> | <p><input checked="" type="checkbox"/></p> | | | | | | | | | | | | | | | | | | |

| | | | | |
|--|-------------------------------------|-------------------------------------|-------------------------------------|--|
| Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm | | | | |
| If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

| Format and Content | |
|--|--|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) |
| If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format? | |

| Overall Format/Content | YES | NO | NA | Comment |
|---|-------------------------------------|-------------------------------------|--------------------------|--|
| If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted). | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Index: Does the submission contain an accurate comprehensive index? | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain. | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA # | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| | | | | |
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| | | | | |
| | | | | |
| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | Shire has stated the following: It is hereby certified that the existing patents for which patent information |

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

| | | | | |
|---|-------------------------------------|--------------------------|-------------------------------------|---|
| | | | | has already been submitted to FDA claim the changed product that is the subject of this supplement. A complete list of the patent information can be located in NDA 21-977/S-022, Module 1.3.5.1. |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Debarment Certification | YES | NO | NA | Comment |
| Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

| | | | | |
|---|-------------------------------------|-------------------------------------|--------------------------|----------------|
| <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i> | | | | |
| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
| <p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| Pediatrics | YES | NO | NA | Comment |
| <u>PREA</u> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Does the application trigger PREA? | | | | |
| <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> | | | | |
| <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> | | | | |
| If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <i>If no, request in 74-day letter</i> | | | | |
| If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <i>If no, request in 74-day letter</i> | | | | |
| <u>BPCA</u> (NDAs/NDA efficacy supplements only): | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| Is this submission a complete response to a pediatric Written Request? | | | | |
| <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | | | | |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| <i>If yes, ensure that the application is also coded with the</i> | | | | |

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

| <i>supporting document category, "Proprietary Name/Request for Review."</i> | | | | |
|---|---|-------------------------------------|-------------------------------------|----------------|
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | | | | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <i>If no, request applicant to submit SPL before the filing date.</i> | | | | |
| Is the PI submitted in PLR format? ⁴ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | | | | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample | | | |

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

| | <input type="checkbox"/> Other (specify) | | | |
|--|--|-------------------------------------|--------------------------|---------|
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: OSI – Consult has not yet been sent Patient Labeling Team - 08/08/2014</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): 8/7/2012 <i>If yes, distribute minutes before filing meeting</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/4/2014 <i>If yes, distribute minutes before filing meeting</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 28, 2014

BLA/NDA/Supp #: NDA 21977/S-037

PROPRIETARY NAME: Vyvanse

ESTABLISHED/PROPER NAME: lisdexamfetamine dimesylate

DOSAGE FORM/STRENGTH: Capsules/20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

APPLICANT: Shire Development LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of Binge Eating Disorder

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|------------|---------------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Hiren Patel | Y |
| | CPMS/TL: | Paul David/Renmeet Grewal | |
| Cross-Discipline Team Leader (CDTL) | Jing Zhang | | |
| Clinical | Reviewer: | Gregory Dubitsky | Y |
| | TL: | Jing Zhang | Y |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |
| OTC Labeling Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | | |
| | TL: | | |

| | | | |
|---|-----------|-------------------|---|
| Clinical Pharmacology | Reviewer: | Andre Jackson | Y |
| | TL: | Hao Zhu | N |
| Biostatistics | Reviewer: | Thomas Birkner | Y |
| | TL: | Peiling Yang | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Ikram Elayan | Y |
| | TL: | Linda Fossom | Y |
| Statistics (carcinogenicity) | Reviewer: | | |
| | TL: | | |
| Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) | Reviewer: | | |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | None | |
| | TL: | David Claffey | Y |
| Quality Microbiology (<i>for sterile products</i>) | Reviewer: | | |
| | TL: | | |
| CMC Labeling Review | Reviewer: | | |
| | TL: | | |
| Facility Review/Inspection | Reviewer: | | |
| | TL: | | |
| OSE/DMEPA (proprietary name) | Reviewer: | | |
| | TL: | Irene Chan | N |
| OSE/DRISK (REMS) | Reviewer: | | |
| | TL: | Kimberly Lehrfeld | N |
| OC/OSI/DSC/PMSB (REMS) | Reviewer: | | |
| | TL: | | |

| | | | |
|----------------------------------|-----------|----------------|---|
| Bioresearch Monitoring (OSI) | Reviewer: | John Lee | N |
| | TL: | Janice Pohlman | N |
| Controlled Substance Staff (CSS) | Reviewer: | | |
| | TL: | | |
| Other reviewers | | | |
| Other attendees | | | |

FILING MEETING DISCUSSION:

| | |
|--|--|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: None</p> | <input type="checkbox"/> Not Applicable |
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
|--|--|
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <ul style="list-style-type: none"> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> |
| <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p>BIostatISTICS</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE |

| | |
|--|--|
| <p>Comments:</p> | <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
|--|--|
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>CMC Labeling Review</u></p> <p>Comments:</p> | <input type="checkbox"/> Review issues for 74-day letter |
| <p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? | <input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? | |
| <ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | <input type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
|---|---|
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| REGULATORY PROJECT MANAGEMENT | |
| <p>Signatory Authority: Mitchell Mathis, MD</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p> | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review |
| ACTIONS ITEMS | |
| <input checked="" type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |

| | |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier) |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input checked="" type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input type="checkbox"/> | Update the PDUFA V DARRTS page (for NME NDAs in the Program) |
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f] |
| <input type="checkbox"/> | Other |

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HIREN PATEL
09/05/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 4, 2014

TO: Hiren Patel, Regulatory Project Manager, Division of Psychiatry Products (DPP)

FROM: Louis Flowers, Safety Regulatory Project Manager, the Office of Surveillance and Epidemiology (OSE)

SUBJECT: Request for OSE Consultation

APPLICATION/DRUG: NDA 21977/S-037/Vyvanse

After the review of the submission for supplement S-037 for NDA 21977, Vyvanse, it was determined that a review was not required from OSE:

- This is an approved product without a REMS and the sponsor is not proposing additional risk mitigation beyond labeling (the MG is not new, just revised to match the PI). Therefore no action is required at this time, since the application did not reveal any new safety issues.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LOUIS R FLOWERS
09/04/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-977/S037

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21977

SUPPL # 037

HFD # 130

Trade Name Vyvanse

Generic Name lisdexamfetamine dimesylate

Applicant Name Shire Development LLC

Approval Date, If Known 1/30/2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21977

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SPD489-343 – “The SPD489-343, Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder

SPD489-344 - “The SPD489-344, Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study SPD489-343 and Study SPD489-344

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 110503 YES ! NO
! Explain:

Investigation #2 !
!

IND # 110503

YES

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

!

!

YES

! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Hiren Patel, PharmD
Title: Senior Regulatory Project Manager

Date: 1/22/2015

Name of Office/Division Director signing form: Mitchell Mathis, MD

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HIREN PATEL
01/30/2015

MITCHELL V Mathis
01/30/2015

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--|--|
| NDA # 21977 BLA # | NDA Supplement # 037 BLA Supplement # | If NDA, Efficacy Supplement Type: SE1 <i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: Vyvanse Established/Proper Name: lisdexamfetamine Dosage Form: Capsules | | Applicant: Shire Development LLC Agent for Applicant (if applicable): |
| RPM: Hiren Patel, PharmD | | Division: Division of Psychiatry Products |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) | | <p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>February 1, 2015</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) | | <input checked="" type="checkbox"/> None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | | <input type="checkbox"/> Received |
| ❖ Application Characteristics ³ | | |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Public communications (<i>approvals only</i>) | |
| • Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| • Indicate what types (if any) of information were issued | <input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | <input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| CONTENTS OF ACTION PACKAGE | |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |

