CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21,977/Supplement 27
Priority or Standard	Standard
Submit Date(s)	June 29, 2012
Received Date(s)	June 29, 2012
PDUFA Goal Date	April 29, 2013
Division / Office	DPP/ODE1
Reviewer Name(s)	Tiffany R. Farchione, MD
Review Completion Date	
Established Name	Lisdexamfetamine dimesylate
Trade Name	Vyvanse®
Therapeutic Class	Stimulant
Applicant	Shire Development, Inc.
Formulation(s)	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg capsules
Dosing Regimen	30 to 70 mg QDay
Indication(s)	Treatment of Attention Deficit Hyperactivity Disorder
Intended Population(s)	Children, Adolescents, and Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that this supplement be approved. In this reviewer's opinion, the sponsor has demonstrated the efficacy and reasonable safety of lisdexamfetamine for the maintenance treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents ages 6-17 years. The sponsor's proposal to add the results from an additional short-term controlled study is also acceptable.

With regard to the sponsor's proposed labeling changes, some changes (b) (4) and made some editorial changes) were made to the sponsor's proposed language in Clinical Studies. In general, other proposed labeling changes are deemed acceptable.

1.2 Risk Benefit Assessment

Lisdexamfetamine has been demonstrated to be reasonably safe and effective in the maintenance treatment of ADHD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This reviewer identified no new major risks that would merit a Risk Evaluation and Mitigation Strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

According to the approval letter of lisdexamfetamine for the treatment of ADHD in children 6-12 years of age, the sponsor agreed to conduct a post-marketing study of efficacy and safety of lisdexamfetamine dimesylate as a treatment for ADHD in pediatric patients ages 13 to 17. This commitment has been fulfilled. No additional postmarketing studies have been identified as necessary based on this review.

2 Introduction and Regulatory Background

2.1 Product Information

Lisdexamfetamine dimesylate is a central nervous system (CNS) stimulant. It is a pro-drug which is converted to the amino acid *l*-lysine and the therapeutically active

compound *d*-amfetamine after being taken orally. It belongs to a central nervous system (CNS) stimulant family. Lisdexamfetamine dimesylate is marketed as Vyvanse and approved in the United States for the treatment of ADHD in children, adolescents, and adults, with dosages of 30 to 70 mg once daily.

2.2 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. Methylin ER (methylphenidate hydrochloride) Extended-Release Tablets (ANDA)
16. Ritalin (methylphenidate hydrochloride) Tablets
17. Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
18. Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
19. Vyvanse (lisdexamfetamine dimesylate) Capsules

Non-stimulants:

1. Intuniv (guanfacine) Extended Release Tablets
2. Strattera (atomoxetine HCl) Capsules
3. Kapvay (clonidine hydrochloride) Extended Release Tablets

2.3 Availability of Proposed Active Ingredient in the United States

Lisdexamfetamine is currently marketed in the US in 20mg, 30mg, 40mg, 50mg, 60mg, and 70mg capsules.

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 ages 6-12 in February, 2007. Intermediate dose strengths of 20, 40, and 60mg were approved in December, 2007. Lisdexamfetamine dimesylate was approved for the treatment of ADHD in adults ages 18-55 in April, 2008, and for adolescents ages 13-17 in November, 2010. In January, 2012, additional labeling language was approved to describe efficacy and safety data related to maintenance treatment of ADHD in adult patients.

On June 29, 2012, this application was submitted as a supplement (S-027) to NDA 21,977 to support approval of lisdexamfetamine for maintenance treatment of ADHD in children and adolescents ages 6-17.

The sponsor has submitted a single study (SPD489-326) in children and adolescents to support the maintenance treatment claim, as well as data from a short-term precursor study (SPD489-325). SPD489-325 included both a placebo control arm and active comparator; subjects completing this study were eligible for inclusion in SPD489-326, regardless of which treatment arm they were in for SPD489-325.

2.6 Other Relevant Background Information

A filing meeting was held on August 13, 2012, and concluded that the application could be filed. It was also decided that this application would be granted standard review status. The Action Due Date was established as April 29, 2013.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A sample of case report forms (CRFs) was reviewed to evaluate the consistency of adverse event information across the CRFs, corresponding narrative summary, and adverse event tabulation. Among the CRFs reviewed, the adverse event information was generally found to be consistent across the above documents. The sponsor

submitted CRFs for all subjects listed as "permanently discontinued" in the adverse event (AE) database, as well as for all subjects who had a serious adverse event (SAE) in the course of the study.

