CLINICAL REVIEW

Application Type	s-NDA
Application Number	21977
Priority or Standard	S
Submission Date	03/31/2011
Received Date	03/31/2011
PDUFA Goal Date	01/31/2012
Division/Office	DPP/OND
Reviewer Name	Maju Mathews, M.D.
Review Completion Date	09/13/2011
Established Name	Lisdexamfetamine Dimesylate
Trade Name	VYVANSE
Therapeutic Class	Stumulant
Applicant	Shire
Formulation	30 mg, 50 mg & 70 mg
Dosing Regimen	Once Daily
Indication	Maintenance Treatment of ADHD
Intended Population	Adults

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

I recommend that the Division of Psychiatry Products take an Approval action for NDA 21-977. In my opinion, the sponsor has demonstrated the efficacy and safety of Vyvanse in the maintenance treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in adults aged 18-55 years of age. Study SPD489-401 was an adequate and well-controlled randomized withdrawal trial designed to demonstrate efficacy of Vyvanse in the maintenance treatment of ADHD. There was a statistically and clinically significant difference in the occurrence of treatment failure during the double-blind treatment phase in subjects treated with Vyvanse compared to placebo.

In my opinion, treatment with Vyvanse was reasonably safe and well tolerated. No labeling recommendations are being made at the time of filing this review. These will be made by Jing Zhang, MD. Final approval is contingent on satisfactory response to the agency's recommendations and mutual agreement on labeling as well as the conclusions of the CMC, pharmacology/toxicology, and clinical pharmacology reviewers.

The sponsor has submitted a Pediatric Development Plan. They have requested a waiver of studies in children under 6 years old and a deferral of studies in children and adolescents aged 6-17. I recommend that the waiver and deferral be granted in the requested age groups.

1.2 Risk Benefit Assessment

Vyvanse has been demonstrated to be safe and effective in the maintenance treatment of ADHD. The benefits of treatment with Vyvanse outweigh the risks associated with it.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Vyvanse is currently marketed. No new safety concerns were identified during the review. Risk Evaluation and Mitigation Strategies are not required at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

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

In the United States (US), SPD489 capsules (30, 50, and 70mg) marketed as VYVANSE®, were approved by the Food and Drug Administration (FDA) for the treatment of ADHD in children aged 6-12 years in February 2007. Intermediate dose strengths of 20, 40, and 60mg were approved for use in children aged 6-12 years in December 2007. SPD489 capsules were approved for the treatment of ADHD in adults in April 2008.

In Canada, SPD489 30 and 50mg capsules, marketed as VYVANSE, were approved for the treatment of ADHD in children aged 6-12 years in February 2009. Intermediate dose strengths of 20, 40, and 60mg were approved in March 2010. Dose strengths of 20, 30, 40, 50, and 60mg were approved for the

treatment of ADHD in adolescents aged 13-17 years and adults in November 2010.

In Brazil, SPD489 30, 50, and 70mg capsules were approved for the treatment of ADHD in children aged 6-12 years in July 2010. The product is not currently marketed in Brazil.

SPD489 capsules are not currently registered in any other markets.

2.2 Tables of Currently Available Treatments for Proposed Indications

The mainstays of approved treatment for ADHD have been the stimulants, methylphenidate and amphetamines. Included in this category are dexmethylphenidate, dextroamphetamine, methamphetamine, and amphetamine single and mixed salts. As listed below, there are numerous immediate-release and extended-release formulations of stimulants available for the treatment of ADHD. Atomoxetine (Strattera) is a non-stimulant drug approved for the treatment of ADHD. It is a selective norepinephrine reuptake inhibitor. Guanfacine and clonidine are α_{2A}-adrenergic receptor agonists.

Available Treatments for ADHD

- Adderall (mixed salts of a single entity amphetamine product) Tablets
- Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules
- Concerta (methylphenidate hydrochloride) Extended-Release Tablets
- Daytrana (methylphenidate) Transdermal System
- Desoxyn (methamphetamine HCl) Tablets
- Focalin (dexmethylphenidate hydrochloride) Tablets
- Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules
- Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
- Methylin (methylphenidate hydrochloride) Oral Solution
- Methylin (methylphenidate hydrochloride) Chewable Tablets
- Ritalin (methylphenidate hydrochloride) Tablets

• Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
• Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
• Strattera (atomoxetine HCl) Capsules
• Vyvanase (lisdexamfetamine: a pro-drug of amphetamine)
• Intuniv (guanfacine)
- Kapvay (clonidine)

2.3 Availability of Proposed Active Ingredients in the United States

Vyvanse is approved for the treatment of ADHD in adults and children and is available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety considerations with stimulants include cardiovascular safety, changes in blood pressure and heart rate, effects on growth (decreased), loss of appetite, aggression, exacerbation of psychosis, tics, and seizures.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Study SPD489-401 was developed as a registration study for a European Marketing Authorization Application. At the time, the sponsor did not intend to use the study to support a significant change in the US labeling for Vyvanse and the study met all of the criteria in 21 CFR 312.2 (b) for exemption. Therefore, the protocol and Statistical Analysis Plan (SAP) for Study SPD489-401 were not submitted under the IND 67,482.

The sponsor did provide a brief summary of Study SPD489-401 in the IND annual report (SN-0280, submitted 21 June 2010) as a ‘non-IND’ study.

However, recently, the sponsor has reconsidered the clinical relevance this study may have for physicians treating ADHD adult patients. As a result, they have submitted a supplemental NDA (S-0022) with these data to update the US Prescribing Information for Vyvanse.

The sponsor had a Pre-sNDA, Type B meeting with the Agency in March 2011, where it was agreed that a sNDA could be filed for maintenance treatment based on this study. The minutes are available in DARRTS filed by Juliette Toure dated 03/10/2011.

2.6 Other Relevant Background Information

None

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

All SPD489 studies were conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, the US Code of Federal Regulations (CFR), and the European Union (EU) Clinical Trials Directive, as well as any other applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

The sponsor has certified that they 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.

3.2 Compliance with Good Clinical Practices

The sponsor has stated that this study was conducted in accordance with Good Clinical Practices.

3.3 Financial Disclosures

The sponsor has provided financial disclosure and arrangements of all clinical investigators. Two of the investigators have declared financial interests. They are (b) (6), M.D, and (b) (6), MD. None of the other investigators have any financial interests to report.

Dr (b) (6) reports receiving $40000 in 2009 from Shire related to speaking and consulting arrangements. Dr (b) (6) reports receiving over $25000 in consulting and speaking arrangements.

Reviewers Comments: *Both these studies are multi-center, double blind, randomized withdrawal trials. Subjects and investigators are blinded and there are a number of safeguards in place. I do not believe that these financial interests have affected the results of the study.*

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

No new information submitted

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

Not submitted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vyvanse is a pro-drug of dextroamphetamine. After oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit/Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to 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

4.4.2 Pharmacodynamics

NRP104 is a prodrug of d-amphetamine.

4.4.3 Pharmacokinetics

After oral administration of 14C Vyvanse, there was a minimal amount of Vyvanse that was essentially cleared by 8 hours after dosing. The majority of radioactivity in the plasma was associated with d-amphetamine and some radioactivity was associated with other moieties, most likely amphetamine metabolites. Essentially all of the 14C was excreted in the urine with trace amount in the feces and excretion was complete within 72 to 96 hours, consistent with the t1/2 of d-amphetamine. Approximately 2% of the administered dose of 14C was recovered in the urine as Vyvanse and 40% was recovered as amphetamine.

The pharmacokinetics of d-amphetamine was linear over doses of Vyvanse ranging from 30 mg to 70 mg in children with ADHD. In healthy adults with histories of stimulant abuse, the pharmacokinetics of d-amphetamine were linear over doses ranging from 30 mg to 130 mg but substantially attenuated between doses of 130 to 150 mg, which the sponsor asserts is consistent with the hydrolysis of Vyvanse to d-amphetamine.

Plasma d-amphetamine concentrations reached a three to four fold lower Cmax at a later Tmax after intravenous administration of Vyvanse than compared to the equivalent dose of d-amphetamine sulfate.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Table 1: Tables of Clinical Studies

Title	Design	Inclusion Criteria	Endpoint
Study No:	This is a	Age 18-55 years	Primary efficacy variable:

SPD489-401: Phase 4, double-blind, multi-center, placebo-controlled, randomized withdrawal, safety and efficacy study of SPD489 in adults aged 18-55 with Attention Deficit Hyperactivity Disorder (ADHD)	randomized withdrawal study, consisting oof 5 phases: (1) screening; (2) baseline; (3) 3-week open label treatment on SPD489; (4) 6-week double blind randomized withdrawal phase; and (5) safety follow up phone call.	of age. Documented diagnosis of ADHD. Baseline ADHD-RS with adult prompts total score of <22 and CGI-S score <3.	occurrence of treatment failure during the double-blind randomized withdrawal phase. Treatment failure: defined as a ≥50% increase (worsening) in the ADHD-RS with adult prompts total score and a ≥2 point increase (worsening) in CGI-S score at any double-blind visit (Visits 4, 5, 6, 7, 8, or 9) relative to Visit 3.

5.2 Review Strategy

For the purpose of this review, study SPD489-401 was reviewed. A list of items reviewed is given below.

Table 2: List of Items Reviewed

Submission Date	Items Reviewed
03/31/2011	• Clinical Study Reports • Application Summary • Proposed Labeling • Financial disclosure information • Case Report Forms

5.3 Discussion of Individual Studies/Clinical Trials

A detailed discussion of the study is under the review of efficacy.

6 REVIEW OF EFFICACY

A. STUDIES PERTINENT TO ADHD CLAIM

Rationale for Selection of Studies for Review

The sponsor conducted one Phase 4, double-blind, multi-center, placebo-controlled, randomized withdrawal safety and efficacy study in adults (18-55 years of age inclusive) diagnosed with ADHD. The efficacy of Vyvanse in the

short term treatment of ADHD has previously been demonstrated. It was hence determined that one study was adequate to demonstrate efficacy for maintenance treatment.