| Action Letters | |
|--|---|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i> | Action(s) and date(s) 1/30/2015 |
| Labeling | |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i> | |
| <ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i> | <input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included |
| ❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i> | |
| <ul style="list-style-type: none"> Most-recent draft labeling | <input type="checkbox"/> Included |
| ❖ Proprietary Name | |
| <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> | |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i> | RPM: <input type="checkbox"/> None 1/30/2015 DMEPA: <input checked="" type="checkbox"/> None DMPP/PLT (DRISK): <input type="checkbox"/> None 1/15/2015 OPDP: <input type="checkbox"/> None 1/20/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None |
| Administrative / Regulatory Documents | |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i> | 9/5/2014 |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | <input checked="" type="checkbox"/> Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i> | <input checked="" type="checkbox"/> Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|--|---|
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>10/22/14</u> If PeRC review not necessary, explain: _____ | |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) | |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | |
| ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | <input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 3/4/2014 <input type="checkbox"/> No mtg 8/7/2012 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A |
| ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None 1/30/2015 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None 1/23/2015 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical | |
| ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review 1/11/2015 <input type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | Clinical Review 1/11/2015 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> N/A |

| | |
|---|---|
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input checked="" type="checkbox"/> None |
| ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) | <input type="checkbox"/> None requested 10/27/2014 |
| Clinical Microbiology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review 1/15/2015 |
| Statistical Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) | <input type="checkbox"/> None requested |
| Nonclinical <input checked="" type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | No separate review |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) | <input type="checkbox"/> None requested |

| Product Quality <input type="checkbox"/> None | |
|--|--|
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> | <input type="checkbox"/> No separate review 1/5/2015 |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> No separate review |
| • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> | <input type="checkbox"/> None |
| ❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | <input checked="" type="checkbox"/> Not needed |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> | <input checked="" type="checkbox"/> None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | 1/5/2015 |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> | |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> | |
| ❖ Facilities Review/Inspection | |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i> | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i> | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) |

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

| Day of Approval Activities | |
|--|--|
| <ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | <input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i> |
| <ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | <input checked="" type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | <input checked="" type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS | <input checked="" type="checkbox"/> Done |

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/s/

HIREN PATEL
02/03/2015

Patel, Hiren

From: Patel, Hiren
Sent: Tuesday, January 13, 2015 10:04 AM
To: McCormick, Kimberly (kmccormick@shire.com)
Subject: Study SPD489-344: AdHoc Outputs Including Subjects from site 015 and 079

Dear Kim,

In the SAP (Version 3.0 effective September 25, 2013, p. 22) for Study 344 you state “The FAS is defined as all randomized subjects who have taken at least 1 dose of investigational product and have 1 post-baseline primary efficacy assessment (number of binge days per week calculated for at least 1 week). All subjects from site 015 and 079 will be excluded from the FAS.”

The essence of the last statement in the definition of the FAS for Study 344 has been challenged by the FDA several times during the IND stage. See excerpts from numerous IND communications between FDA and Shire below.

The following statistical comment was conveyed to you on October 1, 2013 in response to SNs 85 and 88:

“Whether or not Dr. Horne’s site should be removed from the Safety Analysis Set and/or the Full Analysis Set will be a matter of review when the NDA comes in. In the NDA submission, please include detailed justification/documentation to support the removal of this site. You should also include the results with this site included.”

The following statistical comment was conveyed to you on November 19, 2013 in response to SN 93:

“For Study SPD489-343, whether or not Site 079 should be removed from the Safety Analysis Set and/or the Full Analysis Set will be a matter of review when the NDA comes in. In the NDA submission, please include detailed justification/documentation to support the removal of this site. You should also include the results with this site included.”

You responded on December 11, 2013 (SDN 107):

“Please note Site 079 participated in Study SPD489-344 and not SPD489-343. Shire will provide a detailed justification/documentation to support the removal of this site from the Full Analysis Set (FAS) in the sNDA submission. The data set(s) with Site 079 data will be included in the submission.”

The point made above was reiterated in the preliminary comments document (signed March 4, 2014) for the later canceled Pre-NDA meeting under question 1:

“However, please be sure to include data from all sites, including discontinued sites, with your NDA submission. We will want to review your safety and efficacy findings both with and without the discontinued sites.”

[1] Given your definition of the FAS (i.e., randomized, took at least one dose of study medication, and at least one post-baseline primary efficacy assessment) please justify in detail why you believe subjects from sites 15 and 79 should be excluded from this set.

[2] This reviewer was not able to locate any efficacy analysis datasets including subjects from sites 15 and 79 in your submission. Hence we can neither replicate the primary nor the key secondary results of the AdHoc output in section 14.3 of the 344 study report. It appears that only subjects from site 15 (10 subjects out of 11 randomized) are included in the AdHoc efficacy analyses. No subject out of 12 randomized at site 79 is included in the FAS for the AdHoc outputs (see p. 1275, 1276, and 1404 of the 344 study report). Please

provide the location of the complete efficacy analysis ready datasets including subjects from sites 15 and 79 in your submission. If not previously submitted please provide those datasets to us.

Regards,
Hiren

*Hiren D. Patel, Pharm.D., M.S., RAC
LCDR USPHS
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
01/13/2015

Patel, Hiren

From: Patel, Hiren
Sent: Thursday, January 08, 2015 3:13 PM
To: McCormick, Kimberly (kmccormick@shire.com)
Subject: NDA 21977/S-037
Attachments: NDA 21977 - draft-labeling-FDA Edits - 01082015_.docx

Kim,

Please find attached the Division's edits to your draft labeling for NDA 21977/S-037. Please use the last approved labeling as the base document when you respond. Also, clearly delineate all FDA edits and any changes you are proposing to the last approved labeling.

On a side note, you can include the changes that were proposed in pending CBE S-036. However, the changes from CBE S-036 should also be clearly identified.

Finally, we are discussing additional edits that will be provided at a later date.

Please respond by COB January 13th.

Regards,
Hiren

*Hiren D. Patel, Pharm.D., M.S., RAC
LCDR USPHS
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
01/08/2015

Patel, Hiren

From: Patel, Hiren
Sent: Friday, December 19, 2014 6:04 PM
To: McCormick, Kimberly (kmccormick@shire.com)
Subject: NDA 21977/S-037
Attachments: ADHD Efficacy Table_started_1212.docx

Kim,

We have the following information requests at this time:

[1] Label – ADHD efficacy table format update

We updated the ADHD efficacy table format (attached) in section 14 of the proposed label. Please fill in the missing information. If possible, please provide unadjusted CI's for consistency with the current practice across different drug labels. CI's after adjusting for multiple dose arms and key secondary endpoints may become unnecessarily complex for labeling description.

[2] Binge Eating Disorder

Please provide the complete SAS code for both sensitivity analyses under the MNAR assumption for the primary endpoint (Change in Binge Days) such that we can replicate your results. The currently available SAS programs (t_a-sens1.sas and t_a-sens2.sas) are of limited use to us, because they involve several macros and an input dataset which have not been submitted.

Also, please submit the following SAS programs (f_cdf-be.sas, f_cdf-wt.sas, f_cdf-ybocs.sas) used to create the cumulative distribution functions for Change in Binge Days, Percent Change in Body Weight and Change in Y-BOCS-BE, such that we can see the algorithm you employed to impute missing observations.

Regards,
Hiren

*Hiren D. Patel, Pharm.D., M.S., RAC
LCDR USPHS
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
12/19/2014

REQUEST FOR CONSULTATION

TO (Office/Division):
CDER-DCRPQT-RPM
Attention: Devi Kozeli, RAC

FROM (Name, Office/Division, and Phone Number of Requestor):
HFD-130/ Division of Psychiatry Products
Hiren D. Patel, PharmD

DATE
12/4/2014

IND NO.
(b) (4)

NDA NO.
21977/S-037

TYPE OF DOCUMENT
Efficacy Supplement

DATE OF DOCUMENT
8/1/2014

NAME OF DRUG
Vyvanse

PRIORITY CONSIDERATION
Yes

CLASSIFICATION OF DRUG
Treatment of Binge
Eating Disorder

DESIRED COMPLETION DATE
1/9/2015

NAME OF FIRM: (b) (4)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

This supplement is intended to support the approval of Vyvanse[®] (lisdexamfetamine or SPD489), a prodrug of dextroamphetamine, in the treatment of Binge Eating Disorder (BED) in adults. (This drug is currently marketed for the treatment of attention-deficit hyperactivity disorder in patients over age 6 years.) The BED clinical program is comprised of four studies: one Phase 2 dose-finding trial (208), two Phase 3 12-week placebo-controlled trials (343 and 344), and one Phase 3 12-month ongoing, open-label extension study (345). BED patients were mostly obese and female. In the Phase 3 placebo-controlled trials, increases in systolic and diastolic blood pressure (on average about 2-3 mmHg versus placebo) and heart rate (5.4 bpm on drug versus 1.8 bpm on placebo) were observed. These changes were not clearly dose-related but tended to persist over time (12 weeks). In these trials, Vyvanse[®] also produced significant weight reduction and decreased fasting triglyceride levels.