The coding of adverse event investigator terms to preferred terms (PT) was audited. In studies SPD489-325 and SPD489-326, the sponsor used MedDRA coding. The adverse event tabulations for studies SPD489-325 and SPD489-326 were examined, comparing the variables' AE versus PT. In general, it appeared that most verbatim terms were appropriately coded to preferred terms.

3.2 Compliance with Good Clinical Practices

According to the study reports for SPD489-325 and SPD489-326, these studies were conducted in accordance with current applicable regulations, International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) and local ethical and legal requirements, and with the principles of the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989), and 48th (South Africa 1996) World Medical Assemblies, Declaration of Helsinki.

Shire has certified that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

One site was excluded from SPD489-325 by the sponsor for GCP violations. During a site visit to Site 24 (Germany), significant discrepancies were identified. The breach of GCP was identified after subject activity at that site was completed. The sponsor decided to exclude the 15 subjects enrolled at that site from the Full Analysis Set. Sensitivity analyses that included data from subjects enrolled at Site 24 performed on the primary efficacy endpoint (ADHD-RS-IV Total Score), the key secondary endpoint (CGI-I), and on the primary quality of life assessment (the CHIP-CE: PRF Achievement Domain) yielded results that were similar to those obtained from using the FAS.
GCP inspections of short-term study sites were conducted under the original NDA. Jinglin Zhong, PhD (statistical reviewer) evaluated the data from SPD489-326 by site and determined that there were no sites driving the efficacy data. Thus, no additional Office of Scientific Investigations (OSI) GCP inspections were requested for this supplement.

3.3 Financial Disclosures

The sponsor submitted the certification of financial disclosure of clinical investigators participating in studies SPD489-325 and SPD489-326 in compliance with 21 CFR Part 54. No clinical investigator reported participating in any financial arrangement with the sponsor whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study, having proprietary interest in this product

or significant equity interest in the sponsor, or being the recipient of significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new information related to chemistry, manufacturing, and controls in this submission. The sponsor requested a categorical exclusion for an environmental assessment under this supplement. According to the CMC review by Chhagan G. Tele, PhD completed July 9, 2012, this is acceptable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

This efficacy supplement contains no new pharmacology or toxicokinetic studies of lisdexamfetamine dimesylate.

4.4 Clinical Pharmacology

There are no new clinical pharmacology data in this submission that would require a review.

5 Sources of Clinical Data

5.1 Studies/Clinical Trials

Study SPD489-326 is the study on which the sponsor's proposed maintenance claim is based, and is the primary focus of this review. This was a Phase 3, multicenter randomized withdrawal study to evaluate the long-term maintenance of efficacy and safety of SPD489 in children and adolescents (6-17 years of age) with ADHD. The study was conducted at 41 sites in the EU and US. In total, 276 children and adolescents were enrolled; 236 subjects enrolled from Study SPD489-325 (EU subjects) and 40 directly enrolled subjects exclusively from sites in the US. Subjects were recruited from 37 sites in 8 EU countries (Belgium, France, Germany, Hungary, Italy, Poland, Sweden, United Kingdom) and 4 sites in the US, with more subjects enrolled in Germany compared to the other countries.

In addition, Study SPD489-325 is also examined in this review. Study SPD489-325 was a short-term, randomized, double-blind, placebo-controlled study in children and adolescents (6-17 years of age) that included an active reference arm. This study was conducted entirely at European sites (Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden, United Kingdom). Subjects who had been exposed to double-blind test product for a minimum of 4 weeks in Study SPD489-325, reached Visit 4, and completed the 1-week post-treatment washout were evaluated for eligibility to enter SPD489-326.

5.2 Review Strategy

This review consisted of an examination of relevant background clinical information from the original application (NDA 21977), and of efficacy data and safety data from studies SPD489-325 and SPD489-326.

6 Review of Efficacy

Efficacy Summary

The efficacy of lisdexamfetamine for the maintenance treatment of ADHD in children and adolescents was demonstrated in a single double-blind, placebo-controlled, randomized withdrawal study (SPD489-326). The sponsor also submitted data from a short-term trial in children and adolescents (SPD489-325). This product is already labeled for short-term use in this population; the data from SPD489-325 offers additional support for efficacy in children and adolescents.

Jinglin Zhong, PhD (statistical reviewer) confirmed the sponsor's efficacy results. Please see her review dated March 14, 2013.