Study Summaries

Methods/Study Design/Analysis Plan

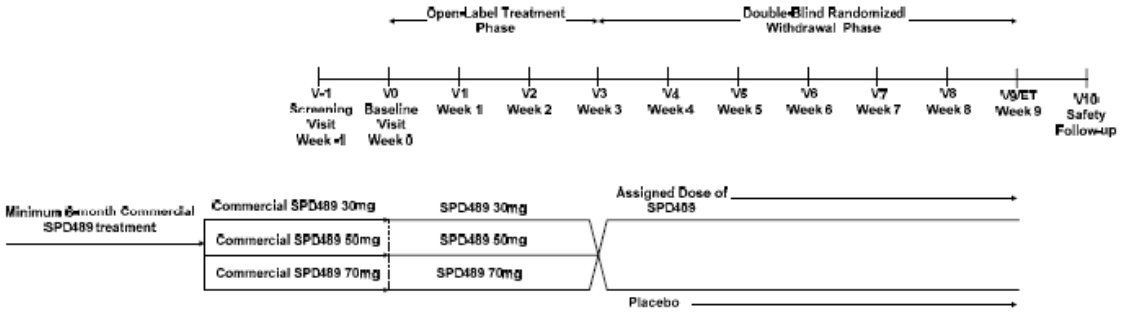
Start Date: **30 April 2009**
Completed date: **08 July 2010**

This was a Phase 4, double-blind, multi-center, placebo-controlled, randomized withdrawal safety and efficacy study in adults (18-55 years of age inclusive) diagnosed with ADHD.

Subjects entered the study having been on stable treatment with commercial SPD489 (30, 50, or 70mg) for a minimum of at least 6 months prior to the start of this study, defined as Visit -1.

The study consisted of 5 phases: (1) screening; (2) baseline; (3) 3-week open-label treatment phase on SPD489; (4) 6-week double-blind randomized withdrawal phase; and (5) safety follow-up phone call.

Figure 1: Study Design



Inclusion Criteria

- Subjects 18-55 years of age, inclusive.

- Female subjects with a negative human chorionic gonadotropin pregnancy test at screening (Visit -1) and a negative urine pregnancy test at baseline (Visit 0) and agree to comply with any applicable contraceptive protocols.

- Subject had a documented diagnosis of ADHD or met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision™ (DSM-IV-TR™) with adult prompts criteria by history for a primary diagnosis of ADHD prior to treatment.

- At Baseline (Visit 0), subject had an ADHD-RS with adult prompts total score of <22 and CGI-S score ≤3.

- Subject had been on stable treatment with commercial SPD489 (30, 50, or 70mg) for a minimum of 6 months preceding the Screening Visit (Visit -1) with acceptable tolerability. Prior treatment with commercial SPD489 in the 6 months preceding Screening Visit (Visit -1) must have been documented by prescription records, prescribing physician notes, or pharmacy records. Those subjects whose primary care physician was someone other than the Principal Investigator were required to provide this documentation to the site.

- Subject had a minimum level of intellectual functioning, as determined by the Investigator.

- Subject was willing and able to comply with all the testing and requirements defined in this protocol.

- Subject was able to swallow a capsule.

- Subject was able to provide written, personally signed, and dated informed consent to participate in the study, in accordance with the International

Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 and applicable regulations, before completing any study-related procedures.

Exclusion Criteria

Subjects were excluded from the study if any of the following criteria were met at Screening (Visit -1) or at Baseline (Visit 0) (if reassessed):

- Subject had a current comorbid psychiatric disorder that was either controlled with medications prohibited in this study or was uncontrolled and associated with significant symptoms.

- Subject was currently considered a suicide risk, had previously made a suicide attempt or had a prior history of, or was currently demonstrating, suicidal ideation.

- Subject had a body mass index (BMI) of <18.5 or ≥40.

- Subject had a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments administered in the study or that might increase risk to the subject.

- Subject had a history of seizures (other than infantile febrile seizures), any tic disorder, or a current diagnosis and/or a known family history of Tourette's Disorder.

- Subject had a known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, transient ischemic attack or stroke or other serious cardiac problems that may place

them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

- Subject had a known family history of sudden cardiac death or ventricular arrhythmia.

- Subject had any clinically significant electrocardiogram (ECG) or clinically significant laboratory abnormality at Screening (Visit -1).

- Subject had current abnormal thyroid function, defined as abnormal screening thyroid stimulating hormone and thyroxine. Treatment with a stable dose of thyroid medication for at least 3 months was permitted.

- Subject had a history of moderate to severe hypertension or had a resting sitting systolic blood pressure (SBP) >139mmHg or diastolic blood pressure (DBP) >89mmHg. Subjects with well-controlled mild or moderate hypertension on a single antihypertensive agent were allowed.

- Subject was taking any medication that was excluded.

- Subject had a documented allergy, hypersensitivity, or intolerance to amphetamines.

- Subject had a recent history (within the past 6 months) of suspected substance abuse or dependence disorder (excluding nicotine) in accordance with DSM-IV-TR™ criteria.

- Subject had a positive urine drug result at the Screening Visit (Visit -1) (with the exception of subject's current stimulant therapy).

- Subject had taken an investigational compound that had a central nervous system (CNS) effect or taken part in a clinical trial for ADHD 6 months prior to the Screening Visit (Visit -1).

- Subject had taken part in an investigational trial within the 30 days prior to the Screening Visit (Visit -1).

- Subject had glaucoma.

- Subject was taking other medications that have CNS effects or affect performance, such as chronic use of sedating antihistamines and decongestant sympathomimetics (7 days prior to Screening [Visit -1]). Stable use of bronchodilator inhalers was not exclusionary.

- Subject was female and pregnant or lactating.

- Subjects who have previously been enrolled into this study and subsequently withdrawn.

- Subject was not well controlled on SPD489 with acceptable tolerability (ADHD-RS with adult prompts score ≥22).

Assessments

Efficacy Measures

ADHD-RS with adult prompts– at the Baseline Visit (Visit 0) and all visits thereafter

The ADHD-RS with adult prompts is completed by the Investigator.

CGI -S – at the Baseline Visit (Visit 0) and all visits thereafter

Safety Measurements

The safety assessments performed in this study include:

• Medical and medication history - Visit -1 (Screening)
• Physical examination - Visit -1 (Screening) and Visit 9/ET
• Adverse events - all visits

All AEs were recorded from the time the informed consent was signed until the follow-up call was conducted. Where possible, a diagnosis rather than a list of symptoms was recorded. If a diagnosis was not made, each symptom was listed individually. If an event worsened, it was recorded as a new event. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 11.1).

• Concomitant medications - all visits

• Height - Visit -1 (Screening)
Height was to be measured without shoes with the subject standing on a flat surface and with chin parallel to the floor. Height was to be recorded to the nearest 0.25in.

• Weight - all visits
Weight was to be measured on a calibrated scale without shoes and recorded to the nearest 0.5lb.

• Clinical laboratory evaluations- Visit -1 (Screening)

Primary Efficacy Variable

The primary efficacy variable was the occurrence of treatment failure during the double-blind randomized withdrawal phase. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS with adult prompts total score and a ≥2 point increase (worsening) in CGI-S score at any double-blind visit (Visits 4, 5,

6, 7, 8, or 9) relative to Visit 3. Subjects who withdrew without providing efficacy data at Visit 9/ET were classified as treatment failures in the primary efficacy analysis.

Determination of Sample Size

Approximately 145 subjects were to be enrolled into the study to achieve at least 116 randomized subjects (58 subjects in each of the SPD489 and placebo groups). The primary efficacy variable was the occurrence of treatment failures during the double-blind randomized withdrawal phase. Treatment failure was defined as ≥50% increase (worsening) in ADHDRS with adult prompts total score and a ≥2 point increase in CGI-S score relative to the respective scores at Visit 3.

To detect a 30 percentage point difference between treatment failure proportions of 20% and 50% in the SPD489 and placebo groups, respectively, at 90% power and a significance level of 0.05 (2-sided) using a Chi-Square test with equal allocation to treatment groups, 116 subjects should be randomized.

It was assumed that 80% of subjects enrolled would be eligible for randomization into the double-blind randomized withdrawal phase. To account for subjects who were not eligible for randomization at Visit 3 and withdraw from the study during open-label conversion, a target of 145 enrolled subjects was established.

Results

Demographics & Baseline Characteristics

Subjects had a mean (standard deviation SD) age of 35.4 (11.6) years and were predominantly white (91.0%). The proportion of female subjects (55.7%) was greater than males. The mean (SD) baseline weight was 167.6 (40.54)lb.

The mean (SD) baseline ADHD-RS with adult prompts total score was 11.2 (4.98), indicating control of ADHD symptoms.

Table 3: Summary of Demographic and Baseline Characteristics

		SPD489			
		30mg (N=14)	**50mg (N=49)**	**70mg (N=59)**	**All Doses (N=122)**
Age (years)	Mean (SD)	34.1 (13.29)	34.7 (11.74)	36.4 (10.22)	35.4 (11.16)
	Median	33.0	32.0	36.0	36.0
	Min, Max	19, 54	18, 54	18, 55	18, 55
Sex					
Male	n (%)	5 (35.7)	21 (42.9)	28 (47.5)	54 (44.3)
Female	n (%)	9 (64.3)	28 (57.1)	31 (52.5)	68 (55.7)
Ethnicity					
Hispanic or Latino	n (%)	1 (7.1)	7 (14.3)	1 (1.7)	9 (7.4)
Not Hispanic or Latino	n (%)	13 (92.9)	42 (85.7)	58 (98.3)	113 (92.6)
Race					
White	n (%)	12 (85.7)	45 (91.8)	54 (91.5)	111 (91.0)
Black or African American	n (%)	1 (7.1)	1 (2.0)	1 (1.7)	3 (2.5)
Native Hawaiian or other Pacific Islander	n (%)	0	0	0	0
Asian	n (%)	0	1 (2.0)	3 (5.1)	4 (3.3)
American Indian or Alaska Native	n (%)	0	0	0	0
Other	n (%)	1 (7.1)	2 (4.1)	1 (1.7)	4 (3.3)
Height (in)	Mean (SD)	66.0 (4.30)	66.7 (3.63)	68.0 (4.09)	67.3 (3.98)
	Median	67.3	66.5	67.0	67.0
	Min, Max	58, 73	59, 75	61, 77	58, 77
Height (cm)	Mean (SD)	167.8 (10.93)	169.5 (9.23)	172.8 (10.38)	170.9 (10.10)
	Median	170.8	168.9	170.2	170.2
	Min, Max	147, 186	150, 189	155, 196	147, 196
Weight (lb)	Mean (SD)	171.0 (52.94)	157.7 (34.51)	175.0 (40.92)	167.6 (40.54)
	Median	163.0	151.5	170.0	163.8
	Min, Max	106, 301	105, 233	107, 270	105, 301
Weight (kg)	Mean (SD)	77.6 (24.04)	71.6 (15.67)	79.4 (18.58)	76.1 (18.41)
	Median	74.0	68.8	77.2	74.3
	Min, Max	48, 137	47, 106	49, 123	47, 137
Body Mass Index (kg/m^2)	Mean (SD)	27.3 (6.227)	24.8 (4.432)	26.4 (5.055)	25.9 (5.007)
	Median	26.72	24.10	25.87	25.07
	Min, Max	19.2, 39.5	18.6, 34.0	18.5, 39.7	18.5, 39.7