Dr. Unger, ODE I Director, has asked that DPP request consultation with DCaRP to address the following. 1) Evaluate the magnitude of cardiovascular risk of Vyvanse[®] in patients with BED in view of the above findings. These patients are generally obese (often morbidly obese) and will likely take Vyvanse[®], if approved for BED, for

several months to years. 2) Recommend any further pre-approval work-up or Postmarketing Requirements (PMRs) that should be requested to more fully characterize the risk/benefit ratio of Vyvanse[®] in this population from a cardiovascular standpoint. Thank you.

EDR Location: <\\CDSESUB1\evsprod\NDA021977\0131>

EDR Location: <\\CDSESUB1\evsprod\NDA021977\021977.enx>

Thank you,
Hiren

| | |
|--|--|
| SIGNATURE OF REQUESTOR | METHOD OF DELIVERY (Check all that apply) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |
| PRINTED NAME AND SIGNATURE OF RECEIVER | PRINTED NAME AND SIGNATURE OF DELIVERER |

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/s/

HIREN PATEL
12/04/2014

MITCHELL V Mathis
12/04/2014

**PeRC PREA Subcommittee Meeting Minutes
October 22, 2014**

PeRC Members Attending:

Wiley Chambers

George Greeley

Rosemary Addy (Did not review Zerbaxa and (b)(4))

Melissa Tassinari

Robert "Skip" Nelson

Tom Smith

Karen Davis-Bruno (Did not review Intuniv, Potiga, Cyramza and Vyvanse)

Kevin Krudys

Olivia Ziolkowski

Barbara Buch

Julia Pinto (Did not review Intuniv, Potiga, Cyramza and Vyvanse)

Dionna Green

Michelle Roth-Cline

Freda Cooner

Daiva Shetty

Diane Murphy

Intuniv (guanfacine) Assessment

- Proposed Indication: ADHD as monotherapy (ages 13-17 years)(efficacy in adolescents was not demonstrated in original NDA)
- This application is in response to PREA PMR #1538-2.
- The PDUFA goal date is November 19, 2014.
- The Division noted that the initial studies using 4 mg/day failed to show efficacy in heavier children. The dose was increased to 7mg/day and was shown to be efficacious for the treatment for ADHD.
- *PeRC Recommendations:*
 - The PeRC agreed with the assessment presented for patients ages 13-17 years
 - The PeRC recommended that the Division provide and update to section 8.4 of the label to show use in this population. DPMH will work with the Division to craft language for this section of the label.



Cyramza (ramicirumab) Full Waiver

- Proposed Indication: Non-small cell lung cancer (NSCLC)
- This application triggered PREA as a new: indication and dosing regimen.
- The PDUFA goal date is December 26, 2014
- *ThePeRC Recommendations:*
 - The PeRC agreed with the Division to grant a full waiver for this product because the disease/condition does not exist in children.

Vyvanse (lisdexamfetamine) Full Waiver

- Proposed Indication: Binge Eating Disorder (BED)
- This application triggered PREA as a new indication.

- The PDUFA goal date is February 1, 2015
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impractical because there are too few patients with this disease/condition.

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/s/

GEORGE E GREELEY
11/05/2014



NDA 21977/S-037

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Shire Development LLC
Attention: Kimberly McCormick, PharmD
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. McCormick:

Please refer to your Supplemental New Drug Application (sNDA) dated August 1, 2014, received August 1, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vyvanse (lisdexamfetamine dimesylate) 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg capsules.

We also refer to your amendments dated August 18, 2014, September 4, 2014, and September 9, 2014.

This supplemental application proposes to add Binge Eating Disorder as an indication.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is February 1, 2015.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 8, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Hiren Patel, PharmD, Senior Regulatory Project Manager, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
09/11/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: September 8, 2014

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D.,M.P.H., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D. Team Leader, GCPAB
CDER OSI PM Track
John Lee, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Gregory Dubitsky, M.D./Clinical Reviewer/Division of Psychiatry Products
Jing Zhang, M.D./Clinical Team Leader/Division of Psychiatry Products
Mitchell Mathis, M.D./Division Director/Division of Psychiatry Products

From: Hiren Patel, PharmD/Regulatory Project Manager/Division of Psychiatry Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21977/S-037
IND#: 110503

Applicant: Shire Development LLC

Applicant contact information:
Kimberly McCormick, PharmD
Director, Global Regulatory Affairs
484-595-8829
kmccormick@shire.com

Drug Proprietary Name: Vyvanse

Generic Drug Name: lisdexamfetamine dimesylate

NME or Original BLA (Yes/No/Not Applicable*): No
Application Submission Date: August 1, 2014

OSI/DGCPC Consult
version: 09/12/2013

Review Priority (Standard or Priority or Not Applicable*): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): Treatment of Binge Eating Disorder

PDUFA: February 1, 2015

Action Goal Date: January 30, 2015

Inspection Summary Goal Date: October 31, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication/Primary endpoint and other endpoints for verification |
|---|-------------|--------------------|--|
| Site #83 Alexander Horwitz Oregon Center for Clinical Investigations 702 Church Street NE Salem, OR 97301 USA Phone 503-540-0100 Email Salem@occi.org Fax 503-540-0030 | SPD489-343 | N=24 | Binge Eating Disorder Change from baseline to Weeks 11/12 in the number of binge eating days/week |
| Site #32 H. Mikel Thomas Clinical Trials Technology 8340 Mission Road Suite 205 Prairie Village, KS 66206 USA Phone 913-381-7180 Alternate 913-314-1606 Email mthomas@cttresearch.com Fax 913-381-7964 | SPD489-344 | N=25 | Binge Eating Disorder Change from baseline to Weeks 11/12 in the number of binge eating days/week |

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects (both sites)
- High treatment responders (specify): (for site 83, E=-46.75 per John Lee)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles. (site 32 was closed by the sponsor for unknown reason - please determine reason for closure)
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact *Name of Hiren Patel* at 301-796-2087.

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/s/

HIREN PATEL
09/08/2014

MITCHELL V Mathis
09/09/2014

REQUEST FOR CONSULTATION

TO (Office/Division): ODE II/Division of Metabolism and Endocrinology Products

FROM (Name, Office/Division, and Phone Number of Requestor):
Hiren Patel, PharmD
ODE 1/Division of Psychiatry Products
301-796-2087

DATE
9/8/2014

IND NO.