6.1 Studies Pertinent to the Efficacy Claim

6.1.1 Rationale for Selection of Study for Review

The sponsor submitted data from two trials—SPD489-325, a short-term, randomized, double-blind, placebo-controlled study in children and adolescents (6-17 years of age) that included an active reference arm; and SPD489-326, double-blind, placebo-controlled, randomized withdrawal study. SPD489-326 is the study on which the sponsor's proposed maintenance claim is based. The sponsor is proposing changes to the Clinical Studies section of labeling based on data from SPD489-325, so that study is reviewed below as well.

6.1.2 Study Summaries

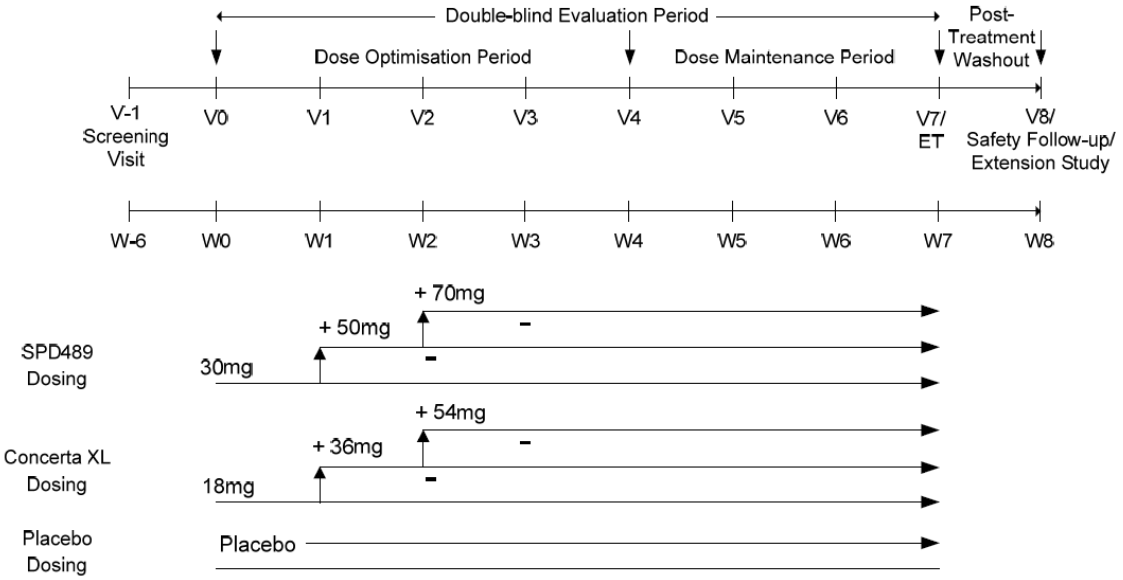
SPD489-325

Methods/Study Design/Analysis Plan

SPD489-325 was a Phase 3, randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled, dose-optimization safety and efficacy study, and the antecedent study to SPD489-326, the study on which the efficacy labeling claim is based. For this study, children and adolescents (6-17 years of age, inclusive) diagnosed with ADHD were randomized to SPD489, Concerta, or placebo (1:1:1) and treated for 7 weeks to evaluate safety and efficacy. After Visit 7 (Day 49) or Early Termination (ET), all subjects stopped taking investigational product and underwent an immediate 1-week washout.

The study consisted of 3 periods, as follows: a Screening and Washout Period (up to 42 days), a 7-week Double-blind Evaluation Period (consisting of a maximum 4-week Dose-Optimization Period followed by a minimum 3-week Dose-Maintenance Period), and a 1-week Washout and Follow-up Period. The total duration of the study was up to 14 weeks. See Figure 1 below (source: SPD489-325 Clinical Study Report, Figure 1, page 19).

Figure 1. SPD489-325 Study Design Flow Chart



Inclusion Criteria

Subjects were males and females, ages 6-17 years at the time of consent, with a primary diagnosis of ADHD based on psychiatric evaluation using DSM-IV-TR criteria. Subjects were also required to have a baseline ADHD Rating Scale (ADHD-RS-IV) Total Score ≥28. A parent or guardian was required to be available to dispense the investigational product at approximately 7:00AM daily for the duration of the study. All subjects were required to have a satisfactory medical assessment, including history,

physical exam, and laboratory test, as well as blood pressure measurements within the 95th percentile for age, sex, and height. Females of child-bearing potential (FOCP) were require to have a negative serum pregnancy test at screening, negative urine pregnancy test at baseline, and be willing to comply with contraceptive requirements.

