CLINICAL REVIEW

Application Type	sNDA
Application Number	021977/Supplement 016
Priority or Standard	Standard
Submit Date	January 14, 2010
Received Date	January 14, 2010
PDUFA Goal Date	November 14, 2010
Division/Office	DPP/ODE1
Reviewer Name	Jenn Sellers, MD, Ph.D.
Review Completion Date	October 10, 2010
Established Name	Lisdexamfetamine Dimesylate
Trade Name	Vyvanse
Therapeutic Class	Stimulant Prodrug
Applicant	Shire Development, Inc.
Formulations	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg Capsules
Dosing Regimen	30 - 70 mg/day
Indication	Attention Deficit Hyperactivity Disorder
Intended Population	Adolescents 13-17 Years Old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Shire submitted this supplemental NDA (sNDA) to seek an indication for Lisdexamfetamine dimesylate in the treatment of ADHD in adolescents aged 13 to 17 years. Based on the available data obtained from this 4-week, randomized, double-blind, placebo-controlled clinical trial, in which both efficacy and safety have been demonstrated, it is recommended that this sNDA be approved.

1.2 Risk Benefit Assessment

The efficacy of lisdexamfetamine dimesylate in improving symptoms of ADHD in adolescents was demonstrated by positive results from a 4-week, randomized, double-blind, placebo-controlled trial (Study 305). Efficacy in adolescent ADHD was observed at the end of the 4-week treatment on both the primary measure ADHD-RS-IV and key secondary measure Clinical Global Impression – Global Improvement (CGI-I).

The safety evaluation demonstrated that the safety profile of lisdexamfetamine dimesylate in the adolescent population was similar to that obtained from pediatric and adult populations and was consistent with the known effects of amphetamine treatment. Lisdexamfetamine dimesylate was generally safe and well tolerated in this population.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

The safety profile of lisdexamfetamine dimesylate in adolescent population was comparable to that obtained from pediatric and adult population. No specific safety concerns had been identified from this submission. Risk Evaluation and Mitigation Strategies are not required at this time.

1.4 Recommendations for Post-market Requirements and Commitments

A one year open label extension safety study of lisdexamfetamine dimesylate in adolescent population (SPD489-306) is ongoing. This study will provide data to evaluate longer-term safety in the target population.

2 Introduction and Regulatory Background

2.1 Product Information

Lisdexamfetamine dimesylate is converted to therapeutically active d-amphetamine after being taken orally. It belongs to a central nervous system (CNS) stimulant family.

Lisdexamfetamine dimesylate was marketed as Vyvanse and approved in the United States for the indication of ADHD in children aged 6 to 12 year in December 2007 and in adults aged 18 to 55 years in April 2008 with the dosage of 30 to 70 mg once daily. In this application, the sponsor is seeking the indication of lisdexamfetamine dimesylate in ADHD in adolescents aged 13 to 17 years.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following is a list of drugs approved under NDA to treat ADHD:

Stimulants:

1. Adderall (mixed salts amphetamine) Tablets
2. Adderall XR (mixed salts amphetamine) Extended-Release Capsules
3. Concerta (methylphenidate hydrochloride) Extended-Release Tablets
4. Daytrana (methylphenidate) Transdermal System
5. Desoxyn (methamphetamine) Tablets
6. Dexedrine (dextroamphetamine sulfate) Capsules
7. Dexedrine (dextroamphetamine sulfate) Spansules
8. Dexedrine (dextroamphetamine sulfate) Tablets
9. Focalin (dexmethylphenidate HCl)
10. Focalin XR (dexmethylphenidate HCl)
11. Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
12. Metadate ER (methylphenidate hydrochloride) Extended-Release Tablets (ANDA)
13. Methylin (methylphenidate hydrochloride) Chewable Tablets
14. Methylin (methylphenidate hydrochloride) Oral Solution
15. Ritalin (methylphenidate hydrochloride) Tablets
16. Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
17. Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
18. Vyvanse (lisdexamfetamine dimesylate)

Non-stimulants:

1. Intuniv (guanfacine) Extended Release Tablets
2. Strattera (atomoxetine HCl) Capsules

2.3 Availability of Proposed Active Ingredient in the United States

Vyvanse is an approved drug in the United States. Also, dextroamphetamine was approved and marketed in US.

2.4 Important Safety Issues with Consideration to Related Drugs

Lisdexamfetamine dimesylate is a CNS stimulant prodrug. Its labeling carries the same class warnings and precautions as other CNS stimulants. No other important safety issues related to this drug were identified from this submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Lisdexamfetamine was developed for this indication under IND 67,482. There was no pre-NDA meeting for this efficacy supplement.

In the US, lisdexamfetamine dimesylate (30, 50, and 70mg), marketed as Vyvanse, was approved by 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 December 2007. Lisdexamfetamine dimesylate was approved for the treatment of ADHD in adults aged 18-55 years in April 2008.

This NDA was submitted to the Agency on January 14, 2010. The Filing Meeting was held on February 26, 2010 and it was concluded that this supplement was fileable. The PDUFA goal date is November 14, 2010.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Adverse event safety data were audited for completeness and accuracy in a 5% sample (N=1) of submitted Case Report Forms (CRFs). The adverse events from the CRF for this subject (026-004) were compared to those in the Narrative Summary in the study body report and those listed in dataset file ae.xpt. No deficiencies or discrepancies were noted.

The Division of Scientific Investigation inspected 3 trial sites which had relatively high enrollments (15, 16 and 9 subjects were enrolled in the sites of Drs. Michael Greenbaum, Linda Harper and Keith Saylor, respectively). Those inspections did not find any deviation from regulations and concluded that the data generated by these sites were acceptable.

The sponsor communicated via email to our Project Manager Juliette Toure on September 28, 2010 that 37 EKGs (17 subjects, 15 of which were randomized and 2 were screened out) were not transmitted to the central reader. They subsequently submitted those missing EKGs to the central reader and submitted the revised EKG analysis results to FDA on October 1, 2010. The final EKG safety profile remained unchanged.

However, this reviewer found that chemistry outliers at endpoint such as elevated bilirubin and ALT did not have follow-ups.

3.2 Compliance with Good Clinical Practices

Study 305 was conducted in accordance with International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) and local ethical and legal requirements, and with the Declaration of Helsinki.

3.3 Financial Disclosures

Among the clinical investigators in this study [redacted] (b) (6) had the following disclosures:

[redacted] (b) (6) earned about $40,000 from Shire in 2008 as a speaker for Vyvanse.

[redacted] (b) (6) received about $50,000 in 2008 as a participant at advisory boards and as a speaker for Shire.

[redacted] (b) (6) received about $30,000 to $50,000 in each year from 2004 to 2009 as a speaker for Shire.

[redacted] (b) (6) owned Shire stock of $62,000 (1162 shares at $53.181 per share) in 2008.

The sites of [redacted] (b) (6) entered [redacted] (b) (4) subjects, respectively. A total of 310 subjects were randomized in this study. Since the number of subjects enrolled by these investigators was relatively small and since study 305 used a randomized, double-blind design, it seems unlikely that these financial arrangements would have biased the overall results of the trial.

The site of Dr. Harper was inspected by DSI/FDA because it entered relatively large number of subjects (16 subjects). DSI found the data generated by this site acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no CMC information provided in this submission.

4.2 Clinical Microbiology

No clinical microbiology study was deemed necessary.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology study was submitted to this sNDA.

4.4 Clinical Pharmacology

No new PK/PD or drug-drug interaction study was submitted to this sNDA.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table summarizes the adolescent ADHD trial: SPD489-305.

Table 1: Summary of the Adolescent ADHD Trial: SPD489-305

Number of Study Sites	45 US sites
Study Dates	October 8, 2008 to April 6, 2009
Study Design	4 week, randomized, double-blind, placebo-controlled, fixed-dose trial to assess the efficacy and safety of lisdexamfetamine treatment (30, 50 or 70mg) compared to placebo in ADHD in adolescents aged 13-17 years
Study Drugs	Lisdexamfetamine 30, 50, 70mg and placebo
Randomized/Treated	314/310 (about 77 - 78 subjects in each treatment group)
Gender/Mean Age (years)	Male (70.3%) female (29.7%)/14.6 (13 - 17)
Endpoints Primary Key Secondary	 Clinician completed ADHD-RS-IV total score CGI-I

5.2 Review Strategy

I have reviewed the Clinical Study Report (CSR) of Study SPD489-305, clinical overview, proposed labeling, financial disclosure certification, audit certificate, patent certification, case report forms, dataset file, debarment certification, exclusivity request, 4 month safety update report and the amendment of analysis of missing EKG data. I have consulted Dr. Yang Yang who is a statistical reviewer for the efficacy analyses. Please refer her review for detailed information in efficacy analyses and conclusions.

5.3 Discussion of Individual Studies/Clinical Trials

Study 305 had the identical design to the Study 301, which was a positive pediatric (aged 6 to 12 years) ADHD trial and supported the indication of Vyvanse in pediatric ADHD patients aged 6 to 12 years. Both trials were 4 week long and used the same fixed dosing 30, 50 and 70mg with the same titration schedule. Study 305 demonstrated the short-term safety and efficacy of lisdexamfetamine dimesylate in adolescent population. Study 306, an ongoing trial, is a longer term open label extension safety study of lisdexamfetamine dimesylate in the adolescent population.

6 Review of Efficacy

A. Rationale for Selection of Studies for Review

This sNDA included only one trial - Study 305.

B. Study Summary

I. Method/Study Design/Analysis Plan

Study 305 was conducted from October 8, 2008 to April 6, 2009 at 45 sites in USA.

Overall Study Design

Study 305 was a 4-week, phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose with titration study designed to assess the efficacy and safety of lisdexamfetamine dimesylate in 314 adolescents (13-17 years of age) with a DSM-IV diagnosis of moderately severe ADHD as defined by baseline ADHD-RS-IV total score ≥28. This trial included the following phases: screening and washout, baseline, 4-week double blind treatment of lisdexamfetamine dimesylate and placebo, and post-treatment follow-up.

Dose and Administration

All eligible subjects were randomized 1:1:1:1 to receive lisdexamfetamine dimesylate 30, 50, 70mg or placebo. The trial had a 3-week titration phase with dose varying with each dose group. The titration schedule is shown in **Table 2**.

Table 2: Forced-Dose Titration Schedule

Treatment Group	Week 1	Week 2	Week 3	Week 4
lisdexamfetamine dimesylate 30mg	30mg	30mg	30mg	30mg
lisdexamfetamine dimesylate 50mg	30mg	50mg	50mg	50mg
lisdexamfetamine dimesylate 70mg	30mg	50mg	70mg	70mg
Placebo	Placebo	Placebo	Placebo	Placebo

Source: Study 305 CSR, Appendix 16.1.1

Study drug was administered once daily around 7:00AM beginning on Day 1.

Selection of Study Population

Key Inclusion Criteria:

1. Male or female adolescents 13 to 17 years of age, inclusive, met Diagnostic and Statistical Manual for Mental Disorder, Fourth Edition – Text Revision™ (DSM-IV-TR™) criteria for a diagnosis of ADHD.

2. Subject had a Baseline ADHD-RS-IV score ≥28.

3. Subject's parent or legally authorized representative (LAR) provided signature of informed consent, and there was documentation of assent by the subject indicating that the subject was aware of the investigational nature of the study and the required procedures and restrictions in accordance with the ICH Good Clinical Practice Guidance (ICH Guidance E6, 1996) and applicable regulations before completing any study-related procedures.

4. Subject and parent/LAR were willing and able to comply with all the testing and requirements defined in this protocol, including oversight of morning dosing. Specifically, the parent/LAR was available upon awakening, at approximately 7:00AM, to dispense the dose of test product for the duration of the study.

5. Subject had blood pressure measurements within the 95th percentile for age, gender, and height at Screening and Baseline.

6. Subjects who were female had a negative serum beta human chorionic gonadotropin (HCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline of this study and agreed to comply with any applicable contraceptive requirements of the protocol.

7. Subject was functioning at an age-appropriate level intellectually, as deemed by the study Investigator.

Key Exclusion Criteria:

1. Subject had a current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis with significant symptoms such as any significant comorbid Axis II disorder or significant Axis I disorder (such as Post Traumatic Stress Disorder, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, depressive or anxiety disorder) or other symptomatic manifestations that, in the opinion of the examining clinician, would contraindicate treatment with lisdexamfetamine dimesylate or confound efficacy or safety assessments. Comorbid psychiatric diagnoses were established with the Screening interview of the K-SADS-PL and additional modules if warranted by the results of the initial interview. Subjects could continue participation in behavioral therapy during the study as long as they had been receiving the therapy for at least 1 month at the time of the Baseline Visit and the therapy did not change during the study.

2. Subject had a conduct disorder. Oppositional defiant disorder was not exclusionary.

3. Subjects with a suicide risk who had history of a suicide attempt or currently had suicidal ideation.

4. Subject was underweight (BMI < 5^{th} percentile).

5. Subject was significantly overweight (BMI >97th percentile).

6. 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.

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

8. Subject had any clinically significant EKG, based on the Principal Investigator's judgment, or laboratory abnormality at Screening or Baseline.

9. Subject had current abnormal thyroid function, as defined as abnormal thyroid stimulating hormone (TSH) at Screening. Treatment with a stable dose of thyroid medication for at least 3 months was permitted.

10. Subject had failed to respond to one or more adequate courses (dose and duration) of amphetamine therapy.

11. 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.