		SPD489			
		30mg (N=14)	50mg (N=49)	70mg (N=59)	All Doses (N=122)
Baseline ADHD-RS with adult prompts					
Total Score	Mean (SD)	10.9 (4.67)	11.6 (4.80)	10.9 (5.26)	11.2 (4.98)
	Median	11.5	11.0	11.0	11.0
	Min, Max	2, 17	3, 21	1, 21	1, 21
Hyperactivity/Impulsivity Subscale Score	Mean (SD)	4.4 (3.25)	4.2 (3.00)	4.0 (2.58)	4.1 (2.81)
	Median	4.5	4.0	4.0	4.0
	Min, Max	0, 9	0, 12	0, 10	0, 12
Inattention Subscale Score	Mean (SD)	6.6 (3.25)	7.4 (3.46)	6.9 (4.03)	7.1 (3.71)
	Median	6.0	7.0	7.0	7.0
	Min, Max	2, 12	0, 15	0, 18	0, 18
Baseline CGI Severity Rating	Mean (SD)	2.2 (0.70)	2.1 (0.71)	2.1 (0.83)	2.1 (0.76)
	Median	2.0	2.0	2.0	2.0
	Min, Max	1, 3	1, 3	1, 3	1, 3

Patient Disposition

Figure 2: Disposition Flow Diagram

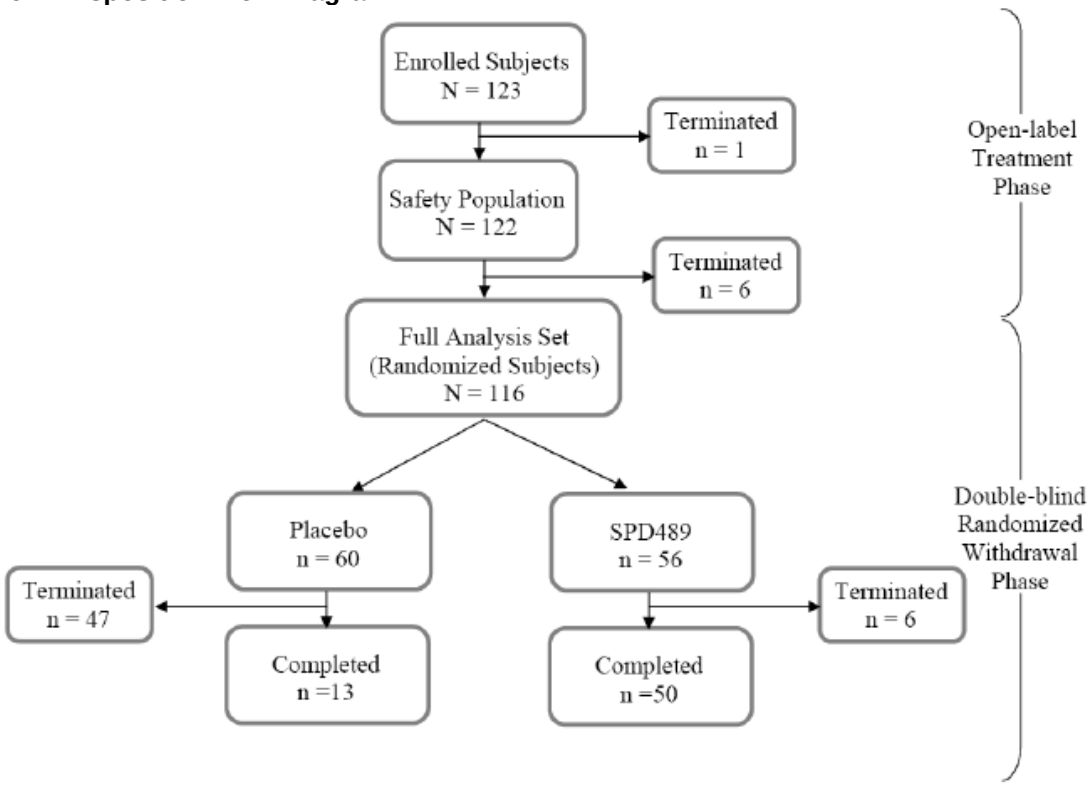


Table 4 presents the disposition for the open-label treatment phase. A total of 123 subjects enrolled in the study. One subject (007-0002), was lost to follow-up prior to taking any investigational product, and therefore the Safety Population (all subjects who entered the open-label treatment phase of the study and took at

least one dose of investigational product) was composed of 122 (99.2%) of the 123 enrolled subjects.

Six additional subjects (018-0001, 018-0015, 028-0005, 029-0001, 032-0001, and 053-0005) discontinued during the open-label treatment phase. Subject 032-0001, who was receiving SPD489 70mg, discontinued due to the AE of lack of efficacy after 20 days of exposure. Subjects 018-0001, 028-0005, and 029-0001 discontinued due to protocol non-compliance. Subject 053-0005 refused further participation in the study. Subject 018-0015 discontinued due to "other" (sent to Afghanistan by company).

Table 4: Summary of Patient Disposition in the Open-label Treatment Phase

	SPD489			
	30mg	50mg	70mg	All Doses
	(N=14) n (%)	(N=50) n (%)	(N=59) n (%)	(N=123) n (%)
Enrolled Subjects[a]	14 (100.0)	50 (100.0)	59 (100.0)	123 (100.0)
Safety Population[b]	14 (100.0)	49 (98.0)	59 (100.0)	122 (99.2)
Full Analysis Set[c]	12 (85.7)	47 (94.0)	57 (96.6)	116 (94.3)
Randomization criteria not met (Visit 3)[d]	0	0	0	0
Early termination[e]	2 (14.3)	3 (6.0)	2 (3.4)	7 (5.7)
Entered double-blind randomized withdrawal phase	12 (85.7)	47 (94.0)	57 (96.6)	116 (94.3)
Randomized to placebo	6 (42.9)	24 (48.0)	30 (50.8)	60 (48.8)
Randomized to SPD489	6 (42.9)	23 (46.0)	27 (45.8)	56 (45.5)
Reason for discontinuation:				
Adverse event(s)[f]	0	0	1 (1.7)	1 (0.8)
Protocol non-adherence/subject non-compliance	2 (14.3)	1 (2.0)	0	3 (2.4)
Refused further participation in the study	0	1 (2.0)	0	1 (0.8)
Lost to follow-up	0	1 (2.0)	0	1 (0.8)
Other	0	0	1 (1.7)	1 (0.8)

Table 5 below presents the disposition for the double-blind randomized withdrawal phase (Visits 3 –9). A total of 116 subjects entered the double-blind randomized withdrawal phase, and all of these subjects were included in the Randomized Safety Population and the FAS. A total of 47 (78.3%) of the 60 subjects randomized to receive placebo terminated from the study, while 6 (10.7%) of the 56 subjects randomized to receive SPD489 terminated from the study. A total of 53 subjects terminated from the study during the double-blind

randomized withdrawal phase; 50 of those subjects met relapse criteria. Of the 50 subjects who met relapse criteria, 45 subjects received placebo and 5 subjects received SPD489.

Table 5: Patient Disposition in the Double-blind Randomized Withdrawal Phase

		SPD489				Total (All Subjects)
	Placebo	30mg	50mg	70mg	All Doses	
	(N=60) n (%)	(N=6) n (%)	(N=23) n (%)	(N=27) n (%)	(N=56) n (%)	(N=116) n (%)
Randomized subjects	60 (100.0)	6 (100.0)	23 (100.0)	27 (100.0)	56 (100.0)	116 (100.0)
Randomized Safety Population[a]	60 (100.0)	6 (100.0)	23 (100.0)	27 (100.0)	56 (100.0)	116 (100.0)
Full Analysis Set[b]	60 (100.0)	6 (100.0)	23 (100.0)	27 (100.0)	56 (100.0)	116 (100.0)
Completed double-blind randomized withdrawal phase through Visit 9	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)	63 (54.3)
Early Termination	47 (78.3)	1 (16.7)	2 (8.7)	3 (11.1)	6 (10.7)	53 (45.7)
Reason for discontinuation:						
Relapse criteria met	45 (75.0)	1 (16.7)	1 (4.3)	3 (11.1)	5 (8.9)	50 (43.1)
Adverse event(s)	1 (1.7)	0	0	0	0	1 (0.9)
Protocol non-adherence/subject non-compliance	1 (1.7)	0	0	0	0	1 (0.9)
Refused further participation in the study	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Other	0	0	1 (4.3)	0	1 (1.8)	1 (0.9)

Table 6: Summary of Subject Completion Status by Visit During the Open-label Treatment Phase