Exclusion Criteria
If, in the opinion of the investigator, lisdexamfetamine would be contraindicated due to a subject's comorbid psychiatric illness, that subject was excluded. Other exclusionary criteria include Conduct Disorder (but not Oppositional Defiant Disorder), concurrent acute illness or unstable medical condition, suicide risk, pregnancy, glaucoma, seizures, abnormal thyroid function, cardiovascular disease or clinically significant ECG, or family history of sudden cardiac death. Subjects were excluded for a recent (within 6 months) history of substance abuse or dependence or a positive urine drug screen. Additional exclusionary criteria included weight less than 50 lbs. or BMI >97th percentile for age.

Assessments

Efficacy Measures

- Attention-deficit/Hyperactivity Disorder Rating Scale – IV (ADHD-RS-IV)
- Clinical Global Impressions (CGI) Scales—CGI-Severity (CGI-S) and CGI-Improvement (CGI-I)
- Conners' Parent Rating Scale – Revised (CPRS-R)

Efficacy Analyses
The primary efficacy variable was the change from Baseline at Endpoint in ADHD-RS-IV Total Score. The ADHD-RS-IV, which was assessed at Baseline (Visit 0) and at Visits 1-8 (Days 7-56), includes 18 items designed to reflect current symptomology of ADHD. A 4-point rating scale (0, never or rarely; 1, sometimes; 2, often; 3, very often) was used for each item. The Full Analysis Set (FAS) was initially defined as all subjects who were randomized and who took at least one dose of investigational product. This population was used for assessing comparative efficacy and quality of life information. However, as noted in Section 3.2 above, the 15 subjects at Site 24 were excluded from the FAS due to breach of GCP.

The primary efficacy analysis was performed on the ADHD-RS-IV change score at Endpoint from Baseline for the FAS, using an ANCOVA model. The primary treatment comparison was lisdexamfetamine versus placebo. The ANCOVA model included treatment group (the effect of interest), the corresponding Baseline score (the covariate), the blocking factors age group (6-12 years or 13-17 years) and country. The null hypothesis stated that there is no difference between lisdexamfetamine and placebo at Endpoint, with the two-sided alternative of a nonzero difference between groups. The primary treatment comparison was evaluated at the 0.05 significance level. For missing data, a LOCF model was used.

Determination of Sample Size

To detect an effect size of at least 0.45 between SPD489 and placebo at 90% power and a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to treatment groups, the sponsor calculated that it was necessary to assess the primary efficacy measure during the Dose Optimization Period or the Dose Maintenance Period for approximately 210 subjects (105 SPD489 and 105 placebo).

It was assumed that 5% of subjects randomized would drop out without providing a post-Baseline ADHD-RS-IV measurement, thus, 222 subjects were to be enrolled (111 SPD489 and 111 placebo). In addition, 111 subjects were to be recruited to the Concerta treatment group to provide reference data on the current standard therapy. The sponsor notes that this study was neither designed nor powered to support inference about comparisons between SPD489 and Concerta.

Enrollment was managed to ensure that a minimum of 25% of enrolled subjects were adolescents (13-17 years). Randomization was stratified by age group (6-12 years or 3-17 years).

Results

Demographics and Baseline Characteristics

Subjects had a mean (standard deviation [SD]) age of 10.9 (2.77) years, with the majority of subjects being 6-12 years of age (71.1%) compared to 13-17 years of age (28.9%). The majority of subjects were male (80.7%) and white (97.0%). The mean (SD) weight was 43.44 (15.455) kg, the mean height was 148.19 (16.457) cm, and the mean BMI was 19.14 (3.392) kg/m2. There were no clinically relevant differences between the groups at baseline with regard to demographic and baseline characteristics. See Table 1 below (source: SPD489-325 Clinical Study Report, Table 4, pages 46-47).

Table 1. Summary of Demographics and Baseline Characteristics (Safety Population)