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

13. Subject had glaucoma.

14. Subject was taking other medications that have central nervous system (CNS) effects or affect performance, such as sedating antihistamines and decongestant sympathomimetics, or are monoamine oxidase inhibitors (during or within 14 days of test or reference product administration). Stable use of bronchodilator inhalers was not exclusionary.

15. Subject was female and was pregnant or lactating.

16. Subject was well controlled on their current ADHD medication with acceptable tolerability.

<u>The Primary and Secondary Efficacy Endpoints</u>

The primary efficacy outcome measure was the mean change from baseline to endpoint in the clinician completed ADHD-RS-IV total score.

ADHD-RS-IV is a psychiatric rating scale for ADHD clinical trials. It consists of 18 items. Each item is scored from 0 (no symptoms) to 3 (severe symptoms) with total scores ranging from 0 - 54. The 18 items may be grouped into two sub-scales: hyperactivity/impulsivity (even number items 2-18) and inattentiveness (odd number items 1-17). It has been accepted by DPP as a valid measurement in ADHD patients.

The key secondary efficacy outcome measure was the clinical global impressions - Improvement (CGI-I) Scale at the endpoint.

The CGI Scale is a standardized assessment tool. Its goal is to allow the clinician to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI Scale is widely used in clinical psychopharmacology trials as an outcome measure. The measure had been accepted by DPP as a reasonable secondary endpoint for many psychiatric clinical trials.

Statistical Methods

A total of 71 subjects per each lisdexamfetamine dimesylate treatment and placebo group were estimated to provide 90% power at the significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to the groups. A total of 300 randomized subjects (75 subjects in each treatment group) were able to account for an anticipated 5% of randomized subjects prematurely discontinuing the trial without providing a post-Baseline ADHD-RS-IV measurement.

The **Enrolled Population** included all subjects who were dispensed study medication at the Baseline visit.

The **Safety Population** included all subjects who took at least one randomized dose of study medication during this trial. The safety assessment used this population dataset.

The **Full Analysis Set (FAS)** included all subjects who took at least one randomized dose of study medication during this trial and had a valid Baseline and at least one post-Baseline follow-up assessment of the primary outcome measure - ADHD-RS-IV Total Score. The efficacy assessment used this data set.

The **Per-Protocol (PP) Population** included all subjects in the FAS who completed the trial and were compliant with the protocol.

The primary efficacy measurement - the ADHD-RS-IV total score was analyzed by a last observation carried forward (LOCF) ANCOVA. The ADHD-RS-IV total score was also analyzed separately for sex, race and age.

II. Results

Demographics

Demographic characteristics for the randomized sample are presented in **Table 3**.

Table 3: Demographic Characteristics (Safety Population)

		Assigned Treatment: Placebo & Lisdexamfetamine Dimesylate					
Characteristic	**Statistic**	**Placebo (N= 77)**	**30 mg (N= 78)**	**50 mg (N= 77)**	**70 mg (N= 78)**	**All Doses (N=233)**	**Overall (N=310)**
Age (years)	N	77	78	77	78	233	310
	Mean	14.5	14.6	14.7	14.4	14.6	14.6
	(SD)	(1.25)	(1.39)	(1.29)	(1.30)	(1.33)	(1.31)
Age Group							
13-14 years	N	41	42	36	44	122	163
	(%)	(53.2%)	(53.8%)	(46.8%)	(56.4%)	(52.4%)	(52.6%)
15-17 years	N	36	36	41	34	111	147
	(%)	(46.8%)	(46.2%)	(53.2%)	(43.6%)	(47.6%)	(47.4%)
Gender							
Male	N	53	59	62	44	165	218
	(%)	(68.8%)	(75.6%)	(80.5%)	(56.4%)	(70.8%)	(70.3%)
Female	N	24	19	15	34	68	92
	(%)	(31.2%)	(24.4%)	(19.5%)	(43.6%)	(29.2%)	(29.7%)
Race							
White	N	66	54	63	62	179	245
	(%)	(85.7%)	(69.2%)	(81.8%)	(79.5%)	(76.8%)	(79.0%)
Black or African American	N	9	12	12	13	37	46
	(%)	(11.7%)	(15.4%)	(15.6%)	(16.7%)	(15.9%)	(14.8%)
Native Hawaiian or pacific Islander	N	0	1	0	0	1	1
	(%)	(0.0%)	(1.3%)	(0.0%)	(0.0%)	(0.4%)	(0.3%)
Asian	N	0	1	0	0	1	1
	(%)	(0.0%)	(1.3%)	(0.0%)	(0.0%)	(0.4%)	(0.3%)
American Indian or Alaska native	N	0	1	0	0	1	1
	(%)	(0.0%)	(1.3%)	(0.0%)	(0.0%)	(0.4%)	(0.3%)
Others	N	2	9	2	3	14	16
	(%)	(2.6%)	(11.5%)	(2.6%)	(3.8%)	(6.0%)	(5.2%)
Weight (kg)	Mean	62.38	65.92	65.04	61.38	64.11	63.68
	(SD)	(13.347)	(15.206)	(13.661)	(10.133)	(13.261)	(13.282)
	Min	36.1	39.0	36.8	39.0	36.8	36.1
	Max	100.2	108.9	100.2	86.6	108.9	108.9
Height (cm)	Mean	166.75	168.04	169.20	166.12	167.78	167.52
	(SD	(10.111)	(9.788)	(9.414)	(8.442)	(9.279)	(9.486)
	Min	139.1	143.0	147.3	148.6	143.0	139.1
	Max	185.4	190.5	193.0	184.2	193.0	193.0
BMI (kg/m^2)	Mean	22.28	23.13	22.52	22.20	22.62	22.53
	(SD)	(3.632)	(3.959)	(3.162)	(3.105)	(3.439)	(3.485)
	Min	16.3	16.4	16.1	16.9	16.1	16.1
	Max	31.4	33.1	32.3	30.8	33.1	33.1

Source: Section 14, Tables 1.2.1 and 1.3, SD = Standard Deviation

The mean age was comparable among the treatment groups. Slightly more than half in all groups except 50 mg group were 13 or 14 years old. Subjects were predominantly male (70.3%) except 70mg group which only had 56.4%. The male predominance was consistent with the prevalence of ADHD (2 times more common in male than in female). Subjects were predominantly white (79%) except the 30mg group which only had 69.2%. The white predominance was consistent with the ethnic profile in most areas. The BMI was comparable among all the treatment groups.

Baseline Disease Characteristics

The baseline disease characteristics which were demonstrated in ADHD-RS-IV total score, the hyperactivity and inattention subscale scores, CGI severity rating and Youth Quality of Life Instrument – Research Version (YQOL-R) total perceptual score were comparable among all the treatment groups. They were summarized in **Table 4**.

Table 4: Baseline Disease Characteristics (Safety Population)

		Assigned Treatment: Placebo & Lisdexamfetamine Dimesylate					
Scale	**Statistic**	**Placebo (N= 77)**	**30 mg (N= 78)**	**50 mg (N= 77)**	**70 mg (N= 78)**	**All Doses (N=233)**	**Overall (N=310)**
Baseline ADHD-RS-IV Total Score	Mean (SD)	38.5 (7.11)	38.3 (6.71)	37.4 (6.37)	37.0 (7.30)	37.6 (6.80)	37.8 (6.88)
Baseline ADHD-RS-IV Hyperactivity/Impulsivity Subscale Score	Mean (SD)	15.7 (6.39)	15.8 (5.73)	14.8 (5.78)	15.1 (6.36)	15.2 (5.95)	15.3 (6.06)
Baseline ADHD-RS-IV Inattention Subscale Score	Mean (SD)	22.8 (3.01)	22.5 (3.48)	22.6 (3.18)	21.9 (3.44)	22.4 (3.37)	22.5 (3.29)
Baseline CGI Severity Rating	Mean (SD)	4.5 (0.62)	4.5 (0.55)	4.5 (0.64)	4.5 (0.60)	4.5 (0.60)	4.5 (0.60)
YQOL-R Total Perceptual Score at Baseline	Mean (SD)	79.2 (11.08)	79.3 (10.03)	80.3 (10.76)	78.8 (15.38)	79.5 (12.26)	79.4 (11.96)

Source: Listings 2.1, 4 and 7.1

Subject Disposition

A total of 314 subjects were randomized. 310 received at least one dose of lisdexamfetamine dimesylate and placebo (safety population). Four subjects (010-005, 012-001, 034-010, and 038-006) were not dosed. One subject (020-005) did not have a post-Baseline ADHD-RS-IV assessment. Therefore, a total of 309 subjects were included in the full analysis set (FAS). However, only 299 subjects were included in the efficacy analysis because 10 subjects did not have post-Baseline assessment and only had post-treatment assessment according to the statistician Dr. Yang Yang.

A total of 265 subjects (84.4%) completed the trial. 237 subjects in the FAS completed the trial and were compliant with the protocol. 49 subjects terminated the trial early (15.6%). Lack of efficacy was the most common single reason for discontinuation for the placebo. AE was the most common reason for discontinuation for the 70 mg group. The disposition of subjects is summarized in **Table 5**.

Table 5: Disposition of All Subjects in Study 305

Enrolled	Placebo	SPD489 Assigned Treatment			SPD489 All Doses	Overall
		30mg	50mg	70mg		
	N=79	N=78	N=79	N=78	N=235	N=314
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	79 (100.0)	78 (100.0)	79 (100.0)	78 (100.0)	235 (100.0)	314 (100.0)
Safety population	77 (97.5)	78 (100.0)	77 (97.5)	78 (100.0)	233 (99.1)	310 (98.7)
Full analysis set	77 (97.5)	78 (100.0)	76 (96.2)	78 (100.0)	232 (98.7)	309 (98.4)
Study completers	69 (87.3)	63 (80.8)	66 (83.5)	67 (85.9)	196 (83.4)	265 (84.4)
Per-protocol population	64 (81.0)	56 (71.8)	60 (75.9)	57 (73.1)	173 (73.6)	237 (75.5)
Early termination	10 (12.7)	15 (19.2)	13 (16.5)	11 (14.1)	39 (16.6)	49 (15.6)
Reason for discontinuation:						
Adverse event(s)	1 (1.3)	3 (3.8)	3 (3.8)	4 (5.1)	10 (4.3)	11 (3.5)
Protocol non-adherence/ subject non-compliance	3 (3.8)	2 (2.6)	2 (2.5)	0	4 (1.7)	7 (2.2)
Refused further participation in the study	0	0	2 (2.5)	2 (2.6)	4 (1.7)	4 (1.3)
Lost to follow-up	1 (1.3)	1 (1.3)	1 (1.3)	3 (3.8)	5 (2.1)	6 (1.9)
Lack of Efficacy	4 (5.1)	4 (5.1)	2 (2.5)	0	6 (2.6)	10 (3.2)
Other	1 (1.3)	5 (6.4)	3 (3.8)	2 (2.6)	10 (4.3)	11 (3.5)

Source: Section 14, Table 1.1.1

Concomitant Medication Use

A listing of prior, concomitant and post-treatment medications for the safety population in the submission (Appendix 16.2, Listing 2.5) was reviewed. Prohibited medications used by subjects which might have confounded the evaluation of efficacy were Benadryl (a sedating antihistamine which could reduce hyperactivity) taken by mouth as needed, melatonin taken once a day as a sleep aid (which might also reduce hyperactivity), and Strattera (a drug approved for ADHD).

Four subjects had taken Benadryl as a concomitant medication during the trial (two from lisdexamfetamine dimesylate 30mg group and two from 70mg group). Given the robust efficacy observed in this trial, it is unlikely that Benadryl use in these subjects would have substantially changed the efficacy result.

Also, three subjects (one from each of lisdexamfetamine dimesylate 30, 50 and 70mg group) had taken melatonin 1 tablet, PO, once a day prior to treatment. The use of melatonin was less likely to affect the efficacy results but might make AE of insomnia better.

One subject from lisdexamfetamine dimesylate 70mg group had taken Strattera prior to the Baseline and did not have enough washout period, which was considered as a protocol deviation for which the subject was discontinued the trial.

No other subjects have used other prohibited medications that could have confounded efficacy results such as other ADHD medications like Adderall or Ritalin. This reviewer concluded that it was unlikely that the concomitant medication use of Benadryl or melatonin during this trial had affected the overall final efficacy outcome.

Protocol Deviations

Clinical major protocol deviations were identified during the trial and were summarized in **Table 6**. A total of 40 subjects had major protocol deviations.

Twenty three subjects did not meet washout specifications. Eighteen of them took ADHD medications and did not meet washout specifications: Six subjects took Concerta (3 in 50mg group, 2 in 70mg group and 1 in placebo); four subjects took Vyvanse (2 from each 30mg and 50mg group); four subjects took Ritalin (3 in 30mg group and 1 in placebo); two subjects took Strattera from 70mg group, one subject in 30mg group took metadate and one in 50mg group took both Concerta and Methyphenidate prior to the treatment. All were from lisdexamfetamine dimesylate treatment group except two subjects. Since the use was prior to baseline, the baseline score would be affected and since efficacy was change from baseline, a biased result favoring lisdexamfetamine seems unlikely.