	SPD489			
	30 mg (N=14) n (%)	50 mg (N=49) n (%)	70 mg (N=59) n (%)	All Doses (N=122) n (%)
Entered open-label treatment phase	14 (100.0)	49 (100.0)	59 (100.0)	122 (100.0)
Early Termination	2 (14.3)	2 (4.1)	2 (3.4)	6 (4.9)
Subjects remaining in study at:				
Visit 1 (Day 7)	12 (85.7)	48 (98.0)	58 (98.3)	118 (96.7)
Visit 2 (Day 14)	12 (85.7)	47 (95.9)	58 (98.3)	117 (95.9)
Visit 3 (Day 21)	12 (85.7)	47 (95.9)	57 (96.6)	116 (95.1)

Table 7: Summary of Subject Completion Status During Double-blind Randomized withdrawal Phase

Double-blind randomized withdrawal phase					
		SPD489			
	Placebo (N=60) n (%)	30 mg (N=6) n (%)	50 mg (N=23) n (%)	70 mg (N=27) n (%)	All Doses (N=56) n (%)
Completed Study	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)
Early Termination	47 (78.3)	1 (16.7)	2 (8.7)	3 (11.1)	6 (10.7)
Subjects remaining in study at:					
Visit 4 (Day 28)	32 (53.3)	5 (83.3)	22 (95.7)	25 (92.6)	52 (92.9)
Visit 5 (Day 35)	22 (36.7)	5 (83.3)	22 (95.7)	25 (92.6)	52 (92.9)
Visit 6 (Day 42)	17 (28.3)	5 (83.3)	21 (91.3)	25 (92.6)	51 (91.1)
Visit 7 (Day 49)	15 (25.0)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)
Visit 8 (Day 56)	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)
Visit 9 (Day 63)	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)

Concomitant Medication Use

During the study, 34.4% of subjects took concomitant medications. The most common medication types (taken by ≥2% of subjects in the Safety Population) are presented in the Table below. The only medications taken by ≥2% of subjects in the Safety Population were the analgesics ibuprofen, naproxen sodium, and paracetamol as well as the antibiotic amoxicillin.

Table 8: Concomitant Medications Use

Preferred Drug Name	SPD489 - All Doses (N=122) n (%)
Subjects who took any concomitant medication	42 (34.4)
Ibuprofen	15 (12.3)
Amoxicillin	3 (2.5)
Naproxen sodium	3 (2.5)
Paracetamol	3 (2.5)

Important Protocol Violations

There were no subjects who became pregnant during the study, nor were there any subjects noted as having a deviation of abuse, misuse, or overdose of investigational product.

A total of 19 subjects had protocol deviations. One of those subjects (007-0002) was not dosed, and 6 of those subjects (018-0001, 018-0015, 028-0005, 029-0001, 032-0001, and 053-0005) did not enter the double-blind randomized withdrawal phase.

Thirteen subjects in the Full Analysis SET (FAS) had a protocol deviation. One subject (005-0004) had 2 deviations (inclusion/exclusion and prohibited medication).

• Five subjects (002-0001, 005-0004, 006-0001, 008-0004, 059-0002) did not meet an inclusion or exclusion criteria. One subject (006-0001) did not meet the screening criteria for ADHD symptoms (exclusion criteria 21), and 1 subject (059-0002) did not meet the CGI-S criteria for randomization. Subject 008-00004 took ADDERALL, and Subject 005- 0004 took DEXTROSTAT within 6 months of Screening (Visit -1). Subject 002-0001 was taking 3 antihypertensive agents.

• Six subjects (002-0007, 005-0004, 018-0014, 027-0002, 052-0005, and 052-0009) took prohibited medications; 5 subjects took commercial SPD489 and 1 subject (027-0002) took DAYQUIL® for flu-like symptoms.

• Subject 044-0004 had an overall compliance rate of 68.8%.

• Subjects 018-0004 and 033-0006 tested positive for drugs of abuse.

Table 9: Summary of Major Protocol Violations (Safety and FAS)

	Safety Population (N=122) n (%)	FAS (N=116) n (%)
Subjects with major protocol deviations	19 (15.6)	13 (11.2)
Major protocol deviation:		
Overall compliance <80% or >120%	7 (5.7)	1 (0.9)
Inclusion/Exclusion criteria	7 (5.7)	5 (4.3)
Prohibited medication	6 (4.9)	6 (5.2)
Pregnant	0	0
Abuse, misuse, or overdose of investigational product	0	0
Other	2 (1.6)	2 (1.7)

Reviewer's Comments: I do not think that the use of concomitant medications affected study outcome.

Efficacy Findings

The FAS was defined as all subjects who were randomized and received at least 1 dose of investigational product. The FAS was composed of data from 116 (94.3%) of the 123 enrolled subjects. One subject was not dosed and 6 additional subjects did not complete the open-label treatment phase.

The primary efficacy analysis compared the proportion of treatment failures accrued by subjects receiving SPD489 (all doses) against placebo at Endpoint. Treatment failure was defined as ≥50% increase in the ADHD-RS with adult prompts total score compared to the score at randomization (Visit 3), and a ≥2 point increase in CGI-S score relative to the CGI-S score at randomization (Visit 3). In the primary efficacy analysis, subjects who withdrew without providing efficacy data were classified as treatment failures. Endpoint was defined as the last post-randomization visit of the double-blind randomized withdrawal phase at which a valid ADHD-RS with adult prompts total score was observed.

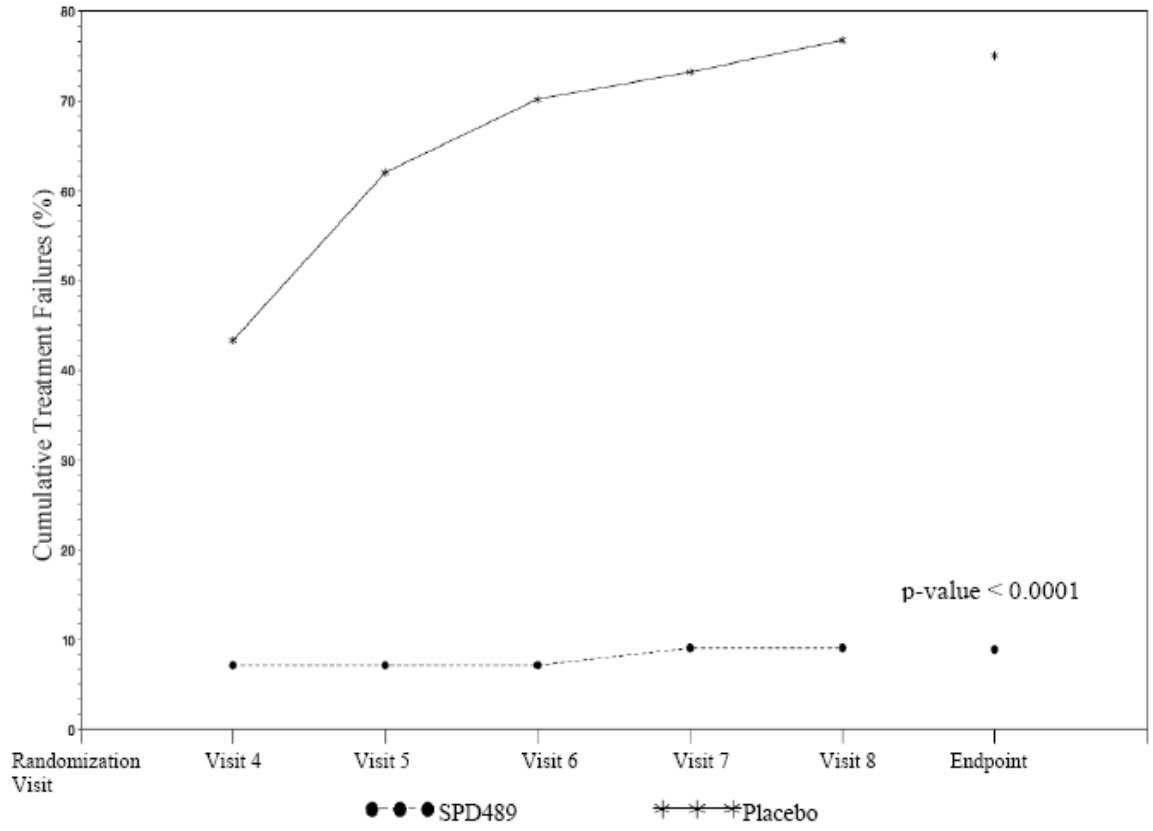
At Endpoint, 45 (75.0%) subjects who received placebo during the double-blind randomized withdrawal phase were categorized as treatment failures, compared to 5 (8.9%) subjects who received SPD489 (statistically significant difference, p value <0.0001).

For subjects receiving placebo, the majority of treatment failures occurred within the first 14 days after subjects were switched from open-label SPD489 treatment to placebo. At Visit 6 (21 days after the start of the double-blind randomized withdrawal phase) and thereafter, few subjects in either treatment group were categorized as a treatment failure.

The cumulative proportion of SPD489-treated subjects who were treatment failures remained small. In placebo-treated subjects, the increase in the

cumulative proportion of treatment failures was largest from Visit 3 to Visit 4, and from Visit 4 to Visit 5, and declined thereafter.

Figure 3: Cumulative Proportion of Treatment Failure by Visit



Sensitivity Analysis

In the sensitivity analysis, subjects who withdrew from the study *for any reason* were classified as treatment failures. The results of the sensitivity analysis supported the primary efficacy analysis. In this analysis, at Endpoint there were 47 (78.3 %) placebo-treated subjects who were treatment failures, and 6 (10.7 %) SPD489- treated subjects who were treatment failures (statistically significant difference, p-value <0.0001).

Effect of Sex

At Endpoint, there was no apparent meaningful difference between the results for males or for females in comparison to the overall FAS, or for male and female subgroups when compared to each other.

Effect of Race

Subjects in this study were 91.0% white. There did not appear to be any meaningful difference between the result for the white subgroup and the overall FAS. The non-white subgroup was very small, so although there did not appear to be any meaningful difference between the results for the non-white race subgroups and the result for the overall FAS, or when the race subgroups were compared to each other, no meaningful conclusion can be drawn.

Key Secondary Endpoints

Time to Treatment Failure

For subjects receiving placebo during the double-blind randomized withdrawal phase, the median duration in the double-blind randomized withdrawal phase was 13.0 days. For subjects receiving any dose of SPD489, the median duration in the double-blind randomized withdrawal phase was 42.0 days; 41.5 days for the 6 subjects receiving 30mg dose strength, 42.0 days for the 23 subjects receiving the 50mg dose strength, and 42.0 days for the 27 subjects receiving the 70mg dose strength.