Characteristics		SPD489 (N=111)	Placebo (N=110)	CONCERTA (N=111)	Total (N=332)
Age (years)	Mean (SD)	10.9 (2.87)	11.0 (2.82)	10.9 (2.63)	10.9 (2.77)
	Median	11.0	11.0	11.0	11.0
	Min, Max	6, 17	6, 17	6, 16	6, 17
Age Group					
6 - 12 years	n (%)	77 (69.4)	79 (71.8)	80 (72.1)	236 (71.1)
13 - 17 years	n (%)	34 (30.6)	31 (28.2)	31 (27.9)	96 (28.9)
Sex					
Male	n (%)	87 (78.4)	91 (82.7)	90 (81.1)	268 (80.7)
Female	n (%)	24 (21.6)	19 (17.3)	21 (18.9)	64 (19.3)
Ethnicity					
Hispanic or Latino	n (%)	2 (1.8)	0 (0.0)	2 (1.8)	4 (1.2)
Not Hispanic or Latino	n (%)	109 (98.2)	110 (100.0)	109 (98.2)	328 (98.8)
Race					
White	n (%)	107 (96.4)	108 (98.2)	107 (96.4)	322 (97.0)
Black or African American	n (%)	1 (0.9)	0	0	1 (0.3)
Native Hawaiian or other Pacific Islander	n (%)	0	0	0	0
Asian	n (%)	1 (0.9)	0	0	1 (0.3)
American Indian or Alaska Native	n (%)	0	0	0	0
Other	n (%)	2 (1.8)	2 (1.8)	4 (3.6)	8 (2.4)
Height (cm)	Mean (SD)	148.74 (17.372)	147.97 (15.392)	147.86 (16.673)	148.19 (16.457)
	Median	148.00	146.25	146.50	146.55
	Min, Max	118.0, 184.0	115.0, 180.0	118.1, 192.0	115.0, 192.0
Weight (kg)	Mean (SD)	44.56 (17.379)	42.64 (13.905)	43.12 (14.938)	43.44 (15.455)
	Median	42.70	40.00	38.30	39.95
	Min, Max	22.7, 92.0	22.7, 79.0	22.7, 87.2	22.7, 92.0
BMI (kg/m^2)	Mean (SD)	19.33 (3.703)	18.97 (3.313)	19.10 (3.158)	19.14 (3.392)
	Median	18.55	18.01	18.62	18.40
	Min, Max	13.9, 29.7	13.9, 27.3	14.3, 29.8	13.9, 29.8
Baseline ADHD-RS-IV Total Score[a]	Mean (SD)	41.0 (7.30)	41.2 (7.24)	40.4 (6.75)	40.9 (7.09)
	Median	41.0	42.0	40.0	41.0
	Min, Max	28, 54	28, 54	28, 54	28, 54

Table 1 (con't.). Summary of Demographics and Baseline Characteristics (Safety Population)

Characteristics		SPD489 (N=111)	Placebo (N=110)	CONCERTA (N=111)	Total (N=332)
Baseline ADHD-RS-IV Hyperactivity/Impulsivity Subscale Score[a]	Mean (SD)	18.5 (6.21)	19.3 (5.13)	18.5 (5.48)	18.8 (5.62)
	Median	20.0	20.0	19.0	20.0
	Min, Max	1, 27	8, 27	1, 27	1, 27
Baseline ADHD-RS-IV Inattention Subscale Score[a]	Mean (SD)	22.6 (3.41)	21.9 (3.72)	21.9 (3.49)	22.1 (3.55)
	Median	23.0	22.0	22.0	23.0
	Min, Max	13, 27	10, 27	14, 27	10, 27
Baseline CGI Severity Rating[a]	Mean (SD)	5.0 (0.80)	4.9 (0.83)	5.0 (0.82)	5.0 (0.82)
	Median	5.0	5.0	5.0	5.0
	Min, Max	4, 7	3, 7	3, 7	3, 7
Baseline CPRS Total Score[b]	Mean (SD)	51.0 (16.36)	53.2 (15.71)	50.5 (17.94)	51.6 (16.69)
	Median	51.0	54.0	52.3	52.8
	Min, Max	5, 80	10, 80	3, 79	3, 80
ADHD Subtype[c]					
Predominantly Inattentive	n (%)	23 (20.7)	16 (14.5)	14 (12.7)	53 (16.0)
Predominantly Hyperactive-Impulsive	n (%)	2 (1.8)	7 (6.4)	1 (0.9)	10 (3.0)
Combined	n (%)	86 (77.5)	87 (79.1)	95 (86.4)	268 (81.0)
Time Since ADHD Diagnosis (yrs)[c]	Mean (SD)	2.44 (2.854)	2.15 (2.613)	2.16 (2.484)	2.25 (2.651)
	Median	1.29	0.90	0.76	0.97
	Min, Max	0.0, 10.9	0.0, 10.2	0.0, 9.0	0.0, 10.9

[a] The following 5 subjects had no Baseline ADHD-RS-IV Total Score, ADHD-RS-IV Hyperactivity/Impulsivity Subscale Score, ADHD-RS-IV Inattention Subscale Score, and CGI Severity Rating: Subjects 06-002, 16-003, and 24-010 in the SPD489 group; Subject 05-006 in the placebo group; and Subject 65-008 in the CONCERTA group.
[b] The following 13 subjects had no Baseline CPRS-R Total Score: Subjects 16-003, 24-010, 42-002, 42-003, and 49-005 in the SPD489 group; Subjects 01-003, 12-013, 19-011, and 26-003 in the placebo group; and Subjects 12-015, 12-018, 19-016, and 39-003 in the CONCERTA group.
[c] One subject in the CONCERTA group (Subject 64-001) was not evaluated for ADHD subtype or for time since ADHD diagnosis.
Note: Percentages are based on the number of subjects with data in each treatment group and total.