Ten subjects did not meet inclusion/exclusion criteria. Two of them (003-002 from placebo, 040-004 from 70mg group) did not meet the inclusion criteria - blood pressure within the 95th percentile at Screening and Baseline. These deviations were identified after the subjects had completed the trial. It's doubtful that high BP would have biased efficacy. Also, the numbers were balanced between drug and placebo, making bias less likely. Eight enrolled subjects met exclusion criteria: 1 subject in 70mg group had a known history of symptomatic cardiovascular disease; 5 subjects (1 in 70mg group, 3 in 50mg group and 1 in 30mg group) had a clinically significant EKG. These 5 subjects discontinued the trial; 1 subject in 30mg group failed to respond to adequate courses of amphetamine therapy. Subject 042-002 in 70mg group, included in the 23 subjects who failed to meet washout specifications, took excluded medication - Strattera so that he also met exclusion criteria. Subject 042-002 had early termination due to protocol deviations.

Of the remaining 8 subjects, 4 subjects (3 in 70mg group and 1 in 50mg group) had an overall treatment compliance that was <80% or >120%; 1 subject in 50mg group became pregnant during the study; 1 subject in placebo group inadvertently took 2 doses on the same day; and 1 subject in placebo group was tested positive for opiates and 1 in 30mg group was tested positive for cannabis at Visit 4.

In conclusion, these protocol deviations would probably not have biased efficacy in favor of the drug.

Table 6: Summary of Major Protocol Deviations (Safety Population)

	Placebo	SPD489			
		30mg	50mg	70mg	All Doses
	N= 77	N=78	N=77	N=78	N=233
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with major protocol deviations	5 (6.5)	11 (14.1)	12 (15.6)	12 (15.4)	35 (15.0)
Major protocol deviation:					
Failure to meet washout specifications	2 (2.6)	8 (10.3)	7 (9.1)	6 (7.7)	21 (9.0)
Did not meet inclusion criteria	1 (1.3)	0	0	1 (1.3)	1 (0.4)
Did not meet exclusion criteria	0	2 (2.6)	3 (3.9)	3 (3.8)	8 (3.4)
Overall treatment compliance is <80% or >120%	0	0	1 (1.3)	3 (3.8)	4 (1.7)
Overdose, abuse, or misuse of study medication[a]	1 (1.3)	0	0	0	0
Pregnancy	0	0	1 (1.3)	0	1 (0.4)
Other deviation	1 (1.3)	1 (1.3)	0	0	1 (0.4)

[a]Subject 033-010 (placebo) inadvertently took 2 doses of study medication on the same day.
Source: Section 14, Table 1.6

Efficacy Findings

Primary Efficacy Endpoint

The primary endpoint was the mean change from baseline to endpoint on the ADHD-RS-IV total score and it was analyzed by an LOCF ANCOVA. The sponsor's full analysis set (FAS) actually only included 299 subjects as shown in **Table 7.** The statistician Dr. Yang Yang found out that the sponsor actually excluded 10 retrieved dropout subjects (1 receiving placebo and 9 receiving lisdexamfetamine dimesylate) who were in the FAS but had one post-baseline ADHD-RS-IV measurement only after the final dose of treatment (post-treatment assessment). Therefore, the actual efficacy analysis set consisted of 299 subjects (placebo: 76; lisdexamfetamine dimesylate 30mg: 76; lisdexamfetamine dimesylate 50mg: 72; lisdexamfetamine dimesylate 70mg: 75) who had at least one post-baseline ADHD-RS-IV measurement during the double blind treatment phase.

There was a statistically significant difference between the treatment groups in favor of lisdexamfetamine dimesylate in the adjusted mean change from baseline to endpoint in the ADHD-RS-IV total score. Differences between all 3 treatment groups on this measure were statistically significant at endpoint and at every study visit.

Table 7 shows the analysis results of LS Mean (SE) change from baseline in the ADHD-RS-IV Total score for placebo and lisdexamfetamine dimesylate (all doses) at endpoint and at each study visit.

Table 7: Analysis of Change from Baseline in ADHD-RS-IV Total Score by Endpoint and at Each Visit (FAS).

	Baseline		Adjusted Change from Baseline						p-value[a]
	n	Mean (SD)	n	LS Mean (SE) Change	Difference in LS Means	95% CI	Effect Size	95% CI	
Endpoint									
Placebo	77	38.5 (7.11)	76	-12.8 (1.25)					
SPD489 30mg	78	38.3 (6.71)	76	-18.3 (1.25)	-5.5	(-9.7,-1.3)	-0.5	(-0.8,-0.2)	0.0056
SPD489 50mg	76	37.3 (6.33)	72	-21.1 (1.28)	-8.3	(-12.5,-4.1)	-0.8	(-1.1,-0.4)	<0.0001
SPD489 70mg	78	37.0 (7.30)	75	-20.7 (1.25)	-7.9	(-12.1,-3.8)	-0.7	(-1.1,-0.4)	<0.0001
Visit 1									
Placebo	77	38.5 (7.11)	76	-6.6 (1.00)					
SPD489 30mg	78	38.3 (6.71)	76	-12.2 (1.00)	-5.6	(-9.0,-2.3)	-0.6	(-1.0,-0.3)	0.0003
SPD489 50mg	76	37.3 (6.33)	72	-12.7 (1.03)	-6.1	(-9.5,-2.7)	-0.7	(-1.0,-0.4)	<0.0001
SPD489 70mg	78	37.0 (7.30)	75	-12.3 (1.01)	-5.7	(-9.1,-2.4)	-0.7	(-1.0,-0.3)	0.0002
Visit 2									
Placebo	77	38.5 (7.11)	75	-10.6 (1.13)					
SPD489 30mg	78	38.3 (6.71)	73	-15.5 (1.15)	-4.9	(-8.7,-1.1)	-0.5	(-0.8,-0.2)	0.0076
SPD489 50mg	76	37.3 (6.33)	71	-18.6 (1.16)	-8.0	(-11.9,-4.2)	-0.8	(-1.2,-0.5)	<0.0001
SPD489 70mg	78	37.0 (7.30)	71	-18.3 (1.16)	-7.8	(-11.6,-3.9)	-0.8	(-1.1,-0.5)	<0.0001
Visit 3									
Placebo	77	38.5 (7.11)	75	-12.0 (1.17)					
SPD489 30mg	78	38.3 (6.71)	69	-17.7 (1.22)	-5.7	(-9.7,-1.7)	-0.6	(-0.9,-0.2)	0.0025
SPD489 50mg	76	37.3 (6.33)	70	-19.9 (1.21)	-7.9	(-11.9,-3.9)	-0.8	(-1.1,-0.4)	<0.0001
SPD489 70mg	78	37.0 (7.30)	70	-21.5 (1.21)	-9.6	(-13.5,-5.6)	-0.9	(-1.3,-0.6)	<0.0001
Visit 4									
Placebo	77	38.5 (7.11)	67	-13.7 (1.27)					
SPD489 30mg	78	38.3 (6.71)	62	-20.2 (1.32)	-6.4	(-10.7,-2.1)	-0.6	(-1.0,-0.3)	0.0016
SPD489 50mg	76	37.3 (6.33)	65	-21.1 (1.29)	-7.4	(-11.6,-3.1)	-0.7	(-1.1,-0.4)	0.0002
SPD489 70mg	78	37.0 (7.30)	65	-21.2 (1.29)	-7.4	(-11.7,-3.1)	-0.7	(-1.1,-0.4)	0.0002

[a] p-value from Dunnett's test compares active doses to Placebo

SE = Standard Error of the Mean; ES = Effect Size; Diff = Difference

Note: Endpoint is the last post-randomization treatment week for which a valid ADHD-RS-IV total score is obtained. Adjusted Effect size is calculated as LS mean difference/square root of mean square error and 95% CI of the effect size is based on the normal distribution of the estimators of effect size. A negative difference in LS Mean (Active - Placebo) indicates a positive effect of the active treatment over the placebo.

Source: Section 14, Table 2.1.1.2

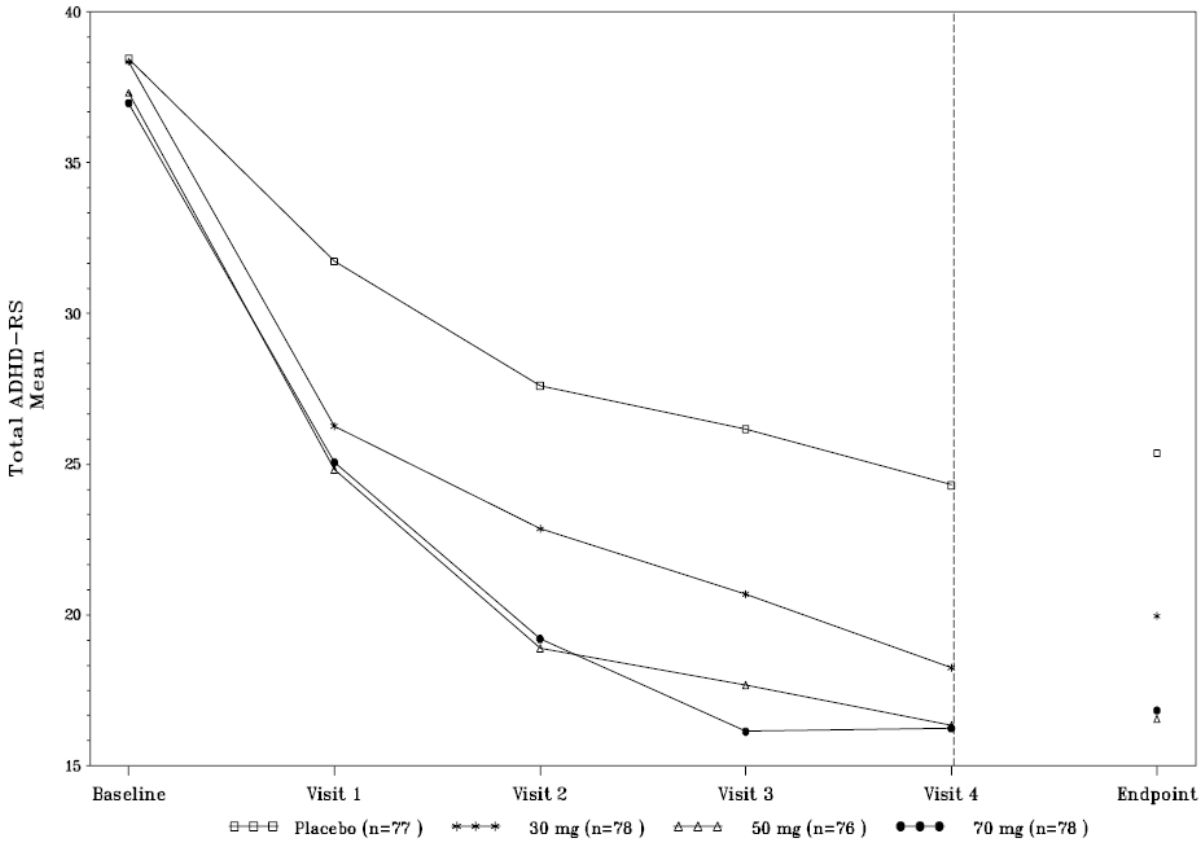
There was a consistent and statistically significant reduction in the ADHD-RS-IV total score for the three lisdexamfetamine dimesylate treatment groups (30, 50 and 70mg) compared to placebo at Visit 1 to Visit 4 and at LOCF endpoint (**Figure 1**). Although this study was not designed to evaluate the dose-response relationship, it appeared that there seemed to be a dose-response in the change from baseline in ADHD-RS-IV total score. However, the 50 and 70mg were not statistically superior to 30mg at visit 4 according to our statistician Yang Yang's calculation.

III. Conclusions

All three lisdexamfetamine dimesylate dose strengths (30, 50 and 70mg) were statistically superior to placebo at endpoint in the primary measure - the ADHD-RS-IV total score.

The statistical reviewer, Yang Yang, Ph.D., has confirmed the efficacy results.

Figure 1: Mean ADHD-RS-IV Total Score by Visit (FAS)



Source: Study-305 CSR, Section 15, Figure 1.

C. Crosscutting Issues

I. Subgroup Analyses

ADHD-RS-IV Hyperactivity/Impulsivity Score

Similar to the results for the ADHD-RS-IV Total score, the mean change from Baseline in the ADHD-RS-IV Hyperactivity/Impulsivity subscale score for all 3 lisdexamfetamine dimesylate treatment groups was statistically significantly different from placebo at endpoint and at all study visits.

ADHD-RS-IV Inattention Score

Similar to the results for the ADHD-RS-IV Total score, the mean change from Baseline in the ADHD-RS-IV Inattention subscale score for all 3 lisdexamfetamine dimesylate treatment groups was statistically significantly different from placebo at endpoint and at all study visits.

Age

The ADHD-RS-IV Total Scores, Hyperactivity/Impulsivity Subscale Score and Inattention Subscale Score were analyzed at endpoint and each visit by age groups: 13 or 14 years old and 15 to 17 years old. Consistent with the primary efficacy result, the mean (SD) ADHD-RS-IV Total score consistently decreased from Visit 1 to Visit 4, and

at every visit there was a consistently larger reduction in lisdexamfetamine dimesylate treatment groups compared to placebo regardless of age group.

Gender

Consistent with the primary efficacy result, the mean (SD) ADHD-RS-IV Total score consistently decreased from Visit 1 to Visit 4 for both males and females and at every visit there was a consistently larger reduction in lisdexamfetamine dimesylate treatment groups compared to placebo. For males, the mean (SD) change in ADHD-RS-IV Total score at endpoint was -12.3 (10.37) for placebo and -20.5 (11.84) for lisdexamfetamine dimesylate (all doses). For females, the mean (SD) change in ADHD-RS-IV Total score at endpoint was -14.4 (11.48) for placebo and -18.5 (10.37) for lisdexamfetamine dimesylate (all doses). It appeared that male subjects had greater improvement in ADHD-RS-IV Total score compared to placebo.