NDA NO.
21977/S-037

TYPE OF DOCUMENT
Supplemental New Drug Application (Efficacy Supplement)

DATE OF DOCUMENT
August 1, 2014

NAME OF DRUG
Vyvanse

PRIORITY CONSIDERATION
Yes

CLASSIFICATION OF DRUG
CNS Stimulant --
Treatment of Binge Eating Disorder

DESIRED COMPLETION DATE
November 9, 2014

NAME OF FIRM: Shire Development LLC

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

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|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS:

This efficacy supplement is intended to support the approval of SPD489 (lisdexamfetamine), a prodrug of dextroamphetamine, in the treatment of Binge Eating Disorder (BED) in adults. (This drug is currently marketed as Vyvanse® for the treatment of attention-deficit hyperactivity disorder.) The BED clinical program is comprised of four studies: one Phase 2 dose-finding trial (208), two Phase 3 12-week placebo-controlled trials (343 and 344), and one Phase 3 12-month open-label extension study (345). BED subjects were mostly obese and female. In Phase 2/3 placebo-controlled trials (11-12 weeks in duration), there was one report of cholecystitis and another of cholelithiasis on drug (N=569) and none on placebo (N=435). In the 12-month study, there were 4 reports of cholecystitis and one of cholelithiasis, all on drug (N=599). Most of these cases were classified as serious. In short-term trials, SPD489 caused appreciable weight loss and reduced fasting triglyceride and total cholesterol levels. In view of these reports,

the possibility that drug-related cholecystitis may have a delayed time to symptom onset, the BED sample studied, and the propensity of SPD489 to decrease weight, triglycerides, and total cholesterol, please provide your opinion as to whether SPD489 may be causally related to the cases of cholecystitis and cholelithiasis. If a causal link is plausible, please suggest language for labeling this risk. Thank you.

EDR Location: [\\CDSESUB1\evsprod\NDA021977\0131](#)

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| SIGNATURE OF REQUESTOR | METHOD OF DELIVERY (Check all that apply) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |
| PRINTED NAME AND SIGNATURE OF RECEIVER | PRINTED NAME AND SIGNATURE OF DELIVERER |

06/18/2013

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/s/

HIREN PATEL
09/08/2014

MITCHELL V Mathis
09/09/2014

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Mail: OSE/DRISK | | FROM: Hiren Patel, Regulatory Project Manager Division of Psychiatry Products 301-796-2087 | | |
| DATE 8/7/2014 | IND NO. | NDA NO.: 21977/S-037 | TYPE OF DOCUMENT Medication Guide | DATE OF DOCUMENT August 1, 2014 |
| NAME OF DRUG Vyvanse | PRIORITY CONSIDERATION Yes | CLASSIFICATION OF DRUG CNS Stimulant | DESIRED COMPLETION DATE January 21, 2015 | |
| NAME OF FIRM: Shire Development LLC | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | <input type="checkbox"/> PRECLINICAL | | |
| COMMENTS/SPECIAL INSTRUCTIONS: Shire has submitted a sNDA with two identically designed pivotal studies to support the approval of Vyvanse for the treatment of Binge Eating Disorder in adults 18-55 years of age. The efficacy supplement includes a revised Medication Guide. Sharepoint Link: Vyvanse BED Documents EDR Location: \\CDSESUB1\evsprod\NDA021977\0131 EDR Location: \\CDSESUB1\evsprod\NDA021977\021977.enx | | | | |

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| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

06/18/2013

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/s/

HIREN PATEL
08/08/2014

MITCHELL V Mathis
08/08/2014

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR PATIENT LABELING REVIEW CONSULTATION | |
| TO: CDER-DMPP-PatientLabelingTeam | | FROM: (Name/Title, Office/Division/Phone number of requestor) Hiren Patel, Regulatory Project Manager Division of Psychiatry Products 301-796-2087 | |
| REQUEST DATE: 8/7/2014 | NDA NO.: 21977/S-037 | TYPE OF DOCUMENTS: Medication Guide | |
| NAME OF DRUG: Vyvanse | PRIORITY CONSIDERATION: Yes | CLASSIFICATION OF DRUG: CNS Stimulant | DESIRED COMPLETION DATE Substantially complete labeling will be provided at a later date. |
| SPONSOR: Shire Development LLC | | PDUFA Date: February 1, 2015 Action Goal Date: January 30, 2015 | |
| TYPE OF LABEL TO REVIEW | | | |
| TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU) | | TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION | |
| REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION | | | |
| EDR link to submission: \\CDSESUB1\evsprod\NDA021977\021977.enx | | | |
| Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format. | | | |
| COMMENTS/SPECIAL INSTRUCTIONS: Filing/Planning Meeting: August 28, 2014 Mid-Cycle Meeting: October 29, 2014 Labeling Meetings: November 6, 2014; November 18, 2014; December 4, 2014; December 16, 2014; January 6, 2015; January 20, 2015; January 26, 2015 Wrap-Up Meeting: January 14, 2015 | | | |
| SIGNATURE OF REQUESTER | | | |
| SIGNATURE OF RECEIVER | | METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS | |

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/s/

HIREN PATEL
08/08/2014

MITCHELL V Mathis
08/08/2014

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

| | |
|-----------------------------|---|
| TO: CDER-OPDP-RPM | FROM: (Name/Title, Office/Division/Phone number of requestor) Hiren Patel, Regulatory Project Manager Division of Psychiatry Products 301-796-2087 |
|-----------------------------|---|

| | | | |
|--------------------------|---------|-------------------------|---|
| REQUEST DATE 8/7/2014 | IND NO. | NDA NO.: 21977/S-037 | TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) |
|--------------------------|---------|-------------------------|---|

| | | | |
|-------------------------|-------------------------------|---|---|
| NAME OF DRUG Vyvanse | PRIORITY CONSIDERATION Yes | CLASSIFICATION OF DRUG CNS Stimulant | DESIRED COMPLETION DATE January 21, 2015 |
|-------------------------|-------------------------------|---|---|

| | |
|--|--|
| NAME OF FIRM: Shire Development LLC | PDUFA Date: February 1, 2015 Action Goal Date: January 30, 2015 |
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TYPE OF LABEL TO REVIEW

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| TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU) | TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION | REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS |
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EDR link to submission: <\\CDSESUB1\evsprod\NDA021977\021977.enx>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: August 28, 2014

Mid-Cycle Meeting: October 29, 2014

Labeling Meetings: November 6, 2014; November 18, 2014; December 4, 2014; December 16, 2014; January 6, 2015; January 20, 2015; January 26, 2015

Wrap-Up Meeting: January 14, 2015

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| SIGNATURE OF RECEIVER | METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND |

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/s/

HIREN PATEL
08/08/2014

MITCHELL V Mathis
08/08/2014



NDA 21977/S-037

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Shire Development LLC
Attention: Kimberly McCormick, Pharm D
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Kimberly:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21977
SUPPLEMENT NUMBER: 037
PRODUCT NAME: Vyvanse (lisdexamfetamine dimesylate) 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg capsules
DATE OF SUBMISSION: AUGUST 1, 2014
DATE OF RECEIPT: AUGUST 1, 2014

This supplemental application provides clinical data for Binge Eating Disorder.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 30, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, contact me at hiren.patel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Hiren D. Patel, Pharm.D., M.S., RAC
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HIREN PATEL
08/07/2014



IND 110503

MEETING PRELIMINARY COMMENTS

Shire

Attention: Kimberly McCormick, PharmD
Associate Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vyvanse® (lisdexamfetamine dimesylate or SPD489) Capsules for the treatment of Binge Eating Disorder (BED).

We also refer to your correspondence, dated and received January 8, 2014, requesting a meeting to discuss the results from the recently completed 2 Phase 3 clinical trials (SPD489-343 and SPD489-344) and to discuss the proposed clinical data package that will support registration for the use of Vyvanse (SPD489) for the treatment of BED.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Tuesday, March 6, 2014, from 11-12pm EST at the White Oak Campus (10903 New Hampshire Ave., Bldg 22, Rm 1415 Silver Spring, 20993-0002) between Shire and Division of Psychiatry Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (email me at Juliette.Toure@fda.hhs.gov). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, email me to discuss the possibility of including these items for discussion at the meeting.