Subject Disposition

Of the 336 subjects who were enrolled and randomized, 332 subjects received at least 1 dose of investigational product and were included in the Safety Population and 4 subjects (23-002, 31-001, 20-002, 16-001) were not dosed and were therefore excluded from the Safety Population and the FAS. Fifteen (15) subjects in the Safety Population, who had been enrolled at Site 24, were also excluded from the FAS (site excluded due to breach of Good Clinical Practice following completion of subject activity in the study).

Of the 336 randomized subjects, 196 subjects (58.3%) completed the study and 139 subjects (41.4%) were prematurely discontinued. The most frequently reported reason for premature discontinuation was lack of efficacy (25.9%).

Concomitant Medications

Of the 332 subjects in the Safety Population, 100 subjects (30.1%) received at least 1 concomitant medication during the study. The percentages of subjects who received at least 1 concomitant medication during the study was similar across treatment groups (SPD489, 27.9%; placebo, 32.7%; Concerta, 29.7%).

The most frequently reported concomitant medications (reported by ≥1.0% of subjects in any treatment group) are presented for subjects in the Safety Population in Table 2 below (source: SPD489-325 Clinical Study Report, Table 6, page 51).

Table 2. Summary of Most Frequently Reported (≥1% of Subjects in any Treatment Group) Concomitant Medications (Safety Population)

	SPD489 (N=111) n (%)	Placebo (N=110) n (%)	CONCERTA (N=111) n (%)	Total[a] (N=332) n (%)
Any Concomitant Medication	**31 (27.9)**	**36 (32.7)**	**33 (29.7)**	**100 (30.1)**
Paracetamol	12 (10.8)	14 (12.7)	14 (12.6)	40 (12.0)
Ibuprofen	9 (8.1)	9 (8.2)	10 (9.0)	28 (8.4)
Amoxicillin	2 (1.8)	1 (0.9)	2 (1.8)	5 (1.5)
Acetylcysteine	1 (0.9)	1 (0.9)	2 (1.8)	4 (1.2)
Cetirizine Hydrochloride	1 (0.9)	2 (1.8)	1 (0.9)	4 (1.2)
Domperidone	1 (0.9)	0	3 (2.7)	4 (1.2)
Nasic	2 (1.8)	1 (0.9)	0	3 (0.9)
Acetylsalicylic Acid	0	2 (1.8)	0	2 (0.6)
Budesonide	0	0	2 (1.8)	2 (0.6)
Cefuroxime	0	2 (1.8)	0	2 (0.6)
Hepatitis A Vaccine	0	0	2 (1.8)	2 (0.6)

[a] Medications are presented in decreasing frequency based on the "Total" column.
Note: Percentages are based on the number of subjects in each treatment group and total.
Note: Subjects could have received more than 1 medication.

Important Protocol Violations

Of the 332 subjects in the Safety Population, 105 subjects (31.6%) had at least 1 major deviation from the protocol. The percentages of subjects with at least 1 major protocol deviation were 34.2, 33.6, and 27.0% for SPD489, placebo, and Concerta, respectively. For additional details, see Table 3 below (source: SPD489-325 Clinical Study Report, Table 8, page 55)

The most frequently recorded major protocol deviation, regardless of treatment group, was violation of inclusion/exclusion criteria. The most frequently reported inclusion criterion violation was blood pressure measurement >95th percentile for age, sex, and height (inclusion criterion #7). This deviation was reported for 42 subjects (SPD489, 17 subjects; placebo, 16 subjects; Concerta, 9 subjects). The most frequent exclusion criterion violated was BMI >97th percentile for age and sex (exclusion criterion #9). This deviation was reported for 15 subjects (SPD489, 4 subjects; placebo, 8 subjects; Concerta, 3 subjects).

The root cause for the majority of these protocol deviations related to site difficulties in the manual plotting of key coordinates such as, age and height; which was necessary to determine the BMI percentile or height percentile for a subject. Errors made in determining these requisite percentiles may also have impacted the determination of the maximum blood pressure level allowed at entry.

The major protocol deviations from these 2 inclusion/exclusion criteria were reviewed by a Shire physician and, while subject values were outside of the protocol defined range, the deviations were generally small and were judged to be not clinically concerning (ie, they did not impact safety and posed no risk to the individual subject).