Table 10: Time to Treatment Failure

		SPD489			
	Placebo (N=60)	30mg (N=6)	50mg (N=23)	70mg (N=27)	All Doses (N=56)
Mean (SD)	18.2 (14.40)	36.0 (14.27)	40.1 (8.66)	39.0 (9.97)	39.1 (9.85)
SE	1.86	5.83	1.81	1.92	1.32
Median	13.0	41.5	42.0	42.0	42.0
Min, Max	1, 44	7, 44	7, 49	5, 45	5, 49

Change from Baseline in ADHD-RS with Adult Prompts Total Score (Key Secondary Analysis)

A summary of the mean (SD) ADHD-RS with adult prompts total score and the mean (SD) change in the ADHD-RS with adult prompts total score from the double-blind randomized withdrawal phase baseline (Visit 3) at Endpoint, and at

Visit 4 and Visit 9 showed that at endpoint, for placebo treated subjects, the mean (SD) score was 27.4 (12.39) and the mean change from baseline (Visit 3) was 16.8 (11.80). This mean increase of approximately 17 points in the ADHD-RS with adult prompts total score indicates a worsening of ADHD symptoms.

At Endpoint, for SPD489-treated subjects, the mean (SD) score was 12.1 (9.96) and the mean change from baseline (Visit 3) was 1.6 (8.63). This mean increase of approximately 2 points in the ADHD-RS with adult prompts total score indicates that ADHD symptoms remained similar to when the subject entered the double-blind randomized withdrawal phase. At Visit 9, for the SPD489-treated subjects who remained in the study, the mean ADHD-RS with adult prompts total score was slightly lower (improved) compared to baseline (Visit 3).

Table 11: Summary of Mean ADHD-RS with Adult Prompts Total Score and the Mean Change from Double-blind Randomized Withdrawal Phase Baseline Visit (Visit 3) (FAS)

	Placebo (N=60)		SPD489 (N=56)	
	Actual Value	Mean Change from Baseline	Actual Value	Mean Change from Baseline
Baseline (Visit 3)[a]				
n	60		56	
Mean (SD)	**10.6 (4.82)**		**10.6 (4.96)**	
Min, Max	1 , 20		0 , 21	
95% CI	9.3 , 11.8		9.2 , 11.9	
Endpoint[b]				
n	60	60	56	56
Mean (SD)	**27.4 (12.39)**	**16.8 (11.80)**	**12.1 (9.96)**	**1.6 (8.63)**
Min, Max	5 , 50	-3 , 44	0 , 47	-9 , 42
95% CI	24.2 , 30.6	13.7 , 19.8	9.4 , 14.8	-0.8 , 3.9
Visit 4				
n	32	32	52	52
Mean (SD)	**17.1 (8.15)**	**6.0 (7.00)**	**10.9 (5.52)**	**0.3 (3.09)**
Min, Max	6 , 44	-2 , 30	0 , 21	-8 , 9
95% CI	14.2 , 20.0	3.4 , 8.5	9.3 , 12.4	-0.5 , 1.2
Visit 9				
n	13	13	50	50
Mean (SD)	**12.9 (5.62)**	**2.4 (4.66)**	**9.7 (5.67)**	**-0.8 (2.97)**
Min, Max	5 , 24	-3 , 12	0 , 23	-9 , 7
95% CI	9.5 , 16.3	-0.4 , 5.2	8.0 , 11.3	-1.7 , 0.0

Table 12: Analysis of Change from Baseline at Endpoint in ADHD-RS with Adult Prompts Total Score (FAS)

		Baseline (Visit 3)	Adjusted Change from Baseline (Visit 3)		
Assigned Treatment	**N**	**Mean (SD)**	**LS Mean**[a] **(SE)**	**Difference (95% CI)**	**Effect Size (95% CI)**
Placebo	60	10.6 (4.82)	16.8 (1.35)		
SPD489	56	10.6 (4.96)	1.6 (1.39)	-15.23 (-19.1, -11.4)	-1.5 (-1.9, -1.1)
			p-value[b]<0.0001		

Clinical Global Impression – Severity

A summary and analysis of the CGI-S at Baseline (Visit 3), Endpoint, and a summary at Visit 4 and Visit 9 shows that there were no subjects at any visit in either treatment group who were characterized as “among the most extremely ill subjects.”

At Endpoint, the Investigator assigned more subjects receiving SPD489 to the “normal, not at all ill” or “borderline mentally ill” categories compared to subjects

receiving placebo. The difference between the CGI-S results for placebo-treated subjects and SPD489-treated subjects was statistically significant (p-value <0.0001).

Table 13: Change in CGI-S

		Placebo (N=60)	SPD489 (N=56)
Baseline (Visit 3)[a]	n	60	56
Normal, not at all ill	n (%)	12 (20.0)	16 (28.6)
Borderline mentally ill	n (%)	25 (41.7)	21 (37.5)
Mildly ill	n (%)	22 (36.7)	19 (33.9)
Moderately ill	n (%)	1 (1.7)	0
Markedly ill	n (%)	0	0
Severely ill	n (%)	0	0
Endpoint[b]	n	60	56
Normal, not at all ill	n (%)	3 (5.0)	18 (32.1)
Borderline mentally ill	n (%)	7 (11.7)	20 (35.7)
Mildly ill	n (%)	7 (11.7)	10 (17.9)
Moderately ill	n (%)	20 (33.3)	4 (7.1)
Markedly ill	n (%)	21 (35.0)	4 (7.1)
Severely ill	n (%)	2 (3.3)	0
		p-value[c] <0 .0001	
Visit 4	n	32	52
Normal, not at all ill	n (%)	1 (3.1)	14 (26.9)
Borderline mentally ill	n (%)	11 (34.4)	20 (38.5)
Mildly ill	n (%)	12 (37.5)	18 (34.6%)
Moderately ill	n (%)	8 (25.0)	0
Markedly ill	n (%)	0	0
Severely ill	n (%)	0	0
Visit 9	n	13	50
Normal, not at all ill	n (%)	3 (23.1)	17 (34.0)
Borderline mentally ill	n (%)	5 (38.5)	20 (40.0)
Mildly ill	n (%)	3 (23.1)	10 (20.0)
Moderately ill	n (%)	2 (15.4)	3 (6.0)
Markedly ill	n (%)	0	0
Severely ill	n (%)	0	0

Pediatric Development

The sponsor has requested a partial waiver for performing pediatric assessments of Vyvanse as maintenance treatment in children with ADHD who are less than 6 years of age.

The sponsors rationale is that studies are impossible or highly impractical because the number of pediatric patients is small. In addition, the diagnostic

criteria of ADHD in children less than 6 is not well defined and pharmaceutical treatment is uncommon in this age group.

The sponsor has also requested a deferral of a study to evaluate the safety and efficacy of Vyvanse for maintenance treatment in children and adolescents aged 6-17 with ADHD.

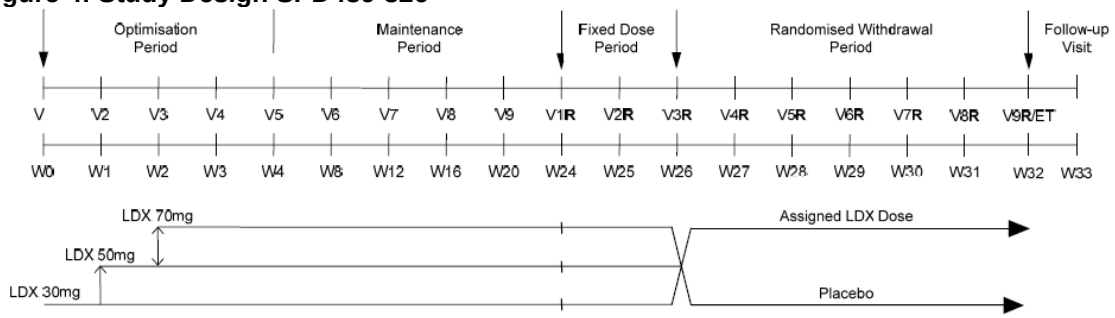
Shire is currently conducting a study to assess maintenance treatment of Vyvanse in children and adolescents aged 6-17 with ADHD. The sponsor believes that this pediatric study will fulfill the PREA requirement for the indication for maintenance treatment in children and adolescents aged 6-17 with ADHD. The protocol for Study SPD489-326 was submitted 1 April 2010 to IND 67,482 (Serial No. 0267), and is currently ongoing and projected to be completed end of first half of 2012.

A brief outline of the study is given below:

Study SPD489-326: *'A Phase III, Double-Blind, Placebo- Controlled, Randomised Withdrawal, Multicentre, Extension, Safety and Efficacy Study of Lisdexamfetamine Dimesylate (LDX) in Children and Adolescents Aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD)'*

SPD489-326 study design includes a 4-week open-label optimization period followed by at least a 22-week open-label period (a 20-week maintenance period and a 2-week fixed dose period, inclusive) to provide long-term efficacy and safety data on SPD489. Eligible subjects will then be randomized to either their assigned dose of SPD489 or placebo to evaluate long-term maintenance of efficacy. Subjects will continue to be followed weekly for clinical response during this 6-week double-blind Randomized Withdrawal Period.

Figure 4: Study Design SPD489-326



Primary objective

The primary objective of this study is to evaluate the long-term maintenance of efficacy of Vyvanse, using a composite endpoint based on the ADHD Rating Scale – IV (ADHD-RS-IV) and Clinical Global Impressions – Severity of Illness (CGI-S) rating scale, via a randomized withdrawal design in children and adolescents diagnosed with moderately symptomatic ADHD. Children and adolescents will be treated with LDX (30, 50, or 70mg/day) for at least 6 months prior to entering a 6-week double-blind randomized (LDX or placebo) withdrawal period.