Race

Consistent with the primary efficacy result, the mean (SD) ADHD-RS-IV Total score consistently decreased from Visit 1 to Visit 4 for both whites and non-whites, and at every visit there was a consistently larger reduction in lisdexamfetamine dimesylate treatment groups compared to placebo. For whites, the mean (SD) change in ADHD-RS-IV Total score at endpoint was -12.9 (10.57) for placebo and -19.9 (11.49) for lisdexamfetamine dimesylate (all doses). For non-whites, the mean (SD) change in ADHD-RS-IV Total score at endpoint was -13.2 (11.98) for placebo and -20.0 (11.38) for lisdexamfetamine dimesylate (all doses).

The statistician Dr. Yang Yang has analyzed the data using SAS 9.2, 2010 and has confirmed the conclusions above.

II. Dose Response

The efficacy results appeared to have a dose-response in the change from baseline in ADHD-RS-IV total score (**Figure 2).** However, 50 and 70mg were not superior to 30mg at Visit 4 according to our statistical analysis.

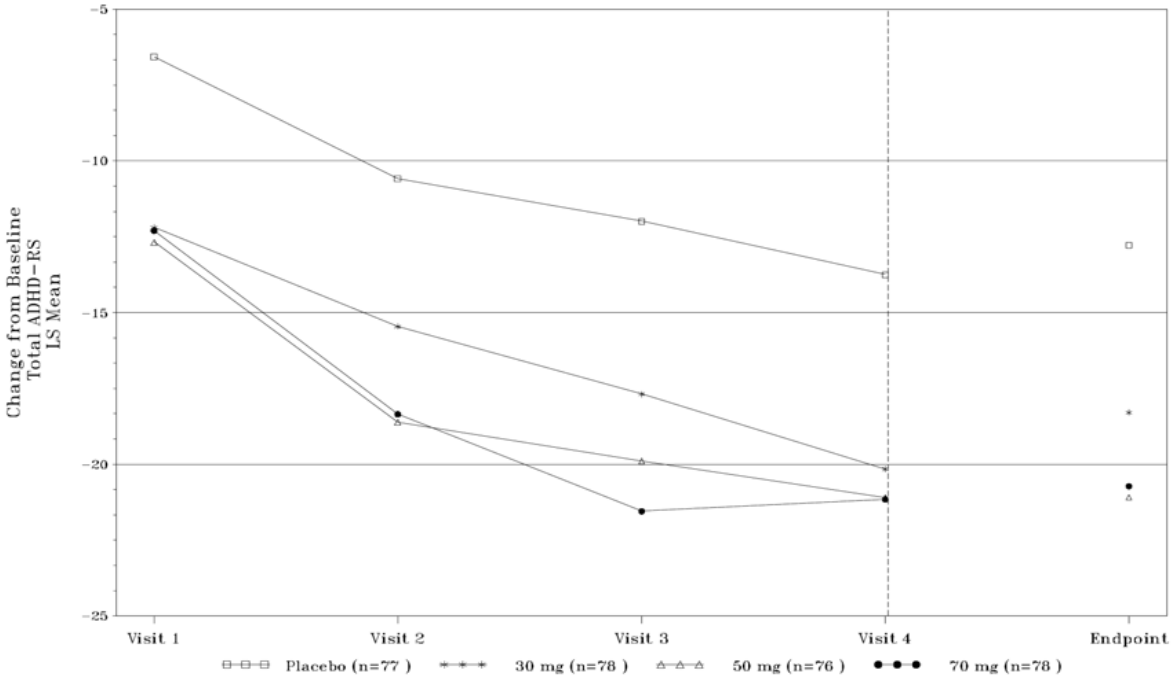
In Visit 1: Subjects in all lisdexamfetamine dimesylate groups have received a 30mg daily dose for 1 week. All three lisdexamfetamine dimesylate groups showed a similar improvement in ADHD-RSIV total score relative to placebo.

In Visit 2: All subjects in lisdexamfetamine dimesylate 50mg and 70mg groups have received 50mg for 1 week. Both the lisdexamfetamine dimesylate 50mg and 70mg groups showed greater improvement than the lisdexamfetamine dimesylate 30mg group compared to placebo in ADHD-RS-IV Total score.

In Visit 3: The subjects in lisdexamfetamine dimesylate 70mg group have received 70 mg for 1 week. Subjects receiving lisdexamfetamine dimesylate 70mg showed greater improvement relative to placebo than subjects receiving lisdexamfetamine dimesylate 50mg, who showed greater improvement than subjects receiving lisdexamfetamine dimesylate 30mg.

In Visit 4: Subjects have received 30, 50, and 70mg daily dose in the lisdexamfetamine dimesylate 30, 50 and 70mg group respectively. 70mg group did not show superiority than 50mg group at this visit.

Figure 2: LS Mean Change from Baseline in ADHD-RS-IV Total by Visit



Source: Sponsor's Report Body; Study SPD489-305 Module 5; Figure 4

III. Key Secondary Endpoints

The CGI-I scale was the key secondary efficacy measure. The CGI-S was measured at Baseline. At each visit after Baseline, the Investigator rated the improvement in a subject's condition using the CGI-I assessment. At all visits, for all dose strengths, lisdexamfetamine dimesylate treatment resulted in statistically significant improvement measured by CGI-I compared to placebo. **Table 8** shows the results of analysis of continuous CGI-I score at endpoint and at each visit.

Table 8: Analysis of Continuous CGI-I Score (Full Analysis Set)

		Assigned Treatment			
Visit	Statistic	Placebo (N= 77)	SPD489-30 mg (N= 78)	SPD489-50 mg (N= 76)	SPD489-70 mg (N= 78)
Endpoint[1]	n	76	76	72	75
	LS Mean (SE)[2]	2.9 (0.12)	2.3 (0.12)	2.0 (0.12)	2.0 (0.12)
	Diff (95% CI)		-0.5 (-0.9, -0.1)	-0.9 (-1.3, -0.5)	-0.9 (-1.3, -0.5)
	p-value[3]		0.0038	<0.0001	<0.0001
Visit 1 (Day 7)	n	76	76	72	75
	LS Mean (SE)[2]	3.5 (0.10)	2.9 (0.10)	2.6 (0.10)	2.7 (0.10)
	Diff (95% CI)		-0.5 (-0.9, -0.2)	-0.8 (-1.2, -0.5)	-0.7 (-1.0, -0.4)
	p-value[3]		0.0005	<0.0001	<0.0001
Visit 2 (Day 14)	n	75	73	71	71
	LS Mean (SE)[2]	3.0 (0.11)	2.6 (0.11)	2.2 (0.12)	2.2 (0.12)
	Diff (95% CI)		-0.4 (-0.8, -0.1)	-0.9 (-1.3, -0.5)	-0.8 (-1.2, -0.5)
	p-value[3]		0.0192	<0.0001	<0.0001
Visit 3 (Day 21)	n	75	69	70	70
	LS Mean (SE)[2]	2.9 (0.12)	2.4 (0.12)	2.1 (0.12)	1.9 (0.12)
	Diff (95% CI)		-0.5 (-0.9, -0.1)	-0.7 (-1.1, -0.3)	-0.9 (-1.3, -0.5)
	p-value[3]		0.0162	<0.0001	<0.0001
Visit 4 (Day 28)	n	67	62	65	65
	LS Mean (SE)[2]	2.8 (0.12)	2.1 (0.13)	1.9 (0.12)	1.9 (0.12)
	Diff (95% CI)		-0.6 (-1.1, -0.2)	-0.8 (-1.3, -0.4)	-0.9 (-1.3, -0.5)
	p-value[3]		0.0009	<0.0001	<0.0001

[1] Endpoint is defined as the last post-randomization treatment week for which a valid CGI-I assessment is obtained.
[2] LS Mean and p-value are based on ANCOVA model for the CGI-I score, treatment groups as a fixed effect and CGI-S as a covariate.
[3] P-value from Dunnett's test to compare active doses to Placebo.
SE = Standard Error of the Mean; Diff = Difference.
Source: Listing 4

IV. Effect Size

The effect size of all lisdexamfetamine dimesylate treatment groups at every visit and endpoint is shown in the previous table (**Table 7)** Adjusted effect size was calculated as LS mean difference/square root of mean square error and 95% CI of the effect size was based on the normal distribution of the estimators of effect size. A negative difference in LS Mean (Active - Placebo) indicated a positive effect of the active treatment over the placebo.

V. Long-Term Efficacy

A long-term study (Study 306) entitled "A Phase III, Open-Label, Extension, Multi-center, Safety and Efficacy Study of lisdexamfetamine dimesylate (LDX) in Adolescents aged 13-17 with Attention Deficit/Hyperactivity Disorder (ADHD)" is being conducted by the sponsor. The efficacy results of Study-306 are not yet available.

VI. Pediatric Development

The application has been taken to the Pediatric Review Committee (PeRC) meeting. PeRC agreed with DPP's assessment that this study has fulfilled the Post Marketing Commitment (PMC).

D. Efficacy Conclusion

Efficacy analysis of the study SPD489-305 in adolescent subjects aged 13-17 with ADHD showed that treatment with all three dose strengths of lisdexamfetamine dimesylate (30, 50 and 70mg) is efficacious in improving the symptoms of ADHD in adolescents, as demonstrated by the results on the primary endpoint, ADHD-RS-IV Total Score.

In this trial, lisdexamfetamine dimesylate showed clinically meaningful and statistically significant improvement compared to placebo at every visit and at endpoint on the primary efficacy measure.

In this trial, the treatment differences of the mean CGI-I score achieved statistically significant improvement for all lisdexamfetamine dimesylate treated groups compared to placebo at endpoint.

There appeared to be a dose-response pattern with respect to efficacy for the primary endpoint in the first 3 weeks of the treatment. However, no additional benefit from the 70 mg dose over the 50mg dose was observed at Week 4.

None of the treatment-by-subgroup interaction terms (age, gender and race) were statistically significant.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A Placebo-controlled adolescent ADHD trial (SPD489-305) was used in this safety review.

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. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

A SAE was any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a cancer
- Is a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Is an important medical event (including pregnancy or overdose)

The sponsor's coding of verbatim adverse event terms to MedDRA preferred terms was audited by examination of ae.xpt in the dataset. My comparison of the verbatim and preferred terms for all subjects in this file revealed no significant coding errors or deficiencies.

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

All Data were from the trial SPD489-305.

7.2 Adequacy of Safety Assessments

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

A total of 233 adolescent subjects received lisdexamfetamine dimesylate in this ADHD adolescent clinical trial.

An overall summary of drug exposure is presented in **Table 9**. The mean (SD) length of exposure was 25.8 (6.40) days for subjects in lisdexamfetamine dimesylate treatment groups and 27.1 (4.20) days for subjects in the placebo group.

Table 9: Overall Summary of Drug Exposure (Safety Population)

Number of Subjects	Placebo	Lisdexamfetamine Dimesylate Assigned Treatment			Lisdexamfetamine Dimesylate
		30mg	50mg	70mg	All Doses
	N=77 n (%)	N=78 n (%)	N=77 n (%)	N=78 n (%)	N=233 n (%)
Length of Exposure					
Mean (SD) (days)	27.1 (4.20)	25.8 (6.29)	25.6 (6.74)	26.0 (6.23)	25.8 (6.40)
Category (days)					
1-7	2 (2.6)	3 (3.8)	4 (5.2)	4 (5.1)	11 (4.7)
8-14	0	4 (5.1)	3 (3.9)	2 (2.6)	9 (3.9)
15-21	2 (2.6)	7 (9.0)	2 (2.6)	3 (3.8)	12 (5.2)
22-28	53 (68.8)	47 (60.3)	53 (68.8)	52 (66.7)	152 (65.2)
>28	20 (26.0)	17 (21.8)	15 (19.5)	17 (21.8)	49 (21.0)

Length of exposure at a visit = last dose date - first dose date + 1 at the visit.
Length of exposure of a subject to a dose is calculated as the sum over all visits of the lengths of exposure to the dose. Percentages are based on the number of subjects in safety population in each group.
Source: Section 14, Table 3.1.1

7.2.2 Explorations for Dose Response

This reviewer has examined the summary of treatment-emergent adverse events reported by >2% of subjects in any one treatment group by system organ class and preferred term in the safety population. The incidence of two common AEs (weight decrease and insomnia) and a few other AEs appeared to be dose-related.

Weight Decrease

The proportion of subjects with weight decrease was 3.8%, 9.1% and 15.4% in the 30, 50 and 70mg lisdexamfetamine dimesylate treatment groups, respectively, while there was no weight decrease in the placebo group. The mean weight decrease was 1.2, 1.9 and 2.3 kg at endpoint in the 30, 50 and 70mg lisdexamfetamine dimesylate treatment groups, respectively while the placebo group had a mean weight gain 0.9 kg.

Insomnia
The proportion of subjects with insomnia was 9.0%, 10.4% and 14.1% in the 30, 50 and 70mg treatment groups, respectively, while only 3.9% of the placebo group reported insomnia.

Other AEs
Diarrhea, nausea, vomiting and dizziness have demonstrated less clear evidence of dose response. The proportions of subjects with these AEs increased with the increase of lisdexamfetamine dimesylate treatment dose.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *In Vitro* testing was conducted in study.