IND 110503 – Vyvanse (lisdexamfetamine)
Shire
Type B, Face to face, Pre-NDA Meeting

Participants:

FDA

| | |
|---------------------------|--|
| Mitchell Mathis, M.D. | Director (Acting), Division of Psychiatry Products |
| Silvana Borges, M.D. | Clinical Team Leader (Acting) |
| Tiffany Farchione, M.D. | Clinical Reviewer |
| David Claffey, Ph.D. | Chemistry Review Team Leader |
| Lyudmila Soldatova, Ph.D. | Chemistry Reviewer |
| Linda Fossom, Ph.D. | Pharmacology/Toxicology Supervisor |
| Arippa Ravindran, Ph.D. | Pharmacology/Toxicology Reviewer |
| Peiling Yang, Ph.D. | Statistics Team Leader |
| Jinglin Zhong, Ph.D. | Statistics Reviewer |
| Valerie Gooding | Regulatory Information Specialist, OBI ESUB Team |
| Lisa Lin | Project Manager, OBI eData Team |
| Juliette Touré, Pharm.D. | Senior Regulatory Project Manager |

Background:

The Sponsor is evaluating SPD489 (lisdexamfetamine) for the treatment of Binge Eating Disorder (BED) under IND 110,503. SPD489 is a prodrug of d-amphetamine, and is currently marketed under the trade name Vyvanse (NDA 21-977) for the treatment of attention deficit hyperactivity disorder (ADHD). Shire also has development programs for lisdexamfetamine under:



Binge Eating Disorder (BED) is a common eating disorder, and is associated with psychopathology, obesity, reduced quality of life, and disability. The recently published Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-V) now includes BED as a formal diagnosis.

The sponsor has completed SPD489-343 and SPD-344, two identically-designed short-term studies intended to evaluate the efficacy of SPD489 compared to placebo in adults with moderate to severe BED as measured by the number of binge days per week. A longer-term, open-label study (SPD489-345) is ongoing. Along with data from the Phase 2 study SPD489-208, the data from these studies will form the basis of a New Drug Application (NDA) with the treatment of binge eating disorder as the proposed indication.

A proposed pediatric study plan (PSP) was submitted October 16, 2013. At that time, the sponsor noted an intent to request a full waiver for pediatric studies under the Pediatric Research Equity

Act (PREA) when the NDA is submitted. On December 12, 2013, FDA responded with the following comments:

1. We have completed our review of the initial Pediatric Study Plan. We acknowledge that you do not intend to conduct studies in pediatric subjects and will submit a request for waiver from all requirements from PREA in a marketing application for Vyvanse® (lisdexamfetamine dimesylate or SPD489) Capsules.
2. When submitting the NDA, Section 8.4 Pediatric Use should clearly state that Vyvanse for the treatment of Binge Eating Disorder has not been studied in children.
3. Please submit a letter within 90 days of receipt of this communication, stating your agreement or disagreement with our understanding of the initial Pediatric Study Plan.

On July 1, 2013, the sponsor notified FDA that Site 015 was being closed. This was followed by an amended statistical analysis plan (SAP) on August 20, 2013, stating an intent to exclude data from Site 015 from the Safety Analysis Set (SAS) and Full Analysis Set (FAS). Although no reason was given for this closure, further communication with the sponsor revealed that the [REDACTED] (b) (7)(A). On September 19, 2013, the sponsor notified FDA of an additional site closure; Site 079 was closed due to inadequate medical oversight, incomplete source documentation, improper entry of study data on behalf of study subjects and failure to follow the study protocol resulting in GCP noncompliance impacting the primary endpoint of the study. Most recently, on February 14, 2014, the sponsor notified FDA that Site 032 was being closed due to concerns regarding signs of investigational drug tampering in [REDACTED] (b) (4) [REDACTED] (b) (4). These closures primarily affect studies SPD249-344 and SPD249-345; however, Site 032 also participated in SPD489-208.

Shire requested a Pre-NDA meeting to discuss the results from the recently completed 2 Phase 3 clinical trials (SPD489-343 and SPD489-344) and to discuss the proposed clinical data package that will support registration for the use of Vyvanse (SPD489) for the treatment of BED. Shire is planning to submit the sNDA in the July/August 2014 timeframe.

Questions:

Clinical Questions

Question 1. Shire believes that the data from the recently completed clinical trials (SPD489-343 and SPD489-344), in addition to the data from the Phase 2 study (SPD489-208) and the interim data from the long-term open-label safety study (SPD489-345) provides an adequate basis for the filing and review of the sNDA to support the approval of SPD489 in the proposed indication as a treatment for binge eating disorder. Does the Agency agree?

Preliminary Comments: Based on this meeting's background information package, it appears you are on track to meet the patient exposure you previously projected during the End of Phase 2 meeting on July 30, 2012. You state that you intend to submit 6-month safety data for 400 subjects and 12-month safety data for 70 subjects with your initial submission, and 6-month safety data for 430 subjects and 12-month safety data for 250 subjects at the time of your 120-Day Safety Update.

It appears that these data will form an adequate basis for filing and review. However, please be sure to include data from all sites, including discontinued sites, with your NDA submission. We will want to review your safety and efficacy findings both with and without the discontinued sites.

Discussion at Meeting:

Question 2. [REDACTED] (b) (4)

Preliminary Comments: [REDACTED] (b) (4)

Discussion at Meeting:

Question 3. Does the Agency agree with the plans for the Safety Update?

Preliminary Comments: *In the meeting package, you estimate the number of patients for whom you will have 6- and 12-month safety data at 120 days. Please provide the number of patients you project to have at 90 days. Our decision will be based on that data.*

Addendum to Preliminary Comments: *In an email dated March 3, 2014, the Agency noted that you included this information in the briefing package, i.e., that you project to have 6-month data on 430 subjects at either 90 or 120 days. You also project to have 12-month data on 250 subjects at 120 days and 190 subjects at 90 days. On face, your plan to submit a safety update at 90 days appears acceptable.*

Discussion at Meeting:

Question 4. Based on the high unmet medical need and lack of available pharmacological treatments for BED, Shire intends to request priority designation for the sNDA at the time of submission. Does the Agency agree with this proposal?

Preliminary Comments: *A decision regarding priority review designations will be made at the time of your sNDA submission. FDA determines whether an application qualifies for priority review for every application, not just when requested by the applicant. However, you may expressly request priority review as described in Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics. If a priority review designation is granted, you will be notified 60 days after your submission.*

Discussion at Meeting:

Statistical Questions

Question 5. Shire plans to combine data from Studies SPD489-343 and SPD489-344 to provide more precise estimation of treatment effects for the ISE. The Statistical Analysis Plan for the ISE, which includes a table of contents for the ISE, has been included in the briefing package for the meeting. Does the Agency agree with the analysis plans for the ISE?

Preliminary Comments: *As the ISE serves for exploratory purposes, we have no objection to your plans.*

Discussion at Meeting:

Question 6. Shire plans to integrate data from Studies SPD489-208, SPD489-343, SPD489-344, and SPD489-345. The full Statistical Analysis Plan for the ISS which includes a table of contents for the ISS have been included in the briefing package for the meeting. Does the Agency agree with the analysis plans for the ISS?

Preliminary Comments: *On face, we have no objection to your plan.*

Discussion at Meeting:

General Questions

eCTD Table of Contents

Question 7. Shire plans to submit the sNDA in eCTD format according to Shire's eCTD Table of Contents. A copy of the proposed eCTD Table of Contents (Appendix 5) has been included in the briefing package. Does the Agency agree that the eCTD Table of Contents is acceptable?

Preliminary Comments: *From a technical standpoint (not content related), the proposed eCTD TOC for the planned sNDA is acceptable. However, please see additional comments below.*

- *Providing a Reviewer's Guide with a high level overview of what is provided in modules 1 through 5 with hyperlinks can be helpful to reviewers. The Reviewer's Guide is usually provided as a separate document in the cover letter section, under section m1.2, with a clear and descriptive leaf title.*
- *1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of each correspondence, table of contents and hyperlinks.*
- *For archival purposes, you should also submit a pdf file of any labeling document submitted in word. Also, when you submit word documents, make sure the leaf*

title includes "word", so reviewers could quickly identify the word version of the document.