Patient population

European children and adolescents (6-17 years of age inclusive at the time of consent for the antecedent study, SPD489-325) who had been exposed to double-blind test product for a minimum of 4 weeks, reached Visit 4, and completed the 1-week post-treatment washout during the SPD489-325 study were evaluable for study eligibility. To ensure that the sample size necessary to assess the primary efficacy measure was met, US children and adolescents (6-17 years of age inclusive) were also evaluated for direct entry into the study.

Enrollment Status

The last patient first visit in Study SPD489-326 took place in March 2011 with a total of 276 subjects enrolled. This is further broken down by region as follows:

• EU: 236 subjects

• US: 40 subjects

As of 17 June 2011, a total of 134 subjects have been randomized. This is further broken down by region as follows:

• EU: 113 subjects

• US: 21 subjects

Subjects are currently active in the study and the last patient last visit is targeted for November 2011.

Reviewer's Comments: I agree with the sponsor's request for waiver of studies in children under 6 and deferral in those aged 6-17.

Efficacy Conclusions

Vyvanse has been shown to be efficacious in the maintenance treatment of ADHD in one randomized withdrawal study. This will have to be confirmed by the biostatistics review. Statistical review is not available at the time of filing this review.

7 REVIEW OF SAFETY

Safety Summary

7.1 Methods

For the purpose of this review, one study was reviewed:

SPD489-401: A Phase 4, double-blind, multicenter, placebo-controlled, randomized withdrawal safety and efficacy study enrolling adults (18-55 years of age inclusive) diagnosed with ADHD.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

SPD489-401: A Phase 4, double-blind, multicenter, placebo-controlled, randomized withdrawal safety and efficacy study enrolling adults (18-55 years of age inclusive) diagnosed with ADHD.

7.1.2 Categorization of Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment.

Each AE requires a complete and thorough description on the AE CRF.
All AEs, including those associated with the protocol, are collected from the time the informed consent is signed until the defined follow-up period and are to be recorded on the appropriate AE pages in the CRF and in source documents.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the subject is still participating in the study.
The medical assessment of intensity is determined by using the following definitions:
Mild: The AE is easily tolerated and does not interfere with usual activity.
Moderate: The AE interferes with usual activity, but the subject is still able to function.
Severe: The AE is incapacitating and the subject is unable to work or complete usual activity.

A SAE was any untoward medical occurrence at any dose that:
• resulted in death
• was life-threatening (defined as an event in which the patient or patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe).
• required inpatient hospitalization or caused prolongation of existing hospitalization
• resulted in persistent or significant disability/incapacity
• was a congenital anomaly/birth defect
Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period. Pregnancy complications such as miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Pharmaceuticals Clinical Trial SAE Form.

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

Not applicable as there was only one study.

7.2 Adequacy of Safety Assessments

Safety evaluations included medical history, physical exams, measurement of vital signs, height, weight, lab tests, ECG's. pregnancy tests, CSSRS etc. Safety assessments were adequate.

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

All subjects were required to document a minimum of 6 months of exposure to commercial SPD489 preceding Screening (Visit -1) in order to be eligible for the study. At Visit 1, 11.5% of the subjects in the study were receiving SPD489 30mg, 40.2% were receiving SPD489 50mg, and 48.4% were receiving SPD489 70mg.

At Visit 3, 116 subjects were randomized to enter the double-blind randomized withdrawal phase; 60 (51.7%) subjects were randomized to receive placebo and 56 subjects continued on the SPD489 dose strength that they were receiving during the open-label treatment phase. A total of 6 (5.2%) of the 116 subjects continued to receive SPD489 30mg, 23 (19.8%) subjects continued to receive SPD489 50mg, and 27 (23.3%) subjects continued to receive SPD489 70mg. At Visit 9, dosing information was available for a total of 63 subjects; 5 (7.9 %) subjects received SPD489 30mg, 21 (33.3%) subjects received SPD489 50mg, and 24 (38.1%) subjects received SPD489 70mg, and the remaining 13 (20.6%) subjects received placebo.

In the placebo treatment group, the mean (SD) length of exposure was 18.0 (14.45) days. For subjects receiving any dose of SPD489, the mean (SD) length of exposure was 39.0 (10.22) days; 35.8 (14.19) days for subjects receiving the 30mg dose strength, 40.1 (8.66) days for subjects receiving the 50mg dose strength, and 38.8 (10.73) days for subjects receiving the 70mg dose strength. During the double-blind randomized withdrawal phase, approximately 90% of subjects receiving SPD489 were dosed for 36-42 days, compared with approximately 22% of the subjects receiving placebo, reflecting the higher early termination rate for placebo-treated subjects.

7.2.2 Explorations for Dose Response

No explorations for dose response were conducted.

7.2.3 Special Animal and/or In Vitro Testing

None done

7.2.4 Routine Clinical Testing

Laboratory testing was done at the time of screening only.

7.2.5 Metabolic, Clearance, and Interaction Workup

None

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

No further evaluations done

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the study.

7.3.2 Nonfatal Serious Adverse Events

During the open label treatment phase, there were no serious adverse events.

One subject discontinued due to a serious adverse event. However this subject was on placebo.

Subject 039-0004, A 18-year-old white male diagnosed with ADHD (combined subtype) without any medical history. Prior to receiving commercial SPD489 (VYVANSE®), he received atomoxetine hydrochloride (STRATTERA®) for ADHD. He did not report taking any other prior medications. At Visit 3 (10 Dec 2009), he was randomized to receive placebo in the double-blind randomized withdrawal phase of the study. Fourteen days after initiation of placebo treatment, (b) (6) , he experienced an episode of suicidal ideation. The subject threatened self-harm (with no specific plan) following an argument with his parents, who then took him to the emergency room. At the emergency room, the subject was reportedly agitated and belligerent. Family conflict had been a recent social stressor, with the subject's parents placing him under increasing pressure.

Investigational product (placebo) was discontinued on 24 Dec 2009. The subject received intramuscular lorazepam/ATIVAN® injections on 24 Dec 2009 and 25 Dec 2009. He began treatment with aripiprazole (ABILIFY) 5mg daily, and was titrated to 7mg daily on 27 Dec 2009. The subject was kept in the emergency room but not admitted to the hospital until (b) (6). He was discharged from the hospital on (b) (6) and treatment with aripiprazole (10mg daily) was ongoing. The subject did not experience any other AE during study participation.

7.3.3 Dropouts and/or Discontinuations

Two subjects terminated due to a TEAE during the study. During the open label treatment phase, one subject terminated due to lack of efficacy. During the double-blind randomized withdrawal phase, one subject terminated due to the SAE of suicidal ideation.

Subject 032-0001 was a 48-year-old white male diagnosed with ADHD (inattentive subtype). He had a medical history that included dormant herpes and a partial disc. Prior to receiving the study drug, he had been receiving CONCERTA and RITALIN for ADHD. The subject received the study drug from 13 June 2009 to 02 Jul 2009. After 20 days of exposure to the study drug, he was discontinued due to “drug ineffective”. The subject did not experience any other AE during study participation.

Subject 039-0004, A 18-year-old white male diagnosed with ADHD (combined subtype) without any medical history. Prior to receiving commercial SPD489 (VYVANSE®), he received atomoxetine hydrochloride (STRATTERA®) for ADHD. He did not report taking any other prior medications. At Visit 3 (10 Dec 2009), he was randomized to receive placebo in the double-blind randomized withdrawal phase of the study. Fourteen days after initiation of placebo treatment, on (b) (6) , he experienced an episode of suicidal ideation. The subject threatened self-harm (with no specific plan) following an argument with his parents, who then took him to the emergency room. At the emergency room, the subject was reportedly agitated and belligerent. Family conflict had been a recent social stressor, with the subject's parents placing him under increasing pressure.

Investigational product (placebo) was discontinued on 24 Dec 2009. The subject received intramuscular lorazepam/ATIVAN® injections on 24 Dec 2009 and 25 Dec 2009. He began treatment with aripiprazole (ABILIFY) 5mg daily, and was titrated to 7mg daily on 27 Dec 2009. The subject was kept in the emergency room but not admitted to the hospital until (b) (6) . He was discharged from the hospital on (b) (6) and treatment with aripiprazole (10mg daily) was ongoing. The subject did not experience any other AE during study participation.

Reviewer’s Comments: There were two subjects who discontinued the study drug. One was in the open label phase and the other in the randomized phase.

The case of interest here is the subject in the randomized phase. This subject was on placebo. This discontinuiation is not related to the study drug.

7.3.5 Submission Specific Primary Safety Concerns

Cardiovascular effects are of concern with drugs in the stimulant class. However, there were no events in this study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events were headache, insomnia, upper respiratory tract infections, fatigue and increased appetite.

Table 14: Summary of Treatment Emergent Adverse Events Reported by >2% of Subjects in Any Treatment Group During the Double-Blind Randomized Withdrawal Phase

	Randomized Treatment Group		
	Placebo (N=60) n (%) AE	SPD489 (N=56) n (%) AE	Total (N=116) n (%) AE
Any Adverse Event	**18 (30.0) 21**	**27 (48.2) 38**	**45 (38.8) 59**
Headache	3 (5.0) 3	8 (14.3) 8	11 (9.5) 11
Insomnia	3 (5.0) 3	3 (5.4) 3	6 (5.2) 6
Upper Respiratory Tract Infection	0	5 (8.9) 5	5 (4.3) 5
Fatigue	1 (1.7) 1	2 (3.6) 3	3 (2.6) 4
Increased Appetite	2 (3.3) 2	1 (1.8) 1	3 (2.6) 3
Joint Sprain	0	2 (3.6) 2	2 (1.7) 2

As can be seen from the above table, there were a greater number of adverse events reported in the study drug group compared to placebo. The rate of headaches was three times higher than that observed with placebo. The rate of fatigue was double that of placebo. Upper respiratory infections was seen in 8.9% of subjects on study drug compared to 0% on placebo.

The sponsor also conducted an analyses of adverse events by race and sex. The aponsor concluded that because of small numbers, it was not possible to draw any conclusions.

Reviewers Comments: I reviewed all adverse events that were reported, irrespective of their frequency. There were no other AE's that were of concern. The observed AE's are in the current label and does not alter the safety profile of this medication.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were obtained only at screening, therefore there was no on-study evaluation of hematology, chemistry, or urinalysis results.