7.2.4 Routine Clinical Testing

Routine clinical testing includes deaths, adverse events (AEs) which include serious AEs and common AEs, safety laboratory tests (hematology, clinical chemistry, urinalysis and serum beta HCG pregnancy test for females), vital signs including systolic blood pressure (SBP) and diastolic blood pressure (DBP), body weight, height and EKG. These routine clinical testing was felt to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance, and interaction workup was conducted in study.

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

CNS stimulants are associated with decreased appetite, weight loss, increased blood pressure and EKG changes. Weight, BP, pulse and EKG were assessed during the trial. CNS stimulants are also associated with psychiatric adverse events, seizure, visual disturbance and tics which were assessed via AEs and physical exams.

7.3 Major Safety Results

7.3.1 Deaths

No death was reported during the conduct of this ADHD trial.

7.3.2 Nonfatal Serious Adverse Events

No SAEs were reported during the conduct of this ADHD trial.

7.3.3 Dropouts and/or Discontinuations

In this adolescent ADHD trial, the overall dropout rate was 15.6% (49/314). The lowest dropout rate was from the placebo group: 12.7% (10/79). The dropout rate of the 30mg, 50mg and 70mg group was 19.2 (15/78), 16.5% (13/79) and 14.1% (11/78) respectively. The overall dropout rates actually decreased with the increase of lisdexamfetamine dimesylate doses. Lack of efficacy was the most common reason of dropout for the placebo group [5.1% (4/79)]. AEs were the most common reason of dropout for the 70 mg group [5.1% (4/78)].

There were a total of 16 subjects who were reported as discontinuing from the trial due to an AE.

Five of these 16 subjects discontinued due to an abnormal baseline EKG (prolonged QT, ventricular hypertrophy, episodic P waves, 1st degree AV block, and PR prolongation). They were identified by the Sponsor as not suitable for study participation based on their Screening/Baseline EKG results and were discontinued after they have started lisdexamfetamine dimesylate treatment. These five subjects should have been excluded from the trial at baseline.

Eleven subjects discontinued due to Treatment Emergent Adverse Events (TEAEs) as shown in **Table 10**. One was from placebo group due to irritation/agitation. Other 10 subjects were from the lisdexamfetamine dimesylate treatment groups due to irritability (2 subjects), abnormal EKG (2 subjects), aggression, decreased appetite, dermatillomania/onychophagia, dyspnea, insomnia and mood swings (1 subject).

The details of 2 discontinuations due to abnormal EKGs are described in 7.4.4 Electrocardiograms (EKGs).

It is worth to mention that one discontinuation was due to dyspnea. According to the narrative summary, subject (018-010) was a 17 years old white male diagnosed with ADHD (predominantly inattentive subtype). He had past medical history of peanut allergy and seasonal allergies. It was unknown whether he had past medical history of asthma. He did not report taking any prior medications. The physical examination was normal at study entry. He was assigned to the lisdexamfetamine 70mg treatment group. Fifteen days after he started lisdexamfetamine, he began experiencing “intermittent moderate dyspnea”. Lisdexamfetamine was discontinued after 22 days of exposure. His shortness of breath resolved 9 days after he discontinued lisdexamfetamine. His respiratory rate was 16 at all visits (Baseline, Visit 1, 2, 3 and ET). His other vital signs and EKGs were all normal. The investigator considered dyspnea to be drug-related. This reviewer disagreed with the investigator’s judgment because of 2 reasons: 1, the subject had normal respiratory rate at all visits. 2. The subject’s shortness of breath did not resolve until 9 days after he had discontinued the drug.

7.3.4 Significant Adverse Events

No other clinically significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

No submission specific primary safety concerns were identified.

Table 10: Summary of Discontinuation Due to TEAEs

Subject Number	Gender/ Age/Race	Preferred term/ AE text	Dose at Onset (mg)	Onset Day	Frequency	Intensity	Relationship	Reason for Discontin-uation	Effect on Dosing
Placebo Treatment Group									
026-004	M/15/W	Irritability/ Irritability	0	5	One Episode	Severe	Related/ Resolved	AE: increasing irritability and agitation	Discontinued
		Agitation/ Agitation	0	5	One Episode	Severe	Related/ Resolved		Discontinued
SPD489 Treatment Groups									
001-003	M/15/W	Electrocardiogram abnormal/ QTcB change greater than 60, ECG abnormal clinically significant	30	5	One Episode	Moderate	Related/ Unresolved	AE: QTcB change > 60, abnormal ECG	Discontinued
002-007	M/15/W	Decreased appetite/ Decreased appetite	30	1	One Episode	Moderate	Related/ Resolved	AE: decreased appetite	Discontinued
		Irritability/ Irritability[a]	30	1	One Episode	Moderate	Related/ Resolved		Discontinued
016-002	F/14/W	Onychophagia/ Nail biting	50	11	Intermittent	Moderate	Related/	AE: nail	Discontinued
016-007	F/16/W	Insomnia/ Insomnia	50	14	Continuous	Severe	Related/ Resolved	AE: insomnia	Discontinued
		Pregnancy/ Pregnancy[a]	50	22	Continuous	Mild	Not Related/ Unresolved		Discontinued
018-010	M/17/W	Dyspnoea/ Shortness of breath	70	16	Intermittent	Moderate	Related/ Resolved	AE: shortness of breath	Discontinued
020-012	F/13/B	Irritability/ Severe irritability	30	3	Continuous	Severe	Related/ Resolved	AE: severe irritability and labile mood	Discontinued
		Mood swings/ Labile mood	30	3	Continuous	Severe	Related/ Resolved		Discontinued
029-004	M/13/W	Electrocardiogram abnormal/ abnormal ECG	30	6	One Episode	Mild	Related/ Resolved	AE: abnormal ECG	Discontinued
033-009	M/16/B	Aggression/ Aggression	30	9	One Episode	Moderate	Related/ Resolved	AE: aggression	None
035-003	F/13/W	Irritability/ Irritability	70	15	Intermittent	Moderate	Related/ Unresolved	AE: irritability	Discontinued
045-010[b]	M/17/W	Decreased appetite/ Decreased appetite	30	1	Intermittent	Severe	Related/ Resolved	Refused further participation in the study	Discontinued
		Insomnia/ Insomnia	30	1	Continuous	Severe	Related/ Resolved		Discontinued

[a]Adverse event associated with discontinuation of study medication, but not the AE reported as leading to discontinuation due to an adverse event.
[b]For subject 045-010, the reason for discontinuation was “refused further participation in the study”
Source: Appendix 16.2, Listings 1.4, 5.1, and 5.5

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 11: Incidence of TEAEs Occurred ≥2% in Lisdexamfetamine Dimesylate Treatment Groups and Placebo Group (Safety Population)

	Placebo	SPD489 Assigned Treatment			SPD489 All Doses
		30mg	50mg	70mg	
	N=77	N=78	N=77	N=78	N=233
	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders					
Lymphadenopathy	2 (2.6)	0	0	0	0
Cardiac disorders					
Palpitations	1 (1.3)	2 (2.6)	1 (1.3)	2 (2.6)	5 (2.1)
Gastrointestinal disorders					
Abdominal pain upper	3 (3.9)	1 (1.3)	0	1 (1.3)	2 (0.9)
Diarrhoea	2 (2.6)	1 (1.3)	2 (2.6)	3 (3.8)	6 (2.6)
Dry mouth	1 (1.3)	0	6 (7.8)	4 (5.1)	10 (4.3)
Nausea	2 (2.6)	1 (1.3)	3 (3.9)	5 (6.4)	9 (3.9)
Stomach discomfort	2 (2.6)	1 (1.3)	2 (2.6)	0	3 (1.3)
Toothache	1 (1.3)	3 (3.8)	0	1 (1.3)	4 (1.7)
Vomiting	4 (5.2)	0	1 (1.3)	2 (2.6)	3 (1.3)
General disorders and administration site conditions					
Fatigue	2 (2.6)	4 (5.1)	2 (2.6)	4 (5.1)	10 (4.3)
Irritability	3 (3.9)	6 (7.7)	2 (2.6)	8 (10.3)	16 (6.9)
Pyrexia	0	0	0	2 (2.6)	2 (0.9)
Infections and infestations					
Nasopharyngitis	1 (1.3)	2 (2.6)	4 (5.2)	1 (1.3)	7 (3.0)
Pharyngitis streptococcal	0	0	2 (2.6)	0	2 (0.9)
Sinusitis	3 (3.9)	0	1 (1.3)	0	1 (0.4)
Upper respiratory tract infection	6 (7.8)	2 (2.6)	4 (5.2)	4 (5.1)	10 (4.3)
Investigations					
Electrocardiogram abnormal	1 (1.3)	2 (2.6)	1 (1.3)	0	3 (1.3)
Weight decreased	0	3 (3.8)	7 (9.1)	12 (15.4)	22 (9.4)
Metabolism and nutrition disorders					
Anorexia	0	1 (1.3)	2 (2.6)	1 (1.3)	4 (1.7)
Decreased appetite	2 (2.6)	29 (37.2)	21 (27.3)	29 (37.2)	79 (33.9)
Musculoskeletal and connective tissue disorders					
Back pain	2 (2.6)	0	0	3 (3.8)	3 (1.3)
Myalgia	2 (2.6)	0	0	0	0
Nervous system disorders					
Dizziness	3 (3.9)	1 (1.3)	4 (5.2)	5 (6.4)	10 (4.3)
Headache	10 (13.0)	9 (11.5)	13 (16.9)	12 (15.4)	34 (14.6)
Somnolence	2 (2.6)	0	0	1 (1.3)	1 (0.4)
Tremor	0	0	2 (2.6)	2 (2.6)	4 (1.7)
Psychiatric disorders					
Affect lability	0	2 (2.6)	0	1 (1.3)	3 (1.3)
Initial insomnia	0	3 (3.8)	1 (1.3)	2 (2.6)	6 (2.6)
Insomnia	3 (3.9)	7 (9.0)	8 (10.4)	11 (14.1)	26 (11.2)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	0	1 (1.3)	0	2 (2.6)	3 (1.3)
Epistaxis	0	3 (3.8)	0	0	3 (1.3)
Nasal congestion	1 (1.3)	1 (1.3)	0	5 (6.4)	6 (2.6)
Vascular disorders					
Orthostatic hypotension	0	0	1 (1.3)	2 (2.6)	3 (1.3)

Source: Section 14, Table 3.2.4.2

Among the TEAEs shown in **Table 11**, decreased appetite, insomnia and decreased weight were common and drug-related (incidence ≥ 5% and at a rate at least twice

placebo). Although the incidence rate of nasopharyngitis and nasal congestion was ≥ 5% and at least twice placebo, the sponsor did not believe that nasopharyngitis and nasal congestion were drug-related because they were most likely caused by viral infection. I agreed with the sponsor's judgment.

7.4.2 Laboratory Findings

a. Extent of Laboratory Testing

Routine assays of hematology, serum chemistry, and urinalysis variables were conducted at Screening and Visit 4 or early termination (ET) visit.

b. Potentially Clinically Significant Laboratory Changes

The sponsor has set criteria (please refer to **Table 22** for chemistry and **Table 23** for hematology) to identify treatment emergent potentially clinically significant (PCS) laboratory changes in subjects with normal baseline values. My analyses focused on comparison of the lisdexamfetamine dimesylate and placebo treatment groups in terms of the proportions of these subjects meeting those criteria during this adolescent ADHD trial. No urine outlier analysis was found in submission.

1) Serum Chemistry

The following table lists the chemistry outliers in Study 305. No chemistry outlier was seen in placebo at the endpoint. The detailed outlier information is shown in **Table 24**.

Table 12: Clinically Significant Chemistry Outliers by Study Defined Abnormal Lab Value Criteria at Endpoint (Safety Population)

Study 305: Chemistry Outliers												
	Placebo			30mg			50mg			70mg		
	N	n	%	N	n	%	N	n	%	N	n	%
↑Bilirubin	0	72	0	0	67	0	1	68	1.5	2	66	3.0
↑ALT	0	72	0	0	67	0	0	68	0	1	66	1.5
↑Glucose	0	72	0	1	66	1.5	1	66	1.5	1	66	1.5
↓ Glucose	0	72	0	2	66	3.0	0	68	0	0	66	0
↑Potassium	0	72	0	0	67	0	2	68	3.0	0	66	0

N=number of subjects with an outlying value.
n=total number of subjects with a lab value at endpoint.
%= N/n x 100%.

Three subjects (1 in 50mg and 2 in 70mg group) had elevated bilirubin (all were 1.7mg/dL) at endpoint. None of them had jaundice or elevated ALT or AST. One subject in 70mg group had elevated ALT (77U/L) at endpoint. No ALT follow-up was found in the submission. The other liver function test was normal for this subject.

The clinical significance of elevated and decreased serum glucose level was doubtful because it was not specified in the protocol whether or not the glucose was fasting.

Two subjects had elevated serum potassium level. It was reassuring that these 2 subjects had a normal renal function test.

2) Hematology

The following table lists the hematology outliers in Study 305.