- *The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.*
- *Case report forms need to be referenced under the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to *The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008)*
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>*

Discussion at Meeting:

Datasets and SAS Programs

Question 8. Shire plans to submit the 4 studies (SPD489-208, SPD489-343, SPD489-344, and SPD489-345) datasets in CDISC SDTM (IG V3.1.2 or later) and ADaM IG (V1.0 or later) format (including ADSL) with associated metadata including the DEFINE.xml. As such, we do not intend to submit patient profiles for these studies. The SAS programs for the phase 3 studies deriving the ADaM datasets based on SDTM data will be included in the sNDA. Additionally, the programs for the primary efficacy (including the permutation test program) and key secondary efficacy analysis will be included in the sNDA. The analysis programs will include the statistical models with the necessary data manipulation steps using the ADaM datasets as source. The data from Study SPD489-208 which was previously submitted on 14 Nov 2012 (Serial No. 0045) will be resubmitted and included in the complete submission package.

Does the Agency agree with the plans for the datasets, SAS programs and the documentation to be included in the sNDA?

Preliminary Comments: *If your previous study data were not collected in SDTM format, you will need to submit the raw data and the programs that convert raw variables to the variables in the SDTM format.*

In addition to the SAS code used to generate the derived variables, please also provide the detailed algorithm to facilitate the derivation.

Please include a list of correspondence history pertaining to this program (including the submission serial numbers and dates of the protocols/SAPs), as well as meetings with FDA.

Discussion at Meeting:

Question 9. Shire intends to submit the summary-level clinical site data for 4 studies (SPD489-208, SPD489-343, SPD489-344, and SPD489-345). Summary level datasets and DEFINE.pdf will be provided by each study in the format described in the draft guidance “Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER’s Inspection Planning” dated December 2012.

Does the Agency agree with the plans for the submission of the summary level clinical site data in the sNDA?

Preliminary Comments: *On face, we have no objections to your plans.*

Discussion at Meeting:

Advisory Committee Meeting Question

Question 10. Does the Agency intend to include an Advisory Committee Meeting during the review of the sNDA?

Preliminary Comments: *It is possible that an Advisory Committee Meeting will be included during the review of this sNDA.*

Discussion at Meeting:

Regulatory Questions

Question 11. As per the FDA’s Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, Shire intends to split the ISE and ISS across Module 2 and Module 5, with the narrative portion located in Section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in Section 5.3.5.3. A clear explanation of where the parts are located will be placed both in Module 2 (Section 2.7.3 or 2.7.4) and in Module 5 (Section 5.3.5.3).

Does the Agency agree?

Preliminary Comments: *On face, your proposal appears acceptable.*

Discussion at Meeting:

Question 12. The Initial Pediatric Study Plan (iPSP) was submitted to the FDA on 16 Oct 2013 (Serial No. 0097). Shire requested a full waiver for the pediatric population (0-17 years of age). On 12 Dec 2013, Shire received a letter from the FDA indicating that they have received and completed their review of our iPSP and acknowledged Shire’s intent to submit a request for a waiver from all requirements from PREA in the upcoming sNDA for Vyvanse in the treatment of BED. As requested, Shire sent a letter acknowledging the FDA’s letter and agreeing with the

FDA's assessment on 16 Dec 2013. On 17 Jan 2014, Shire received a letter from the FDA which indicated that they have completed their review of the iPSP and have agreed with our request for a full pediatric waiver. They had no further comments and no additional review was required. The agreed upon pediatric plan will be reflected in Module 1 of the sNDA.

Preliminary Comments: *We concur with your plan to include the agreed upon iPSP with your sNDA submission.*

Discussion at Meeting:

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--|---|---|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| 1. | | | | |
| 2. | | | | |

You should provide to the Regulatory Project Manager a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, email me at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Touré, PharmD, RAC
 CDR, United States Public Health Service
 Senior Regulatory Project Manager
 Division of Psychiatry Products
 Office of Drug Evaluation 1
 Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIETTE T TOURE
03/04/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110503

MEETING MINUTES

Shire
Attention: Tracey M. Henderson
Associate Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Ms. Henderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vyvanse® (lisdexamfetamine dimesylate or SPD489) 20mg, 30mg, 40mg, 50mg, 60mg, 70mg Capsules.

We also refer to the meeting between representatives of your firm and the FDA on July 30, 2012. The purpose of the meeting was to discuss the results of Study SPD489-208 and the Sponsor's Phase 3 clinical development program intended to support use of SPD489 for the treatment of patients with BED.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, email Juliette Touré, PharmD, Senior Regulatory Project Manager at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Agency of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: July 30, 2012, 1pm EST
Meeting Location: 10903 New Hampshire Ave
White Oak Campus, Bldg. 22, Rm 4249
Silver Spring, MD 20993-0002

Application Number: IND 110503
Product Name: Vyvanse® (lisdexamfetamine dimesylate or SPD489)
Indication: Binge Eating Disorder
Sponsor/Applicant Name: Shire

Meeting Chair: Thomas P. Laughren, MD, Director, Agency of Psychiatry Products (DPP)
Meeting Recorder: Juliette Touré, PharmD, SRPM, DPP

FDA ATTENDEES

| | |
|--------------------------|---|
| Thomas Laughren, M.D. | Agency Director, DPP |
| Mitchell Mathis, M.D. | Deputy Agency Director |
| Tiffany Farchione, M.D. | Clinical Reviewer |
| Chhagan Tele, Ph.D. | Chemistry Review Team Leader |
| Linda Fossom, Ph.D. | Pharmacology/Toxicology Supervisor |
| Arippa Ravindran, Ph.D. | Pharmacology/Toxicology Reviewer |
| Hao Zhu, Ph.D. | Clinical Pharmacology Team Leader |
| Andre Jackson, Ph.D. | Clinical Pharmacology Reviewer |
| Mike Pacanowski, Ph.D. | Genomics Group Team Leader, OCP |
| Jeffery Kraft, Ph.D. | Reviewer, Genomics Group, OCP |
| Sue-Jane Wang, Ph.D. | Associate Director for Pharmacogenomics and Adaptive Design, Biostatistics Lead for the CDER Biomarker Qualification Program, Office of Biostatistics |
| Peiling Yang, Ph.D. | Statistics Team Leader |
| Jinglin Zhong, Ph.D. | Statistics Reviewer |
| Renmeet Grewal, Pharm.D. | Senior Regulatory Project Manager, RPM Team Leader |
| Juliette Touré, Pharm.D. | Senior Regulatory Project Manager |

SPONSOR ATTENDEES

| | |
|---------------------------|--|
| Maria Gasior, M.D., Ph.D. | Senior Director, Clinical Medicine |
| Tim Whitaker, M.D. | Vice President, Clinical Medicine |
| (b) (4) | (b) (4) |
| Martin Armstrong, Ph.D. | Associate Director, Translational Medicine |

| | |
|-------------------------------------|---|
| M. Celeste Ferreira-Cornwell, Ph.D. | Director, Global Clinical Programs |
| Colleen Anderson | Director, Global Clinical Programs |
| Michael L Nessly, M.S. | Group Leader, Biostatistics |
| Joseph Gao, Ph.D. | Director, Biostatistics |
| Camilla Simpson, M.Sc. | Vice President, Global Regulatory Affairs |
| Jennifer Pavillard | Director, Global Regulatory Affairs |
| Tracey Henderson, M.S., M.B.A. | Associate Director, Global Regulatory Affairs |
| Kim McCormick, Pharm.D. | Director, Global Regulatory Affairs |
| Amir Shojaei, Pharm.D., Ph.D. | Product Strategy Lead |

1.0 BACKGROUND

The Sponsor is evaluating SPD489 (lisdexamfetamine) for the treatment of Binge Eating Disorder (BED) under IND 110,503. SPD489 is a prodrug of d-amphetamine, and is currently marketed under the trade name Vyvanse (NDA 21-977) for the treatment of attention deficit hyperactivity disorder (ADHD). Shire also has the development programs for lisdexamfetamine under:

[REDACTED] (b) (4)

Binge Eating Disorder (BED) is a common eating disorder, and is associated with psychopathology, obesity, reduced quality of life, and disability. In the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV), BED is classified as an Eating Disorder Not Otherwise Specified (NOS), with research criteria listed in the appendix. BED has been proposed for inclusion as a formal diagnosis in the forthcoming DSM-V.