Of the 105 subjects with at least 1 major protocol deviation, 4 subjects (SPD489, Subjects 44-003 and 59-002; placebo, Subject 04-001; CONCERTA, Subject 26-011) had a treatment emergent SAE. None of these SAEs, which included gastroesophageal reflux disease (SPD489), appendicitis (SPD489), hematoma (placebo), and overdose (Concerta), were plausibly related to the respective protocol deviation.

One subject each in the SPD489 (05-012) and placebo (65-016) groups who had a major protocol deviation was discontinued from the study due to a TEAE. Subject 05-012 (SPD489) deviated from inclusion criterion #7 (blood pressure measurement >95th percentile for age, sex, and height) and exclusion criterion #16 (documented tic disorder) and was discontinued due to a TEAE of anorexia (moderate in intensity and judged by the Investigator to be related to investigational product). Subject 65-016 (placebo), who had a clinically significant ECG at Screening (deviation from exclusion criterion #12), was discontinued due to TEAEs of agitation and impulsive behavior. Both of these TEAEs were moderate in intensity and were judged by the Investigator to not be related to investigational product.

No pregnancies were reported during this study.

Table 3. Summary of Major Protocol Deviations (Safety Population)

	SPD489 (N=111) n (%)	Placebo (N=110) n (%)	CONCERTA (N=111) n (%)	Total[a] (N=332) n (%)
Subjects with Major Protocol Deviations	38 (34.2)	37 (33.6)	30 (27.0)	105 (31.6)
Major Protocol Deviation:				
Violation of Inclusion/Exclusion Criteria	29 (26.1)	33 (30.0)	22 (19.8)	84 (25.3)
Abuse, misuse, or overdose of investigational product	5 (4.5)	1 (0.9)	4 (3.6)	10 (3.0)
Overall compliance <80% or >120%	2 (1.8)	2 (1.8)	1 (0.9)	5 (1.5)
Insufficient washout of prohibited medications	3 (2.7)	1 (0.9)	2 (1.8)	6 (1.8)
Took prohibited medication for >2 consecutive days during dose optimization or maintenance periods	1 (0.9)	3 (2.7)	0	4 (1.2)
Pregnant	0	0	0	0
Other	2 (1.8)	2 (1.8)	4 (3.6)	8 (2.4)

[a] Major protocol deviations are presented in decreasing frequency based on the "Total" column.
Note: Percentages are based on the number of subjects in each treatment group and total.

Efficacy Findings

Of the 336 randomized subjects, 317 subjects were included in the FAS. Of the 19 subjects excluded from the FAS, 4 subjects were not dosed and 15 subjects had been enrolled at Site 24. Of the 4 subjects not dosed, 2 were randomized to SPD489 (23-002 and 31-001), 1 was randomized to placebo (20-002), and 1 was randomized to Concerta (16-001).

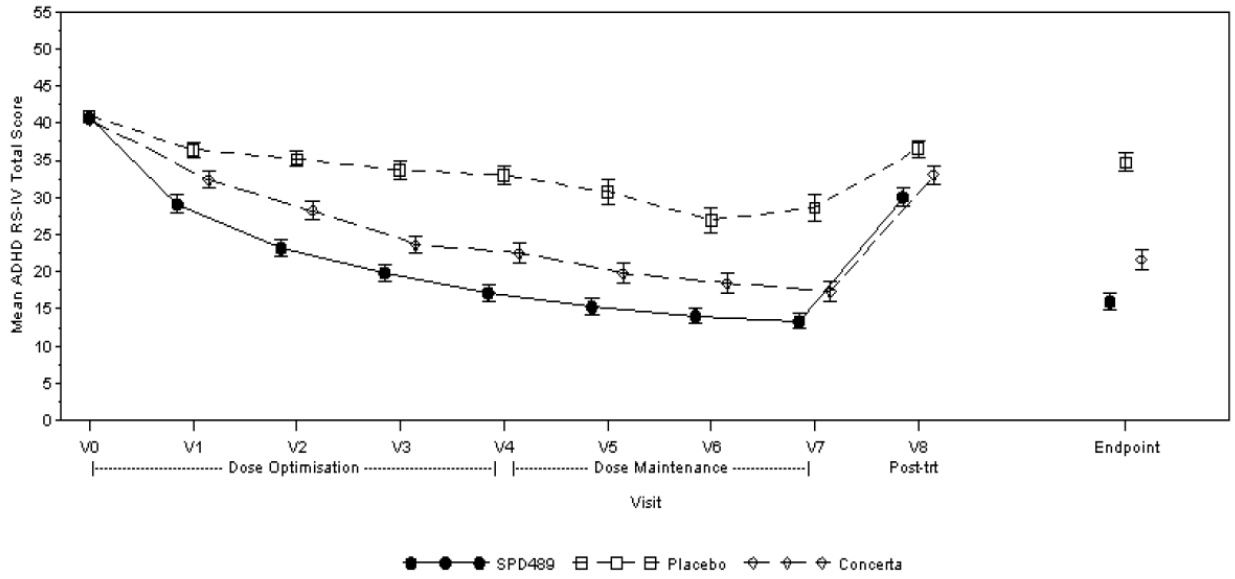
Change from baseline in the ADHD Rating Scale-IV (ADHD-RS-IV) Total Score at Endpoint was the primary endpoint for SPD489-325. Mean ADHD-RS-IV scores at baseline were similar across groups. Results of the primary efficacy analysis show that mean decreases (representing improvement) from baseline at Endpoint in ADHD-RS-IV Total Score were of statistically significantly greater magnitude for the SPD489 group compared to placebo (-24.7 $\pm$ 10.15 vs -6.3 $\pm$ 10.02, respectively; p <0.001) See Table 4 (source: SPD489-325 Clinical Study Report, Table 9, page 58) and Figure 2 below (source: SPD489-325 Clinical Study Report, Figure 3, page 60).