Table 13: Clinically Significant Hematology Outliers by Study Defined Abnormal Lab Value Criteria at Endpoint (Safety Population)

Study 305: Hematology Outliers												
	Placebo			30mg			50mg			70mg		
	N	n	%	N	n	%	N	n	%	N	n	%
↓leukocytes	0	71	0	0	66	0	1	68	1.5	0	64	0
↑leukocytes	0	71	0	0	66	0	1	68	1.5	0	64	0
↓ neutrophils	1	71	1.4	0	66	0	1	68	1.5	1	64	1.6
↓%neutrophils	0	71	0	0	66	0	0	68	0	1	64	1.6
↑%lymphocytes	0	71	0	1	66	1.5	0	68	0	0	64	0
↑%eosinophils	0	71	0	0	66	0	1	68	1.5	0	64	0
↑%eosinophils & ↓%neutrophils	0	71	0	0	66	0	0	68	0	1	64	1.6
↓leukocytes & ↓ neutrophils & ↓%neutrophils	0	71	0	0	66	0	1	68	1.5	0	64	0
↑%lymphocytes & ↓ neutrophils & ↓%neutrophils	0	71	0	0	66	0	0	68	0	1	64	1.6
↑%lymphocytes & ↓%neutrophils	1	71	1.4	0	66	0	0	68	0	0	64	0

N=number of subjects with an outlying value.
n=total number of subjects with a lab value at endpoint.
%= N/n x 100%.

3) Urinalysis

The sponsor did not conduct a standard analysis of outlier results for urinalysis. They did provide a shift analysis of urine specific gravity and urine pH only. They did analysis of cross-tabulated subjects by result category (normal, low, or high) at baseline versus endpoint. For both specific gravity and pH, there were no subjects in any treatment group who had a normal value at baseline and had a high or low result at endpoint. There were, however, a number of subjects (6% to 17% in each group) who had a normal value at baseline and were missing an endpoint value.

c. Median Change from Baseline in Laboratory Values

Between Baseline and endpoint, there were no notable differences in mean (SD) chemistry, hematology or urinalysis laboratory results nor were there any notable differences between results for subjects receiving placebo compared to subjects receiving lisdexamfetamine dimesylate.

d. Dropouts due to Abnormal Laboratory Findings

There were no dropouts due to abnormal laboratory findings.

7.4.3 Vital Sign Data

a. Vital Sign Assessments

Systolic blood pressure (BP), diastolic BP and pulse rate were measured at screening, baseline and each weekly visit during this 4 week double-blind adolescent ADHD trial. Blood pressure and pulse were determined after subjects have remained seated for at least 5 minutes.

b. Potentially Clinically Significant Vital Sign Changes

The sponsor identified subjects who experienced a potentially clinically significant (PCS) vital sign changes by the criteria shown in the table below. The percentage of subjects who met outlier criteria at endpoint for both SBP and DBP was generally similar across the placebo and lisdexamfetamine dimesylate treatment groups except DBP $\geq$ 80 mmHg was more common in 50 and 70mg group.

Table 14: Outlier Analysis for Blood Pressure at Endpoint (Safety Population)

		Assigned Treatment				
		Placebo N= 77 n (%)	SPD489 30mg N= 78 n (%)	SPD489 50mg N= 77 n (%)	SPD489 70mg N= 78 n (%)	SPD489 All Doses N=233 n (%)
Overall on-therapy (Endpoint)		76	76	72	75	223
Systolic BP						
<70mmHg		0	0	0	0	0
≥120mmHg		19 (25.0)	23 (30.3)	20 (27.8)	20 (26.7)	63 (28.3)
≥120mmHg and increase ≥10mmHg from Baseline		5 (6.6)	6 (7.9)	5 (6.9)	5 (6.7)	16 (7.2)
≥120mmHg	at 2 consecutive visits	16 (21.1)	11 (14.5)	16 (22.2)	11 (14.7)	38 (17.0)
	and increase ≥10mmHg from Baseline on 2 consecutive visits	3 (3.9)	2 (2.6)	2 (2.8)	1 (1.3)	5 (2.2)
	at 2 consecutive visits, one of which is Endpoint	16 (21.1)	11 (14.5)	16 (22.2)	11 (14.7)	38 (17.0)
	and increase ≥10mmHg from Baseline on 2 consecutive visits, one of which is Endpoint	3 (3.9)	2 (2.6)	2 (2.8)	1 (1.3)	5 (2.2)
≥130mmHg	at 2 consecutive visits	2 (2.6)	2 (2.6)	2 (2.8)	3 (4.0)	7 (3.1)
	and increase ≥10mmHg from Baseline on 2 consecutive visits	0	2 (2.6)	1 (1.4)	0	3 (1.3)
	at 2 consecutive visits, one of which is Endpoint	2 (2.6)	2 (2.6)	2 (2.8)	3 (4.0)	7 (3.1)
	and increase ≥10mmHg from Baseline on 2 consecutive visits, one of which is Endpoint	0	2 (2.6)	1 (1.4)	0	3 (1.3)
Diastolic BP						
<50mmHg		0	0	0	0	0
≥80mmHg		4 (5.3)	0	7 (9.7)	5 (6.7)	12 (5.4)
≥80mmHg and increase ≥10mmHg from Baseline		2 (2.6)	0	3 (4.2)	4 (5.3)	7 (3.1)
≥80mmHg	at 2 consecutive visits	0	0	2 (2.8)	2 (2.7)	4 (1.8)
	and increase ≥10mmHg from Baseline on 2 consecutive visits	0	0	1 (1.4)	2 (2.7)	3 (1.3)
	at 2 consecutive visits, one of which is Endpoint	0	0	2 (2.8)	2 (2.7)	4 (1.8)
	and increase ≥10mmHg from Baseline on 2 consecutive visits, one of which is Endpoint	0	0	1 (1.4)	2 (2.7)	3 (1.3)
≥90mmHg	at 2 consecutive visits	0	0	0	0	0
	and increase ≥10mmHg from Baseline on 2 consecutive visits	0	0	0	0	0

Source: Section 14, Table 3.4.3.1 and 3.4.3.2

For pulse, more subjects in lisdexamfetamine dimesylate treatment groups met outlier criteria than placebo.

Table 15: Outlier Analysis for Pulse at Endpoint (Safety Population)

		Assigned Treatment				SPD489 All Doses N=233 n (%)
		Placebo N= 77 n (%)	SPD489 30mg N= 78 n (%)	SPD489 50mg N= 77 n (%)	SPD489 70mg N= 78 n (%)	
Pulse						
<50bpm		0	0	1 (1.4)	0	1 (0.4)
≥100bpm		1 (1.3)	4 (5.3)	1 (1.4)	3 (4.0)	8 (3.6)
≥100bpm and increase ≥15mmHg from Baseline		1 (1.3)	3 (3.9)	1 (1.4)	3 (4.0)	7 (3.1)
≥100bpm	at 2 consecutive visits	0	1 (1.3)	0	2 (2.7)	3 (1.3)
	and increase ≥15bpm from Baseline on 2 consecutive visits	0	1 (1.3)	0	2 (2.7)	3 (1.3)
	at 2 consecutive visits including Endpoint	0	1 (1.3)	0	2 (2.7)	3 (1.3)
	and increase ≥15bpm from Baseline on 2 consecutive visits including Endpoint	0	1 (1.3)	0	2 (2.7)	3 (1.3)
≥110bpm	at 2 consecutive visits	0	0	0	0	0
	and increase ≥15bpm from Baseline on 2 consecutive visits	0	0	0	0	0
≥120bpm	at 2 consecutive visits	0	0	0	0	0
	and increase ≥15bpm from Baseline on 2 consecutive visits	0	0	0	0	0

Source: Section 14, Table 3.4.3.1 and 3.4.3.2

c. Mean Change from Baseline in Vital Sign Measures

A greater mean change from baseline was seen in DBP in lisdexamfetamine dimesylate 70mg group and in pulse in all lisdexamfetamine dimesylate treatment groups at the endpoint.

For SBP, mean changes were similar across the groups at the endpoint: approximately 2.2mmHg for placebo and -1.1, 0.3 and 2.3mmHg for lisdexamfetamine dimesylate 30, 50 and 70mg groups respectively.

For DBP, mean changes were 0.5mmHg for placebo and -0.6, 0.4 and 3.9mmHg for lisdexamfetamine dimesylate 30, 50 and 70mg groups respectively at the endpoint.

For pulse, mean changes were 0.8bpm for placebo and 4.7, 3.7 and 6.0bpm for 30, 50 and 70mg group respectively at the endpoint.

d. Dropouts due to Vital Sign Abnormalities

There were no dropouts due to vital sign abnormalities.

Weight

a. Weight Assessments

Weight was measured at screening, baseline and each weekly visit during this 4 week double-blind adolescent ADHD trial.

b. Potentially Clinically Significant Weight Changes

Fourteen subjects had ≥7% weight decrease. The largest percentage in weight decrease from Baseline to endpoint was 9.3% for subject 022-010 in lisdexamfetamine dimesylate 70mg group. This 13-year old white male had a weight 64.3kg (BMI 22.4) at Baseline and 58.3kg (BMI 19.7) at Visit 4 (study completion). **Table 16** shows the summary of PCI weight change category by visit and treatment (safety population).

Table 16: Summary of PCI Weight Change Category by Visit and Treatment (Safety Population)

		Assigned Treatment				
		Placebo	SPD489			
	Change in weight from Baseline	N= 77	30 mg N= 78	50 mg N= 77	70 mg N= 78	All Doses N=233
Visit 1	Number of subjects	76	76	72	75	223
	Decrease ≥7%, n(%)	0	0	0	0	0
	Increase ≥7%, n(%)	0	0	0	0	0
Visit 2	Number of subjects	75	73	71	71	215
	Decrease ≥7%, n(%)	0	0	1 (1.4)	1 (1.4)	2 (0.9)
	Increase ≥7%, n(%)	0	1 (1.4)	0	0	1 (0.5)
Visit 3	Number of subjects	75	69	70	70	209
	Decrease ≥7%, n(%)	0	0	2 (2.9)	6 (8.6)	8 (3.8)
	Increase ≥7%, n(%)	1 (1.3)	0	0	0	0
Visit 4	Number of subjects	67	62	65	65	192
	Decrease ≥7%, n(%)	0	0	4 (6.2)	5 (7.7)	9 (4.7)
	Increase ≥7%, n(%)	1 (1.5)	0	0	0	0
Endpoint	Number of subjects	76	76	72	75	223
	Decrease ≥7%, n(%)	0	0	4 (5.6)	5 (6.7)	9 (4.0)
	Increase ≥7%, n(%)	1 (1.3)	0	0	0	0

Source: Section 14, Table 3.4.3.1

c. Mean Weight Changes from Baseline

Overall weight decrease was only seen in lisdexamfetamine dimesylate treatment groups while the placebo had an overall weight gain. The mean weight decrease was 1.23, 1.92 and 2.26 kg in 30, 50 and 70 mg group respectively while the placebo had a mean weight gain 0.9 kg as shown in **Table 17.**

d. Dropouts due to Weight Changes

There were no dropouts due to weight changes.

Table 17: Mean (SD) and Mean (SD) Change from Baseline in Weight by Visit and Actual Dose (Safety Population)

		Actual Treatment			
		Placebo N= 78	SPD489 30mg N=232	SPD489 50mg N=145	SPD489 70mg N= 71
Weight (kg)					
Baseline	n	77	233		
	Mean (SD)	62.38 (13.347)	64.11 (13.261)		
	Min, Max	36.1, 100.2	36.8, 108.9		
Visit 1	n	77	222		
	Mean (SD)	62.62 (13.370)	62.94 (13.051)		
	Min, Max	35.8, 101.8	36.0, 108.9		
	Mean (SD) change	0.39 (0.820)	-1.00 (1.021)		
Visit 2	n	75	73	142	
	Mean (SD)	62.63 (13.550)	64.91 (15.206)	61.31 (11.697)	
	Min, Max	35.8, 102.3	39.0, 108.9	35.4, 98.0	
	Mean (SD) change	0.55 (1.138)	-0.88 (1.387)	-1.50 (1.251)	
Visit 3	n	75	69	70	70
	Mean (SD)	62.75 (13.558)	65.61 (14.939)	62.59 (12.797)	59.37 (10.324)
	Min, Max	35.4, 103.4	41.3, 108.9	35.2, 96.2	37.9, 85.3
	Mean (SD) change	0.68 (1.297)	-1.03 (1.231)	-1.73 (1.492)	-2.04 (1.536)
Visit 4	n	67	62	65	65
	Mean (SD)	63.03 (13.708)	66.42 (15.122)	62.05 (13.143)	58.80 (9.881)
	Min, Max	35.4, 103.9	41.3, 108.4	34.9, 95.5	38.1, 83.9
	Mean (SD) change	1.03 (1.333)	-1.35 (1.323)	-2.06 (1.772)	-2.36 (1.450)
Endpoint	n	76	81	72	70
	Mean (SD)	63.11 (13.577)	64.69 (14.634)	62.07 (12.699)	59.35 (10.224)
	Min, Max	35.4, 103.9	39.0, 108.4	34.9, 95.5	38.1, 83.9
	Mean (SD) change	0.90 (1.348)	-1.23 (1.260)	-1.92 (1.786)	-2.26 (1.575)

Source: Section 14, Table 3.4.2

7.4.4 Electrocardiograms (EKGs)

a. EKG Assessments

A twelve-lead EKG was measured at screening, baseline and weekly during this 4 week double-blind trial. Three EKGs were recorded with approximately 10 minutes between each EKG for the Baseline evaluation. The average of these 3 EKGs was used to calculate the mean change from Baseline.