In describing the rationale for studying SPD489 in BED, the Sponsor notes evidence suggesting possible shared pathology, potentially mediated through dopamine (DA) and norepinephrine (NE) neurotransmission and the brain's reward circuitry. [REDACTED] (b) (4)

[REDACTED]

The Sponsor completed SPD489-208, and submitted the study report to the IND on June 21, 2012. A total of 266 subjects were included in their analysis set. Subjects were randomized to receive placebo (N=65), or one of three doses of the investigational drug (30mg, N=68; 50mg, N=67; 70mg, N=66). Across groups, baseline binge days per week were similar (~4.5 mean binge days per week). The Sponsor presented change from baseline data as log-transformed binge days per week (primary endpoint) and non-transformed binge days per week (proposed primary endpoint for Phase 3 trials). The Sponsor reports that the mean change from baseline in binge days per week showed a statistically significant reduction of 0.76 for 50mg and 0.89 for 70mg of SPD489 versus placebo, respectively. See Table 1 below derived from Sponsor's

submission. In the study report synopsis, the Sponsor states, “Key opinion leaders have confirmed that these results translate into a clinically meaningful benefit to subjects which is seen at a mean reduction of ≥ 0.5 binge days per week.” No references were cited to support this statement in the synopsis. The study report body also states that these are clinically meaningful differences, but does not cite references or provide statistical support for this statement.

| Table 1: Means and Mean Change from Baseline by Treatment Group | | | | | | | | |
|---|-------------------|----------------------|-----------------------|----------------------|-----------------------|----------------------|-----------------------|----------------------|
| | Placebo (N=65) | | SPD489 30mg (N=68) | | SPD489 50mg (N=67) | | SPD489 70mg (N=66) | |
| Visit | Actual Value | Change from Baseline | Actual Value | Change from Baseline | Actual Value | Change from Baseline | Actual Value | Change from Baseline |
| Log Transformed Number of Binge Days Per Week | | | | | | | | |
| Baseline (Day 0) | | | | | | | | |
| n | 65 | NA | 68 | NA | 67 | NA | 66 | NA |
| Mean (SD) | 1.64 (0.255) | | 1.68 (0.260) | | 1.69 (0.224) | | 1.68 (0.223) | |
| Visit 8 (Week 11) | | | | | | | | |
| n | 50 | 50 | 53 | 53 | 55 | 55 | 55 | 55 |
| Mean (SD) | 0.54 (0.634) | -1.10 (0.727) | 0.42 (0.617) | -1.25 (0.623) | 0.18 (0.380) | -1.51 (0.426) | 0.07 (0.236) | -1.61 (0.293) |
| Nontransformed Number of Binge Days Per Week | | | | | | | | |
| Baseline (Day 0) | | | | | | | | |
| n | 65 | NA | 68 | NA | 67 | NA | 66 | NA |
| Mean (SD) | 4.33 (1.354) | | 4.57 (1.449) | | 4.58 (1.266) | | 4.50 (1.256) | |
| Visit 8 (Week 11) | | | | | | | | |
| n | 50 | 50 | 53 | 53 | 55 | 55 | 55 | 55 |
| Mean (SD) | 1.13 (1.557) | -3.17 (2.153) | 0.89 (1.489) | -3.60 (1.860) | 0.31 (0.695) | -4.23 (1.437) | 0.11 (0.397) | -4.36 (1.192) |

With regard to select additional analyses, the mean decreases in binge episodes were numerically greater across all treatment groups (from 5.80 to 1.17 for 30 mg, 5.58 to 0.44 for 50 mg and 5.50 to 0.46 for 70 mg) than in the placebo group (from 5.22 to 1.34), with statistically significant differences compared to placebo in the 50mg and 70mg treatment groups. The Sponsor also reports that subjects in the treatment groups lost weight compared to those receiving placebo. Mean change in weight from baseline to Visit 8 (Week 11) was -0.01lbs in the placebo group, compared to -7.26lbs in the 30mg group, -10.87lbs in the 50mg group, and -11.03lbs in the 70mg group.

Proposed Short Term Studies (SPD489-343 and SPD489-344)

Based on the results of SPD489-208, the Sponsor is proposing two identical Phase 3 placebo-controlled efficacy and safety studies (SPD489-343 and SPD489-344). According to the protocol synopsis provided in the briefing package, the Sponsor intends to randomize 356 subjects (ages 18-55 yrs) in each trial, and estimates approximately 267 subjects will complete each trial. Each study will be 12-weeks in duration and enroll adults aged 18-55 diagnosed with BED. Subjects will be randomized in a 1:1 ratio to receive either an optimized dose of SPD489 (50mg or 70mg) or placebo. The proposed studies include a 4-week dose optimization period and an 8-week dose-maintenance period.

During the dose optimization phase, the starting titration dose for all subjects assigned to SPD489 will be 30mg/day and those 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 assigned to SPD489 treatment 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 once from 70mg to 50mg during the dose optimization period in the event the 70mg dose is not tolerated, with 50mg being the lowest possible dose. Once a dose reduction has occurred, the subject is not permitted to have their dose changed for the duration of the study. Visit 3 (Week 3) will be the last visit when dose changes are permitted. Subjects who are unable to tolerate investigational product will be discontinued from the study.

Study Objectives

Primary:

To demonstrate the efficacy of SPD489 compared with placebo in adults (18-55 years of age inclusive) with BED at Visit 8 (Weeks 11 & 12) 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.

Key Secondary:

1. To demonstrate the efficacy of SPD489 compared with placebo on the global impressions of BED improvement as measured by the Clinical Global Impression of Improvement (CGI-I) scale at the end of study.
2. To demonstrate the efficacy of SPD489 compared with placebo on 4-week cessation from binge eating behavior (free from binge episodes in the respective period) at the end of study.
3. To demonstrate the efficacy of SPD489 compared with placebo on the change from Baseline (Visit 0) in body weight at Visit 8 (Week 12).
4. To demonstrate the efficacy of SPD489 compared with placebo on the change from Screening (Visit -1) in triglycerides (TG) from fasted samples at Visit 9 (Week 13).

The Sponsor describes plans to incorporate additional pre-specified analyses in the 2 proposed Phase 3 studies to evaluate the effects of SPD489 on weight as well as fasting metabolic parameters such as triglycerides (TG), total cholesterol (TC), hemoglobin A1c (HbA1c). Weight and TG will be included as key secondary endpoints. TC and HbA1c will be secondary endpoints to be added in a testing sequence for control of type I error, and LDL, HDL will be exploratory endpoints. The Sponsor plans to evaluate the relationship between the reduction in binge eating days and changes in medical parameters, and the changes in weight related to changes in medical parameters as exploratory analyses. (b) (4)

Proposed Open-Label Extension (SPD489-345)

Subjects who complete 1 of the antecedent studies (SPD489-208, SPD489-343, or SPD489-344) will be assessed for eligibility to enter Study SPD489-345, a 12-month, long-term, open-label, extension study. The Sponsor anticipates that approximately 530 subjects will enter the long-term extension study, with approximately 212 subjects completing. Based on current proposed timelines, the Sponsor anticipates up to 530 subjects from the Phase 2 and 3 trials for BED will enter the long-term safety study. At the time of the NDA, the Sponsor proposes submitting an interim data cut from Study SPD489-345 that would include approximately 59 subjects who will have completed the long-term study, and 168 subjects who will have 6 months of data. At the

time of the Day 120 Safety Update Report, new and updated safety data collected since the NDA interim data cut will be submitted. It is anticipated that this update will include a total of approximately 309 subjects who have completed the long-term study, and 374 subjects with 6 months of data. Table 2 provides estimated BED subjects exposures to SPD489.

| | Minimum Duration of Exposure to SPD489 | | | | |
|-----------------------|--|----------|----------|----------|-----------|
| | Enrolled | 3 months | 6 months | 9 months | 12 months |
| At Initial Submission | 530 | 289 | 168 | 92 | 59 |
| At Day 120 | 530 | 428 | 374 | 321 | 309 |

Note: Does not include exposure in the placebo-controlled, short-term Phase 2 and 3 trials. In Study SPD489-208, 204 subjects had up to 11 weeks of exposure to SPD489. It is anticipated that approximately 356 subjects in the Phase 3 trials will have up to an additional 12 weeks of exposure to SPD489.