7.4.3 Vital Signs

Vital signs were measured at each visit during the study. During the open-label treatment phase, subjects who had been receiving the study drug for at least 6 months had small increases from baseline in pulse rate,SBP, and DBP.

Table 15: Summary of Vital Signs During the Open Label Treatment Phase

		SPD489					
		30 mg (N=14)		50 mg (N=49)		70 mg (N=59)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Pulse Rate (beats/minute)							
Baseline (Visit 0)	n	14		49		59	
	Mean	**78.6**		**78.9**		**81.0**	
	SD	6.78		10.02		9.46	
	Min, Max	65, 90		57, 102		60, 100	
Visit 1 (Week 1)	n	12	12	48	48	58	58
	Mean	**82.8**	**3.9**	**80.3**	**1.5**	**81.0**	**-0.3**
	SD	6.05	6.95	10.58	8.36	10.08	8.41
	Min, Max	73, 96	-5, 16	60, 104	-15, 24	60, 100	-20, 22
Visit 2 (Week 2)	n	12	12	47	47	58	58
	Mean	**84.4**	**5.6**	**79.4**	**0.3**	**83.2**	**1.9**
	SD	7.88	10.47	10.48	7.97	9.44	7.88
	Min, Max	68, 95	-14, 21	60, 100	-18, 17	62, 102	-17, 26
Visit 3 (Week 3)	n	12	12	47	47	57	57
	Mean	**87.4**	**8.6**	**79.3**	**0.2**	**82.5**	**1.2**
	SD	7.74	8.53	9.36	9.77	10.30	9.23
	Min, Max	76, 100	-5, 22	62, 106	-18, 27	64, 102	-25, 24

Table 16: Summary of Vital Signs During the Open Label Treatment Phase

		SPD489					
		30 mg (N=14)		50 mg (N=49)		70 mg (N=59)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Systolic Blood Pressure (mmHg)							
Baseline (Visit 0)	n	14		49		59	
	Mean	**119.1**		**118.7**		**121.6**	
	SD	10.78		11.98		9.44	
	Min, Max	95, 132		89, 138		100, 138	
Visit 1 (Week 1)	n	12	12	48	48	58	58
	Mean	**120.7**	**2.8**	**118.6**	**0.1**	**122.8**	**1.1**
	SD	10.39	6.28	11.39	7.01	10.27	7.35
	Min, Max	105, 137	-7, 12	89, 140	-15, 18	98, 143	-16, 19
Visit 2 (Week 2)	n	12	12	47	47	58	58
	Mean	**118.7**	**0.8**	**120.0**	**1.8**	**122.1**	**0.4**
	SD	14.11	15.49	9.44	8.19	10.21	6.49
	Min, Max	94, 139	-25, 31	94, 138	-13, 31	99, 142	-18, 15
Visit 3 (Week 3)	n	12	12	47	47	57	57
	Mean	**119.1**	**1.2**	**118.9**	**0.7**	**121.6**	**0.0**
	SD	8.24	8.64	11.05	8.62	10.44	7.11
	Min, Max	107, 132	-13, 15	83, 138	-19, 27	93, 140	-13, 16

Table 17: Summary of Vital Signs During the Open Label Treatment Phase

		SPD489					
		30 mg (N=14)		50 mg (N=49)		70 mg (N=59)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Diastolic Blood Pressure (mmHg)							
Baseline (Visit 0)	n	14		49		59	
	Mean	**76.9**		**75.2**		**76.9**	
	SD	6.87		8.40		6.88	
	Min, Max	60, 88		50, 89		61, 88	
Visit 1 (Week 1)	n	12	12	48	48	58	58
	Mean	**78.3**	**2.0**	**76.7**	**1.5**	**78.7**	**1.7**
	SD	6.41	8.73	7.53	5.38	7.27	4.72
	Min, Max	68, 88	-15, 14	59, 88	-8, 18	59, 94	-7, 13
Visit 2 (Week 2)	n	12	12	47	47	58	58
	Mean	**77.1**	**0.8**	**76.7**	**1.6**	**77.0**	**0.1**
	SD	7.75	6.99	8.25	6.21	7.83	5.35
	Min, Max	63, 87	-12, 11	58, 94	-12, 26	58, 93	-11, 9
Visit 3 (Week 3)	n	12	12	47	47	57	57
	Mean	**77.7**	**1.4**	**76.7**	**1.6**	**77.8**	**0.8**
	SD	4.12	6.53	7.34	5.55	7.05	5.73
	Min, Max	71, 84	-8, 13	55, 92	-15, 14	61, 92	-12, 21

The mean change on pulse rate, SBP and DBP during the randomized withdrawal phase for the baseline, and visits 4, 6, 9 and endpoint were slightly higher for the drug treated subjects compared to placebo.

Table 18: Mean Change on Vital Signs in Randomized Withdrawal Phase

		Placebo (N=60)		SPD489 30 mg (N=6)		SPD489 50 mg (N=23)		SPD489 70 mg (N=27)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Pulse Rate (beats/minute)									
Baseline (Visit 0)	n	60		6		23		27	
	Mean	**79.9**		**77.3**		**80.1**		**81.5**	
	SD	9.30		8.55		10.37		9.32	
	Min, Max	57, 98		65, 87		64, 102		66, 100	
Visit 4 (Week 4)	n	32	32	5	5	22	22	25	25
	Mean	**78.6**	**-1.7**	**80.8**	**5.4**	**79.3**	**-0.3**	**83.8**	**2.2**
	SD	8.64	9.19	9.23	5.13	10.71	11.41	9.44	7.76
	Min, Max	62, 98	-28, 18	66, 88	-1, 11	60, 100	-23, 26	66, 100	-9, 18
Visit 6 (Week 6)	n	17	17	5	5	21	21	25	25
	Mean	**76.1**	**-3.1**	**83.6**	**8.2**	**79.8**	**0.3**	**83.4**	**1.8**
	SD	8.64	9.55	5.86	5.72	10.32	10.00	12.61	8.97
	Min, Max	64, 94	-21, 12	76, 91	-1, 14	62, 98	-22, 28	66, 109	-22, 17
Visit 9 (Week 9)	n	13	13	5	5	21	21	24	24
	Mean	**75.5**	**-2.5**	**76.8**	**1.4**	**76.5**	**-2.9**	**82.3**	**1.3**
	SD	10.49	6.80	13.44	11.55	8.75	8.69	9.98	9.56
	Min, Max	58, 94	-13, 9	57, 89	-8, 18	66, 104	-20, 12	68, 102	-18, 18
Endpoint	n	60	60	6	6	23	23	27	27
	Mean	**77.3**	**-2.6**	**78.2**	**0.8**	**77.6**	**-2.5**	**82.6**	**1.0**
	SD	8.52	10.46	12.48	10.42	9.09	8.50	9.52	9.05
	Min, Max	58, 94	-32, 23	57, 89	-8, 18	66, 104	-20, 12	68, 102	-18, 18

Table 19: Mean Change on Vital Signs in Randomized Withdrawal Phase

		Placebo (N=60)		SPD489 30 mg (N=6)		SPD489 50 mg (N=23)		SPD489 70 mg (N=27)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Systolic Blood Pressure (mmHg)									
Baseline (Visit 0)	n	60		6		23		27	
	Mean	**118.7**		**123.7**		**120.0**		**121.5**	
	SD	11.25		8.45		12.26		8.59	
	Min, Max	91, 138		109, 130		89, 138		105, 137	
Visit 4 (Week 4)	n	32	32	5	5	22	22	25	25
	Mean	**118.2**	**-1.6**	**120.0**	**-4.6**	**120.5**	**-1.0**	**120.6**	**-0.8**
	SD	10.45	8.71	13.36	7.16	10.78	5.30	10.93	7.49
	Min, Max	95, 135	-24, 12	102, 134	-11, 4	95, 136	-9, 14	99, 139	-17, 11
Visit 6 (Week 6)	n	17	17	5	5	21	21	25	25
	Mean	**117.4**	**-0.7**	**121.8**	**-2.8**	**122.5**	**0.9**	**121.2**	**-0.2**
	SD	12.37	8.24	12.91	4.76	10.28	7.86	13.17	8.34
	Min, Max	92, 136	-20, 11	101, 134	-8, 4	100, 138	-20, 16	101, 142	-17, 15
Visit 9 (Week 9)	n	13	13	5	5	21	21	24	24
	Mean	**115.5**	**-1.2**	**123.8**	**-0.8**	**118.8**	**-2.8**	**119.4**	**-1.7**
	SD	10.70	7.97	8.41	9.01	10.21	8.03	12.22	8.00
	Min, Max	98, 128	-18, 15	116, 137	-11, 7	99, 136	-17, 12	89, 138	-16, 14
Endpoint	n	60	60	6	6	23	23	27	27
	Mean	**118.9**	**0.2**	**119.8**	**-3.8**	**118.1**	**-1.9**	**120.0**	**-1.5**
	SD	11.74	8.73	12.29	10.96	10.03	8.91	12.16	8.30
	Min, Max	89, 140	-20, 19	100, 137	-19, 7	99, 136	-17, 19	89, 138	-16, 14