According to Shire's phone communication on September 28, 2010, there were some missing EKG data: 37 EKGs (17 subjects, 15 of which were randomized and 2 were screened out) were not transmitted to the central reader. Those missing EKG data were subsequently submitted to the central reader. The revised EKG analysis was submitted to FDA on October 1, 2010. I have reviewed both the EKG analysis in the submission dated January 14, 2010 and the revised analysis including the missing EKGs dated October 1, 2010.

b. Potentially Clinically Significant EKG Changes

The sponsor identified subjects who experienced a potentially clinically significant (PCS) EKG change by the criteria shown in **Table 18**. The sponsor stated in the submission dated October 1, 2010 that the revised analysis including the missing EKGs did not add additional EKG outliers at endpoint which was confirmed by this reviewer.

Table 18: EKG Outlier Analysis at Endpoint (Safety Population)

	Placebo N= 77 n (%)	SPD489 30mg N= 78 n (%)	SPD489 50mg N= 77 n (%)	SPD489 70mg N= 78 n (%)
Outlier Criteria	**76**	**76**	**72**	**75**
Heart rate ≤50 bpm	2 (2.6)	0	0	1 (1.3)
≥100 bpm	0	4 (5.3)	1 (1.4)	2 (2.7)
PR Interval ≥200 msec	1 (1.3)	0	0	0
QRS Interval ≥120 msec	0	0	1 (1.4)	0
QT Interval ≥480 msec	0	0	0	0
QTcF ≥450 msec and <480 msec	0	1 (1.3)	0	0
≥480 msec and <500 msec	0	0	0	0
≥500 msec	0	0	0	0
QTcB ≥450 msec and <480 msec	1 (1.3)	0	2 (2.8)	0
≥480 msec and <500 msec	0	1 (1.3)	0	0
≥500 msec	0	0	0	0
Outlier Criteria -Change from Baseline				
QT ≥30-<60 msec	6 (7.9)	4 (5.3)	2 (2.8)	4 (5.3)
≥60 msec	0	2 (2.6)	1 (1.4)	0
QTcB ≥30-<60 msec	10 (13.2)	7 (9.2)	5 (6.9)	8 (10.7)
≥60 msec	0	1 (1.3)	3 (4.2)	1 (1.3)
QTcF ≥30-<60 msec	7 (9.2)	1 (1.3)	3 (4.2)	3 (4.0)
≥60 msec	0	1 (1.3)	2 (2.8)	0

Source: Section 14, Table 3.5.5 in the original submission.

c. Mean EKG Changes from Baseline to Endpoint

Heart rate, PR interval, QRS interval, QT interval had greater changes from baseline to endpoint in lisdexamfetamine dimesylate treatment groups compared to placebo.

For heart rate, mean changes were 1.1 bpm for placebo and 2.8, 3.1 and 2.0 bpm for lisdexamfetamine 30, 50 and 70mg groups respectively at endpoint.

For PR interval, mean changes were -0.5 msec for placebo and -1.2, -4.1 and -3.5 msec for lisdexamfetamine 30, 50 and 70mg groups respectively at endpoint.

For QRS interval, mean changes were 0.1 msec for placebo and 0.6, 0.5 and 0.2 msec for lisdexamfetamine 30, 50 and 70mg groups respectively at endpoint.

The QT interval decreased from Baseline in all lisdexamfetamine dimesylate treatment groups: -2.5, -3.9 and -2.4 for 30, 50 and 70 mg respectively while it increased 0.5 for placebo at endpoint.

For QTcB interval, mean changes were 4.0 msec for placebo and 6.5, 3.4 and 1.2 msec for lisdexamfetamine 30, 50 and 70mg groups respectively at endpoint.

For QTcF Interval, mean changes for the placebo was 2.8 msec and 3.2, 0.9 and -0.1 for 30, 50 and 70 mg respectively at endpoint.

d. Dropouts due to EKG Changes

There were a total of 2 dropouts due to clinically significant abnormal EKGs, both in the 30mg dose group.

Subject 001-003 was a 15 year old white male. At Baseline, 3 EKGs were recorded with QTcF intervals of 354.1, 400.5 and 430.3 msec, all were not considered clinically significant by the Investigator. The EKG acquired at Visit 1 showed QTcF interval of 479msec (increased 84msec from the average QTcF at Baseline) which was considered “abnormal significant” by the central reader and “clinically significant” by the Investigator. The study medication was discontinued after 11 days of exposure. Subsequently, 2 additional EKGs were recorded: QTcF interval was 383.2msec 3 days after the last dose of study medication. 52 days after the last dose of study medication, QTcF interval was 354.7msec but had unspecific T wave abnormality.

Subject 029-004, a 13 year old white male, had 4 EKGs recorded with QTcF interval of 376.4, 389.6, 397.6 and 390.0msec at Baseline. At Visit 1, EKG with QTcB increased to 456msec (<60msec increase from Baseline) was considered “abnormal significant” by the central reader. The Investigator identified sinus tachycardia (HR = 110bpm) and considered “clinically significant”. The QTcF interval, considered more accurate correction in subjects with tachycardia, was normal (412.5msec). Study medication was discontinued after 13 days of exposure and the tachycardia event resolved on that day. Two ECGs acquired at that time were considered “abnormal not significant” by the central reader and “not clinically significant” by the Investigator (QTcB and QTcF were normal, QTcB change >30msec from Baseline, HR = 87bpm).

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this indication.

7.4.6 Immunogenicity

No immunogenicity study was conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to **Table 11**.

7.5.2 Time Dependency for Adverse Events

The time dependency for adverse events was not studied in this submission.

7.5.3 Drug-Demographic Interactions

An analysis of AEs by age was shown in the following table.

Table 19: Summary of TEAEs Reported by ≥5% of Subjects Receiving Either Placebo or Lisdexamfetamine (all doses) by Age Group and the Frequency in the Lisdexamfetamine (all doses) Treatment Groups (Safety Population)

Preferred term	Placebo	SPD489			
		30 mg	50 mg	70 mg	All Doses
Number of subjects	n (%)	n (%)	n (%)	n (%)	n (%)
13-14 year old subjects					
Decreased appetite	2 (4.9)	15 (35.7)	10 (27.8)	16 (36.4)	41 (33.6)
Headache	6 (14.6)	5 (11.9)	4 (11.1)	4 (9.1)	13 (10.7)
Insomnia	2 (4.9)	3 (7.1)	2 (5.6)	7 (15.9)	12 (9.8)
Weight decreased	0	0	4 (11.1)	6 (13.6)	10 (8.2)
Irritability	0	3 (7.1)	1 (2.8)	5 (11.4)	9 (7.4)
Fatigue	1 (2.4)	3 (7.1)	1 (2.8)	3 (6.8)	7 (5.7)
Upper respiratory tract infection	3 (7.3)	0	1 (2.8)	2 (4.5)	3 (2.5)
Abdominal pain upper	3 (7.3)	0	0	1 (2.3)	1 (0.8)
15-17 year old subjects					
Decreased appetite	0	14 (38.9)	11 (26.8)	13 (38.2)	38 (34.2)
Headache	4 (11.1)	4 (11.1)	9 (22.0)	8 (23.5)	21 (18.9)
Insomnia	1 (2.8)	4 (11.1)	6 (14.6)	4 (11.8)	14 (12.6)
Weight decreased	0	3 (8.3)	3 (7.3)	6 (17.6)	12 (10.8)
Dizziness	2 (5.6)	0	4 (9.8)	3 (8.8)	7 (6.3)
Irritability	3 (8.3)	3 (8.3)	1 (2.4)	3 (8.8)	7 (6.3)
Upper respiratory tract infection	3 (8.3)	2 (5.6)	3 (7.3)	2 (5.9)	7 (6.3)
Nausea	2 (5.6)	0	2 (4.9)	2 (5.9)	4 (3.6)
Vomiting	3 (8.3)	0	0	1 (2.9)	1 (0.9)
Myalgia	2 (5.6)	0	0	0	0

Source: Section 14, Table 3.2.4.3

Irritability was common and treatment related in 13-14 year old subjects but not in the 15-17 year old group because the incidence was high in the placebo group of older subjects. This AE profile was slightly different from that in pediatric group (6-12 year old) which included decreased appetite, dizziness, dry mouth, irritability, insomnia, upper abdominal pain, nausea, vomiting, and decreased weight. Systematic analyses of AEs by gender and race were not conducted. On October 8, 2010, we requested sponsor to perform the analyses.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied in this submission.

7.5.5 Drug-Drug Interactions

Lisdexamfetamine dimesylate is a marketed drug in the USA since 2007. Drug-drug interaction profile had been established and has been addressed in current approved Vyvanse labeling. No drug-drug interaction studies were conducted in this trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity study has been conducted.

7.6.2 Human Reproduction and Pregnancy Data

One subject (016-007) in 50mg group was found to be pregnancy test positive after she has taken the drug for 3 weeks (her serum pregnancy test was negative at Screening and urine pregnancy test was negative at Baseline). She was discontinued due to insomnia at Week 3. The pregnancy was found out after her early termination. The pregnancy was ongoing at last visit and the outcome of the pregnancy was unknown.

7.6.3 Pediatrics and Assessment of Effects on Growth

This was a short-term (4 week) efficacy trial. The one year open label safety trial is ongoing and the sponsoring is monitoring the effects of lisdexamfetamine dimesylate on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose of lisdexamfetamine dimesylate was found in this trial. There is no new information on abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

A one year open label safety trial (Study 306) is ongoing. A 4-month safety update report was submitted by the Sponsor on May 14, 2010 for this sNDA. The following is a brief summary of the safety report.

Death
No deaths have been reported so far during the conduct of this open-label trial.

SAEs
Six subjects reported SAEs during this study period prior to the 4-month safety update cut-off date. Syncope or syncope vasovagal was reported for 3 subjects (see **Table 20**). Two subjects experienced aggression, and 1 subject experienced left testicular torsion causing bilateral hydrocele. Subject 032-006 (aggression) and Subject 041-007 (testicular torsion/hydrocele) discontinued from the study, but the other 4 subjects continued to participate Study 306.

Table 20: Listing of Subjects with Serious Adverse Events

Subject ID	Gender/ Age/ Race	Preferred Term /AE Text	Start Date	Start Day	Stop Date	Onset Dose (mg)	Antecedent Treatment (mg)	Frequency/ Intensity	Relation-ship/ Outcome	Effects on Dosing/ Treatment	SAE?/ Treatment Emergent?
007-007	F/15/W	Syncope/ syncope	22 May 2009	72	22 May 2009	70	70	One episode/ mild	Not related/ resolved	None/ none	Yes/Yes
024-010	F/17/W	Syncope/ syncope episode	02 Dec 2009	334	02 Dec 2009	30	70	One episode/ mild	Not related/ resolved	None/ none	Yes/Yes
032-006	F/14/W	Aggression/ aggression	25 Feb 2009	42	28 Feb 2009	70	70	One episode/ moderate	Not related/ resolved	Dose discontinued/ Non-pharmacologic	Yes/Yes
040-008	F/15/W	Syncope vasovagal/ vasovagal syncopal episode	10 Apr 2009	21	10 Apr 2009	70	70	One episode/ moderate	Related/ resolved	None/ none	Yes/Yes
041-003	M/17/B	Aggression/ extreme temper outburst	26 Oct 2009	301	28 Oct 2009	70	50	Continuous/ moderate	Not related/ resolved	None/ none	Yes/Yes
041-007	M/13/W	Hydrocele/ left testicular torsion causing bilateral hydrocele	10 Sep 2009	197	10 Sep 2009	50	70	Continuous/ severe	Not related/ resolved	Interrupted/ Pharmacologic and Non-pharmacologic	Yes/Yes
		Testicular torsion/ left testicular torsion causing bilateral hydrocele	10 Sep 2009	197	10 Sep 2009	50		Continuous/ severe	Not related/ resolved	Interrupted/ Pharmacologic and Non-pharmacologic	Yes/Yes

Source: Appendix 16.2, Listing 5.6

Dropouts
There were 17 dropouts in this study period. Refer to **Table 21.**

Subject 044-001 discontinued due to an abnormal EKG. This was a 13 year-old, white female diagnosed with ADHD (combined subtype). Physical exam was normal at study entry. In antecedent Study SPD489-305, she received placebo and was terminated due to lack of efficacy. She was screened for Study SPD489-306 on the same date and started her lisdexamfetamine 30mg the next day. Her EKG abnormality was described by the EKG Central Reader as QTcB change >60msec relative to baseline at the

termination visit for Study SPD489-305 while she was on placebo. She has received the study drug for 5 days. No follow-up EKG was described in the narrative summary. This reviewer believed that this subject with an abnormal EKG at ET visit for Study 305 should not have been included in Study 306.