Proposed Randomized Withdrawal Study (b) (4)

The Sponsor is proposing a randomized withdrawal study to support maintenance of effect in adults with moderate to severe BED. This study (b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

2. DISCUSSION

The purpose of the meeting is to review the design and objectives of the Phase 3 development program intended to support approval and use of SPD489 for the treatment of patients with BED.

2.1. Clinical Questions

Question 1. Does the Agency agree that Study SPD489-208 is an adequate and well-controlled study that provides sufficient dose response information to support the doses selected for the two 12-week, flexible-dose Phase 3 studies (SPD489-343 and SPD489-344)?

Preliminary Comments: *Based on the synopsis included in the meeting package, the proposed studies are acceptable. We will conduct a full review when the detailed protocols are submitted under the IND, and offer additional comments at that time. We do, however, recommend a fixed-dose design for at least one of the two Phase 3 studies.*

Discussion at Meeting: *We discussed the value of conducting a fixed-dose design and the non-linear, ceiling effect at the 70mg dose, as compared to the 30 and 50mg doses. The Sponsor noted that Study SPD489-208 provided dose-response data demonstrating that 50mg is the minimally effective dose and that doses higher than 70mg are unlikely to provide additional benefit. The Agency agreed with the Sponsor's proposal to move forward with two flexible dose studies using 50mg and 70mg.*

Question 2a. Does the Agency agree that the efficacy and safety endpoints in Studies SPD489-343 and SPD489-344 are appropriate to demonstrate the efficacy and safety of SPD489 in the treatment of BED and to support its use in the proposed indication?

Preliminary Comments: *During the pre-IND meeting for IND 110,503, there was a discussion of the relative merits of binge days vs. binge episodes as a primary endpoint. FDA's preliminary comments at that time were:*

On face, using binge episodes per week seems reasonable and may give a more nuanced view of drug effect. Given that the proposed trial will collect diary information, exploratory analyses from this POC trial could provide support for this strategy. The Sponsor may also wish to consider collecting calorie counts or other clinically relevant information that could inform efficacy analyses.

Of note, the current DSM-IV research criteria for BED specify that binge eating occurs at least "two days per week for six months". The proposed DSM-V criteria do not specify days vs. episodes, stating instead that binge eating should occur "at least once a week for three months" in order to fulfill diagnostic criteria. The text accompanying the DSM-IV criteria suggests that research should address whether it is better to count days or episodes. The Sponsor should submit any studies supporting the utility of counting binge episodes over days prior to initiating future pivotal phase 3 protocols.

While we agreed that calorie counts were not necessary, the question of whether binge episodes or binge days is a more appropriate endpoint has not yet been addressed, so we would appreciate more discussion on this point. Also, while you state clinically

meaningful benefit to subjects may be seen at a mean reduction of ≥ 0.5 binge days per week, we ask that you provide additional support for this assertion.

Discussion at Meeting: *The Sponsor stated that, while binge episodes and binge days are both acceptable standards of measuring of efficacy, there is no consensus in the field as to which may be superior. The Sponsor noted that, when not punctuated by purging (as in bulimia nervosa), it can be difficult to distinguish when one binge episode ends and another starts. The Sponsor also stated that patients generally measure the status of their condition in terms of good and bad "days." Given these factors, the Sponsor believes that measuring binge days is more valid and reliable. The Agency found the Sponsor's rationale acceptable.*

The Sponsor also explained its rationale for determining a clinically meaningful effect. The Sponsor acknowledged that there is currently no data or literature to suggest the proposed threshold of ≥ 0.5 ; however, a mean reduction of ≥ 0.5 binge days per week would translate to about a 50% effect. The Sponsor informally surveyed a panel of expert clinicians who agreed that a mean reduction of ≥ 0.5 binge days per week would be clinically meaningful.

Question 2b. [REDACTED] (b) (4)

Preliminary Comments: [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

The final labeling language will be a matter of review when the NDA supplement is submitted.

Discussion at Meeting: *No further discussion.*

Question 2c. Does the Agency agree that the duration of the two Phase 3 clinical studies (SPD489-343 and SPD489-344) is appropriate to assess the efficacy of SPD489 for the proposed indication?

Preliminary Comments: *Based on the study synopsis, the duration is acceptable.*

Discussion at Meeting: *No further discussion.*

Question 2d. Does the Agency agree that Studies SPD489-343 and SPD489-344 are appropriately designed to demonstrate SPD489 treatment effect in adults with BED?

Preliminary Comments: *Based on the study synopsis included in the meeting package, the design for the planned Phase 3 trials is acceptable.*

Discussion at Meeting: *No further discussion.*

Question 2e. Does the Agency agree with the statistical approaches for each of the proposed 12-week Phase 3 studies (SPD489-343 and SPD489-344) in BED?

Preliminary Comments: *In principle, we have no objection to your proposed analysis plan for the primary endpoint if you can justify the adequacy of normality approximation to the distribution of the novice efficacy variable. Please share with us your explorations of model diagnostics such as histograms of both the transformed and the non-transformed primary endpoints in the completed phase II trial.*

The concerns above also apply to your proposed key secondary endpoints, depending on the nature of the distribution. The assessment frequency of a key secondary needs to be sufficient. See also our preliminary comments under Q2c.

Discussion at Meeting: *No further discussion.*

Question 2f. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

Preliminary Comments: [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Discussion at Meeting: [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

Question 5a. Evaluating potential post-approval studies for the BED indication, Shire is considering the following study concepts. [REDACTED] (b) (4)

Preliminary Comments: [REDACTED] (b) (4)

Discussion at Meeting: *No further discussion.*

Question 5b. Does the Agency agree that a randomized-withdrawal study design, as described, is appropriate to support a maintenance of effect indication in adults with BED?

Preliminary Comments: [REDACTED] (b) (4)

Discussion at Meeting: [REDACTED] (b) (4)

[REDACTED] (b) (4)

Question 6. Shire has a comprehensive program of clinical pharmacology studies to understand the pharmacokinetic and metabolic profile of SPD489 in humans. Does the Agency agree that these are sufficient to support the use of SPD489 in the proposed indication?

Preliminary Comments: *Yes, we agree.*

Discussion at Meeting: *No further discussion.*

2.2. Non-Clinical Question

Question 7. Does the Agency agree the nonclinical program is sufficient to support the clinical development program and marketing application for SPD489 for use in the proposed indication?

Preliminary Comments: *Yes, we agree.*

Discussion at Meeting: *No further discussion.*

2.3. Regulatory Question

Question 8. Does the Agency agree with Shire's proposed plan to request a deferral for adolescents (ages 13 to 17 years) and a partial waiver in the children (ages 0 to 12 years) for this proposed indication?

Preliminary Comments: *The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a pediatric plan has been submitted and a request for a waiver or deferral has been granted.*

A pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to: 1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and 2) support dosing and administration for each pediatric subpopulation for which the product has been assessed to be safe and effective.

A pediatric plan should address all relevant pediatric subpopulations and the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, you plan to request a waiver or deferral of pediatric studies.

Each Pediatric Plan should contain the following:

- (1) certification of the grounds for deferring the assessments;*
- (2) a description of the planned or ongoing studies;*
- (3) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and*
- (4) a timeline including protocol submission date, study completion date, and the date final studies will be submitted.*

We likely would agree to a partial waiver in birth to 12 years of age in the treatment of binge eating disorder, because studies are highly impractical due to the low prevalence of this disorder in this age range, and deferral of studies in patients 13 to 17 years of age. You will need to submit data to support your partial waiver request.

Discussion at Meeting: *No further discussion.*

Note: The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.

General Comments for the Sponsor:

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND Sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for Sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS P LAUGHREN
08/07/2012