Table 20: Mean Change on Vital Signs in Randomized Withdrawal Phase

		Placebo (N=60)		SPD489 30 mg (N=6)		SPD489 50 mg (N=23)		SPD489 70 mg (N=27)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Diastolic Blood Pressure (mmHg)									
Baseline (Visit 0)	n	60		6		23		27	
	Mean	**75.1**		**79.2**		**76.5**		**77.3**	
	SD	8.48		5.49		7.06		6.15	
	Min, Max	50, 89		70, 85		64, 88		61, 86	
Visit 4 (Week 4)	n	32	32	5	5	22	22	25	25
	Mean	**74.4**	**-1.4**	**82.0**	**1.0**	**77.1**	**0.2**	**75.9**	**-0.9**
	SD	7.67	5.05	3.74	6.36	7.33	5.29	7.53	5.71
	Min, Max	55, 88	-16, 6	78, 86	-5, 10	62, 89	-10, 9	53, 86	-14, 7
Visit 6 (Week 6)	n	17	17	5	5	21	21	25	25
	Mean	**73.5**	**-1.6**	**82.6**	**1.6**	**77.2**	**0.2**	**76.5**	**-0.3**
	SD	8.35	4.76	5.32	8.08	6.79	4.97	7.74	7.73
	Min, Max	60, 88	-8, 11	75, 89	-8, 10	62, 92	-9, 8	62, 90	-16, 17
Visit 9 (Week 9)	n	13	13	5	5	21	21	24	24
	Mean	**73.9**	**-1.2**	**80.8**	**-0.2**	**76.9**	**-0.1**	**74.9**	**-1.8**
	SD	10.22	5.84	6.65	7.98	8.53	6.02	6.41	5.46
	Min, Max	53, 86	-13, 8	71, 87	-8, 11	64, 92	-15, 10	57, 83	-12, 15
Endpoint	n	60	60	6	6	23	23	27	27
	Mean	**76.0**	**0.9**	**81.3**	**2.2**	**77.0**	**0.5**	**75.3**	**-1.9**
	SD	8.09	5.99	6.09	9.20	8.18	6.35	6.69	6.04
	Min, Max	53, 90	-17, 17	71, 87	-8, 14	64, 92	-15, 13	57, 86	-16, 15

The technical criteria established for potentially clinically important (PCI) values of pulse rate, blood pressure, and temperature are shown in the table below. For the PCI summary, Endpoint was defined as the last valid vital sign measurement obtained after Baseline (Visit 0). If there were multiple assessments at the last visit, the worst case was taken as the Endpoint value.

Table 21: Criteria for Vital Sign Outliets

Vital Sign or Anthropometric Measurement	Outlier Criteria
Oral/Tympanic Temperature	< 95 °F
	> 102.2 °F
Systolic Blood Pressure	< 90 mmHg
	≥ 140 mmHg
	≥ 140 mmHg at 2 consecutive visits
	≥ 150 mmHg
Diastolic Blood Pressure	< 60 mmHg
	≥ 90 mmHg
	≥ 90 mmHg at 2 consecutive visits
	≥ 100 mmHg
Pulse	≤ 50 beats/minute
	≥ 100 beats/minute
	≥ 100 beats/minute at 2 consecutive visits
	≥ 110 beats/minute

Of the 122 subjects in the Safety Population, 12 subjects met PCI criteria at Endpoint.

Two subjects met PCI criteria for elevated pulse rate results:
• Pulse rate ≥ 100bpm: Subject 027-0002
• Pulse rate ≥ 100bpm (on 2 consecutive visits: Subject 033-0001

Four subjects met PCI criteria for elevated blood pressure results:
• SBP ≥140bpm and DBP ≥90bpm: Subject 033-0002
• SBP ≥140bpm: Subject 026-0003
• DBP ≥90bpm: Subject 002-0001, Subject 030-0007

Six subjects met PCI criteria for low blood pressure results:
• SBP <90bpm and DBP <60bpm: Subject 033-0006
• SBP <90bpm: Subject 012-0002 and Subject 024-0001
• DBP <60bpm: Subjects 005-0004, Subject 033-0003, and Subject 046-0001

Two subjects had changes in vital signs that were reported as TEAEs. Subject 029-0006, a 30 year-old white male, reported 1 episode of mild heart rate increased during the open-label treatment phase while receiving SPD489 70mg. His pulse rate had increased to 96bpm from a Screening (Visit -1) pulse rate of 61bpm. At study exit, the subjects pulse rate was 70bpm. This episode, considered related to investigational product by the Investigator, resolved without treatment. The subject was randomized to placebo during the double-blind randomized withdrawal phase and completed the study. He did not report any other AEs.

Subject 030-0007, a 48 year-old white male with no documented cardiovascular history, reported 1 episode of mild increased DBP during the double-blind randomized withdrawal phase while receiving SPD489 50mg. The result met the PCI criteria of DBP ≥90bpm. His DBP had increased to 92mmHg from a screening DBP of 86mmHg. At study exit, the subject's DBP was 90mmHg. This episode, considered related to investigational product by the Investigator, resolved without treatment. The subject completed the study and did not report any other AEs.

Reviewer's Comments: The changes in blood pressure and pulse rates were mild. Overall, the rates observed in subjects on the drug were no different from that observed with placebo. I do not believe that these observations alter the safety profile of the drug.

7.4.4 Electrocardiograms (ECG's)

ECG results were obtained only at screening. There was no on study evaluation.

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

Not included in this submission.

7.5 Other Safety Explorations

Weight

Weight was measured at each visit during the study. Weight was measured in pounds and is presented in kilograms.

Generally, mean weight appeared to remain stable throughout the study. During the double blind randomized withdrawal phase, subjects receiving placebo had a slight increase in mean weight compared to Baseline (Visit 0), while subjects receiving SPD489 were essentially unchanged.

Table 22: Summary of Weight During the Double-Blind Randomized Withdrawal Period

		Placebo (N=60)		SPD489					
				30 mg (N=6)		50 mg (N=23)		70 mg (N=27)	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Weight (kg)									
Baseline (Visit 0)	n	60		6		23		27	
	Mean	**76.5**		**71.1**		**73.3**		**78.1**	
	SD	19.66		10.74		15.71		18.73	
	Min, Max	47, 137		56, 84		48, 101		49, 123	
Visit 4 (Day 28)	n	32	32	5	5	22	22	25	25
	Mean	**83.7**	**0.5**	**72.4**	**-0.2**	**73.8**	**-0.2**	**77.5**	**-0.1**
	SD	19.94	1.58	12.23	1.55	15.44	1.06	19.09	1.20
	Min, Max	48, 136	-4, 3	55, 86	-1, 2	48, 101	-4, 2	49, 124	-3, 3
Visit 6 (Day 42)	n	17	17	5	5	21	21	25	25
	Mean	**84.0**	**0.8**	**72.7**	**0.1**	**74.6**	**-0.1**	**77.6**	**0.0**
	SD	23.23	2.76	12.29	1.37	15.29	1.92	19.37	1.61
	Min, Max	48, 135	-8, 4	55, 86	-1, 2	48, 100	-5, 4	47, 126	-5, 4
Visit 9 (Day 63)	n	13	13	5	5	21	21	24	24
	Mean	**87.4**	**1.1**	**72.4**	**-0.2**	**74.9**	**0.1**	**78.0**	**-0.3**
	SD	24.59	3.41	11.77	0.66	15.33	2.16	19.38	1.64
	Min, Max	49, 134	-7, 6	56, 84	-1, 1	49, 100	-6, 5	48, 125	-4, 3
Endpoint	n	60	60	6	6	23	23	27	27
	Mean	**77.4**	**0.9**	**70.9**	**-0.2**	**73.4**	**0.2**	**77.8**	**-0.3**
	SD	19.45	2.02	11.13	0.59	15.35	2.09	19.44	1.56
	Min, Max	46, 134	-7, 6	56, 84	-1, 1	49, 100	-6, 5	48, 125	-4, 3

Body mass index categories were defined as follows:

- Underweight (BMI < 18.5)
- Healthy weight (18.5 ≤ BMI < 25.0)
- At risk of overweight (25.0 ≤ BMI < 30.0)
- Overweight (BMI ≥ 30.0)

One subject met the PCI criteria for a ≥7% decrease in weight from Baseline (Visit 0) and 1 subject met the PCI criteria for a ≥7% increase in weight from Baseline (Visit 0). Neither of these changes was reported as a TEAE.

Subject 027-0003, a 20 year-old white male, met the PCI criteria for a ≥7% decrease in weight from baseline to Endpoint. He received SPD489 50mg throughout the study. The subject weighed 80.8kg at Baseline (Visit 0) and 74.9kg at Endpoint (a 7.3% decrease). His BMI category shifted from “at risk of overweight” at Baseline (Visit 0) to “healthy weight” at Visit 9. He completed the study.

Subject 013-0004, a 38 year-old white female, met the PCI criteria for a ≥7% increase in weight from baseline to Endpoint. She received SPD489 70mg during the open-label treatment phase and placebo during the double-blind randomized withdrawal phase. The subject weighed 66.3kg at Baseline (Visit 0) and at 72.0kg Endpoint (an 8.6% increase). Her screening BMI category was “at risk of overweight,” her baseline BMI category was “healthy weight,” and she remained in this BMI category until the double-blind randomized withdrawal phase. At Visit 4 of the double-blind randomized withdrawal phase, she returned to the “at risk of overweight” BMI category where she remained. She completed the study.

Reviewer’s Comments: Loss of appetite and weight loss are both known AE with stimulants. I do not think that these findings alter the safety profile of this medication.

7.5.1 Dose Dependency for Adverse Events

No analysis was conducted.

7.5.2 Time Dependency for Adverse Events

No analysis was conducted.

7.5.3 Drug-Demographic Interactions

No analysis was conducted.

7.5.4 Drug-Disease Interactions

No analysis was conducted.

7.5.5 Drug-Drug Interactions

No analysis was conducted.

7.6 Additional Safety Evaluations

None

7.6.1 Human Carcinogenicity

Not included in this submission.

7.6.2 Human Reproduction and Pregnancy Data

Not included in this submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not included in this submission.

7.7 Additional Submissions/Safety Issues

Not applicable

8 POSTMARKET EXPERIENCE

9 APPENDICES

9.1 Literature Review/References

The sponsor conducted a literature search on 18 March 2011 utilizing OvidSP Medline and Embase. The Embase database was current to 2011 week 09. The OvidSP Medline database was current to March week 1 2011. The search period for this review was from 4 October 2010 through end of 28 February 2011.
The search performed identified a total of 16 not previously reported publications inclusive of 14 publications specific for Vyvanse, 1 clinical review related to ADHD disease state and treatment, and 1 clinical trial report listing Vyvanse as a

concomitant medication.

There is no new safety information that would alter the safety profile of the drug.

9.2 Labeling Recommendations

Will be reviewed by Dr Jing Zhang, MD.

9.3 Advisory Committee Meeting

Not applicable.

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

/s/

MAJU MATHEWS
09/13/2011

JING ZHANG
09/16/2011