Table 21: Listing of Subjects with Adverse Events Leading to Dose Discontinuation or Who Discontinued Due to an Adverse Event in Study SPD489-306 (Safety Population)

Subject ID	Gender/ Age/ Race	Preferred Term /AE Text	Start Date	Start Day	Stop Date	Onset Dose (mg)	Antecedent Treatment (mg)	Frequency/ Intensity	Relation-ship/ Outcome	SAE	TEAE	Termin-ated due to AE?	Study Drug Discon-tinued due to AE?
005-002	M/14/W	Irritability/ Increased Irritability	15 May 2009	92	16 Jun 2009	50	30	Intermittent/ Moderate	Related/ Resolved	No	Yes	Yes	Yes
		Depressed Mood/ Depressed Mood	20 Feb 2009	8	16 Jun 2009	50	30	Intermittent/ Moderate	Related/ Resolved	No	Yes	Yes	Yes
011-001	F/15/W	Insomnia/ Insomnia	05 Feb 2009	23	18 Mar 2009	50	Placebo	Intermittent/ Moderate	Related/ Resolved	No	Yes	Yes	Yes
016-012	F/16/W	Alanine Aminotransferase Increased/ Elevated Alt	16 Feb 2009	-1	14 May 2009		70	Continuous/ Mild	Related/ Resolved	No	No	Yes	Yes
019-001	M/16/W	Abdominal Pain/ Abdominal Pain	20 Mar 2009	86	01 Apr 2009	50	Placebo	Intermittent/ Moderate	Not Related/ Resolved	No	Yes	Yes	Yes
024-011	M/14/O	Insomnia/ Worsening Insomnia	03 Jan 2009	1	12 Jan 2009	30	30	Continuous/ Moderate	Related/ Resolved	No	Yes	Yes	Yes
025-007	F/14/W	Electrocardiogram QT Prolonged/ Prolonged QTcB	21 Jan 2009	-1			Placebo	One Episode/ Mild	Not Related/ Unresolved	No	No	Yes	Yes
027-008	M/13/W	Tic/ Tics	01 Apr 2009	37		30	70	Intermittent/ Mild	Related/ Unknown	No	Yes	Yes	Yes
029-007	M/14/W	Aggression/ Aggressive Behavior	20 Jan 2009	14		50	50	Continuous/ Severe	Related/ Unresolved	No	Yes	Yes	Yes
032-006	F/14/W	Aggression/ Aggression	25 Feb 2009	42	28 Feb 2009	70	70	One Episode/ Moderate	Not Related/ Resolved	Yes	Yes	Yes	Yes
033-012	M/14/W	Abdominal Pain Upper/Stomach Pain	28 Apr 2009	55	05 Jun 2009	50	50	Intermittent/ Mild	Related/ Resolved	No	Yes	Yes	No
036-001	M/13/W	Depression/ Depressive Disorder NOS	18 Feb 2009	22	19 Mar 2009	70	70	Continuous/ Mild	Related/ Resolved	No	Yes	Yes	Yes
036-002	M/13/W	Drug Misuse/ Study Drug Misuse	27 Mar 2009	57	22 Apr 2009	50	50	One Episode/ Mild	Not Related/ Resolved	No	Yes	No	Yes
039-005	M/14/W	Weight Decreased/ Weight Loss	25 Mar 2009	22	30 Jun 2009	70	Placebo	Continuous/ Mild	Related/ Resolved	No	Yes	Yes	Yes
042-001	M/14/W	Depressed Mood/ Depressed Mood	10 May 2009	55		70	30	Intermittent/ Mild	Not Related/ Unresolved	No	Yes	Yes	Yes
043-001	M/16/W	Blood Pressure Increased/ Elevated Blood Pressure	29 Dec 2008	24	16 Jan 2009	70	50	Continuous/ Moderate	Related/ Resolved	No	Yes	Yes	Yes
043-011	M/13/W	Suicidal Ideation/ Suicidal Ideation	25 Feb 2009	1	26 Feb 2009	30	50	Intermittent/ Moderate	Related/ Resolved	No	Yes	Yes	Yes
044-001	F/13/W	Electrocardiogram abnormal[b]/ Abnormal ECG	03 Dec 2008	21 in ante-cedent study		Placebo	Placebo	One Episode/ Mild	Related/ Unresolved	No	No[a]	Yes	No[a]

Source: Appendix 16.2, Listings 1.2, 5.1. and 5.5 ; SPD489-305 CSR.

TEAEs
The most frequently (≥5%) occurring TEAEs were decreased appetite (20.7%), upper respiratory tract infection (19.5%), headache (19.2%), weight decreased (15.4%), irritability (11.7%), insomnia (9.8%), nasopharyngitis (6.8%), influenza (6.4%), and dizziness (5.3%).

Others
There were no new trends in vital signs, labs and EKGs.

Weight - A total of 6 subjects (018-003, 025-010, 037-005, 038-008, 039-005, and 041-001) had transitioned from the healthy weight BMI category at Baseline to the underweight BMI category at endpoint (025-010, 037-005, 038-008, 039-005, and 041-001), or at Visit 10/Week 24 (025-010 and 041-001), or at Visit 13/Week 36 (018-003, 025-010, 037-005, and 041-001).

8 Postmarket Experience

Vyvanse has not been withdrawn from the market worldwide for any reason. A listing of all postmarketing spontaneous safety reports was not included in this submission. On October 4, 2010, we requested the sponsor to send in all post-marketing spontaneous reports for patients 13 to 17 years old.

Two postmarketing case reports were reviewed by Mark Ritter, M.D., a Medical Officer at DPP:

Subject SPV1-2010-00076 was a 14 year old male, taking concomitant azithromycin and loratidine, was prescribed Vyvanse for his ADHD symptoms. He was hospitalized in [redacted] (b) (6) for vomiting and jaundice and subsequently was diagnosed with a drug-induced hepatitis after liver needle biopsy was taken. The patient was discharged and went home. However the patient took a single dose of Vyvanse and experienced abdominal pain and vomiting and re-admitted to the hospital.

Subject SPV1-2010-01045 was also a 14 year old previously healthy male who developed scleral icterus and generalized jaundice 5 months after initiating therapy with Vyvanse 30mg. After one week of worsening jaundice and darkening urine, the patient was admitted to the hospital for additional testing. Tests for viral infection, congenital, medical or autoimmune infections or reactions were all negative. Subsequent liver biopsy was indicative for a drug-induced hepatitis: eosinophilic hepatitis.

As a result, the sponsor sent in a CBE that added eosinophilic hepatitis to the post-marketing section of the label. This labeling supplement was reviewed and approved on September 28, 2010.

9 Appendices

9.1 Literature Review/References

The submission dated January 14, 2010 did not include a literature search. On October 4, 2010, we have requested the sponsor to do a search of the published literature for articles pertaining to lisdexamfetamine.

9.2 Labeling Recommendations

The undersigned reviewer has reviewed all the proposed labeling changes. The changes are acceptable.

In **Table 11** of this review, regarding the incidence of TEAEs occurred ≥2% in lisdexamfetamine dimesylate treatment groups and placebo group (safety population), nasopharyngitis was reported in 2.6%, 5.2% and 1.3% in subjects treated with lisdexamfetamine 30, 50 and 70mg respectively and in 1.3% of subjects receiving placebo. However, the sponsor did not include nasopharyngitis in the labeling: adverse reactions reported by 2% or more of adolescent (aged 13 to 17 years) subjects taking Vyvanse in a 4-week clinical trial. The sponsor stated in their justification report "Nasopharyngitis in Subjects Treated with Vyvanse" dated November 2009 that there was no basis to believe there was a causal relationship between lisdexamfetamine and the occurrence of nasopharyngitis, which was most likely caused by viral infection. I agree with the sponsor's judgment.

9.3 Advisory Committee Meeting

No advisory committee meeting is planed for this submission.

Table 22: Outlier Criteria for Chemistry Panel

Test Name	Outlier Criteria
Chemistry Panel	
Bilirubin	>1.5 x ULN
Alkaline phosphatase	>2.5 x ULN (or alternatively >400U/L**)
Transaminase, SGOT, AST	>2.5 x ULN
Transaminase, SGPT, ALT	>2.5 x ULN
Urea nitrogen (BUN)	>2.5 x ULN* (or alternatively H >30mg/dl**)
Creatinine, serum	>1.5 x ULN (or alternatively H >2mg/dl**)
Glucose, blood	<55mg/dl or >160mg/dl
Calcium	<8mg/dl or >11.5mg/dl
Total protein, plasma or serum	<5g/dl* or >9g/dl*
Albumin	<3g/dl
Sodium	<130mmol/l (grade III) or >150mmol/l
Potassium, serum/plasma	<3mmol/l (grade III) or >5.5mmol
Uric acid, serum	>10mg/dl Males** and >8mg/dl Females**
Gamma Glutamyl Transpeptidase (GGT)	>2.5 X ULN
Phosphorus	<2.5mg/dl or >5mg/dl**
Lactate dehydrogenase (LDH)	>3 x ULN*
Thyroid Stimulating Hormone (TSH)	<LLN* or >2 x ULN*
Cholesterol	>300mg/dl**

*The NCI has not specified a value, Shire physicians have agreed on values provided
** Values taken from the Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, Table 7.1.7.3.2.1 pp 70-72. US DHHS FDA CDER, February 2005.
Source: SPD489-305 SAP

Table 23: Outlier Criteria for Hematology Panel

Test Name	Outlier Criteria
Hematology and Differential Panel	
Hemoglobin	<10g/dl
Platelet count	<75,000/mm^3 or >500,000/mm^3*
White Blood Cell Count (WBC)	<3000/mm^3 or >16,000/mm^3*
Neutrophils	<1500/mm^3 or <40%*
Lymphocytes	<10% or > 50%
Monocytes	>25%
Eosinophils	>10%

*The NCI has not specified a value, Shire physicians have agreed on values provided
Source: SPD489-305 SAP

Table 24: Clinically Significant Chemistry Outliers by Study Defined Abnormal Lab Value Criteria at Endpoint in Subjects with Normal Baseline Values (Safety Population)

Subject Number/ Treatment Group	Gender /Age /Race	Test Name	Visit	Result (Conventional Unit)	Result (Si Unit)	Range Flag	Reference Range
042-002 SPD489-70mg	M/14/W	Bilirubin	ET	1.7mg/dL	29umol/L	High	0 - 19 umol/L
012-002 SPD489-50mg	M/15/W	Bilirubin	Screening (11/12/2008)	1.9mg/dL	32umol/L	High	
			Visit 4 (12/23/2008)	2.8mg/dL	48umol/L	High	
021-019 SPD489-50mg	M/13/O	Bilirubin	Visit 4	1.7mg/dL	29umol/L	High	
024-004 SPD489-70mg	M/13/W	Bilirubin	Visit 4	1.7mg/dL	29umol/L	High	
008-004 SPD489-30mg	M/15/B	Glucose	Visit 4	38mg/dL	2.1mmol/L	Low	3.9 - 7.8 mmol/L
015-001 SPD489-30mg	M/14/O	Glucose	Visit 4	51mg/dL	2.8mmol/L	Low	
021-018 SPD489-50mg	M/16/W	Glucose	Visit 4	163mg/dL	9.0mmol/L	High	
038-005 SPD489-70mg	M/15/W	Glucose	Visit 4	172mg/dL	9.5mmol/L	High	
021-003 SPD489-30mg	M/16/W	Glucose	Visit 4	162mg/dL	9.0mmol/L	High	
007-009 SPD489-50mg	M/17/W	Potassium	Visit 4	5.8mEq/L	5.8mEq/L	High	3.6 - 5.2 mEq/L
021-017 SPD489-50mg	M/14/W	Potassium	Visit 4	5.7mEq/L	5.7mEq/L	High	
016-012 SPD489-70mg	F/16/W	ALT	Visit 4	77U/L	77U/L	High	5 - 20 U/L

Source: Listing 6.4: Listing of Outliers: Chemistry.

Table 25: Clinically Significant Hematology Outliers by Study Defined Abnormal Lab Value Criteria at Endpoint in Subjects with Normal Baseline Values (Safety Population)

Subject Number/ Treatment Group	Gender /Age /Race	Test Name	Visit	Result (Conventional Unit)	Result (Si Unit)	Range Flag	Reference Range
031-007 SPD489-50mg	M/16/W	Leukocytes	ET	16.28 x10^9/L	16.28x10^9/L	High	4.4 - 10.5 x10^9/L
044-002 SPD489-50mg	M/14/W	Leukocytes	Visit 4	2.26 x10^9/L	2.26 x10^9/L	Low	
003-004 SPD489-50mg	M/17/B	Neutrophils	ET	1.36 x10^9/L	1.36 x10^9/L	Low	2.1 – 7 x10^9/L
043-001 SPD489-50mg	M/16/W	%eosinophils	Visit 4	10.7%	10.7%	High	0 - 4.5%
018-005 SPD489-70mg	M/16/W	%neutrophils	Visit 4	34.0%	34.0%	Low	43.2-76.7%
018-005 SPD489-70mg	M/16/W	Neutrophils	Visit 4	1.09 x10^9/L	1.09 x10^9/L	Low	2.1 – 7 x10^9/L
016-016 SPD489-30mg	F/13/O	%lymphocyte	Visit 4	52.0%	52.0%	High	14.5- 39.6%
025-008 SPD489-70mg	F/13/W	%eosinophils	Visit 4	11.5%	11.5%	High	0 - 3.7%
		%neutrophils	Visit 4	38.4%	38.4%	Low	43.2-76.7%
029-014 SPD489-50mg	M/13/W	Leukocytes	Visit 4	2.21 x10^9/L	2.21 x10^9/L	Low	4.4 - 10.5 x10^9/L
		Neutrophils	Visit 4	0.80 x10^9/L	0.80 x10^9/L	Low	2.1 - 7 x10^9/L
		%neutrophils	Visit 4	36.2%	36.2%	Low	43.2-76.7%
041-006 SPD489-70mg	M/14/B	%lymphocyte	Visit 4	53.7%	53.7%	High	13 - 41.1%
		Neutrophils	Visit 4	1.25 x10^9/L	1.25 x10^9/L	Low	2.1 - 7 x10^9/L
		%neutrophils	Visit 4	38.4%	38.4%	Low	43.2 - 76.7%

Source: Listing 6.3: Listing of Outliers: Hematology

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/s/

JENN W SELLERS
10/13/2010

JING ZHANG
10/13/2010