The sponsor does not claim superiority of SPD489 (-24.7 $\pm$ 10.15, placebo-subtracted difference = -18.4) versus Concerta (-18.9 $\pm$ 12.92, placebo-subtracted difference = -12.6). Although SPD489 resulted in numerically greater improvement than Concerta, this difference was not statistically significant.

Table 4. Summary of Actual Values and Changes From Baseline in ADHD-RS-IV Total Score (Full Analysis Set)

	SPD489 (N=104)		Placebo (N=106)		CONCERTA (N=107)	
Visit	Actual value	Change from Baseline	Actual value	Change from Baseline	Actual value	Change from Baseline
Baseline (Day 0)						
n	102		105		106	
Mean	40.7		41.0		40.5	
SD	7.31		7.14		6.72	
Min, Max	28, 54		28, 54		28, 54	
95% CI	39.3, 42.2		39.6, 42.4		39.2, 41.8	
Endpoint						
n	100	98	104	104	104	103
Mean	16.0	-24.7	34.8	-6.3	21.7	-18.9
SD	10.44	10.15	11.89	10.02	13.30	12.92
Min, Max	0, 45	-46, 0	6, 54	-33, 14	0, 49	-50, 6
95% CI	13.9, 18.1	-26.7, -22.6	32.4, 37.1	-8.3, -4.4	19.1, 24.3	-21.4, -16.4

Figure 2. Mean ADHD-RS-IV Total Score by Visit (Full Analysis Set)



Note: Error bars extend one standard error of the mean above and below the mean.
Endpoint is the last on-treatment, post-Baseline visit of the Dose Optimisation or Dose Maintenance Period (Visits 1-7) with a non-missing assessment.

Source: Table 2.1.1.1.1

Program: f_rsiv.sas, Output: f_rsiv-1.rtf, Generated on: 07JUN2011 13:52, Page 1 of 1

Post-trt = Post-treatment and reflects the 1-week interval between Visit 7 and Visit 8. Visit 7 was the last day of treatment and the interval between Visits 7 and 8 is defined as the post-treatment washout period.

SPD489-326
Methods/Study Design/Analysis Plan

SPD489-326 was a Phase 3, double-blind, placebo-controlled, randomized withdrawal, multicenter (41 sites, EU and US), extension study to evaluate the long-term maintenance of efficacy and safety of SPD489 in children and adolescents (6-17 years of age) with ADHD. Subjects who had been exposed to double-blind test product for a minimum of 4 weeks, reached Visit 4, and completed the 1-week post-treatment washout during Study SPD489-325 were evaluated for study eligibility. The sponsor notes that, to ensure the sample size necessary to assess the primary efficacy measure was met, US children and adolescents were added to the originally planned population of EU subjects.

The SPD489-326 study was originally designed to evaluate the long-term safety and efficacy of SPD489 for the treatment of ADHD in children and adolescents as an open-label study. National scientific advice within the EU determined the requirement for the evaluation of the long-term maintenance of efficacy in this population. The SPD489-326 study was amended to include a double-blind randomized withdrawal phase in order to evaluate the long-term maintenance of efficacy.

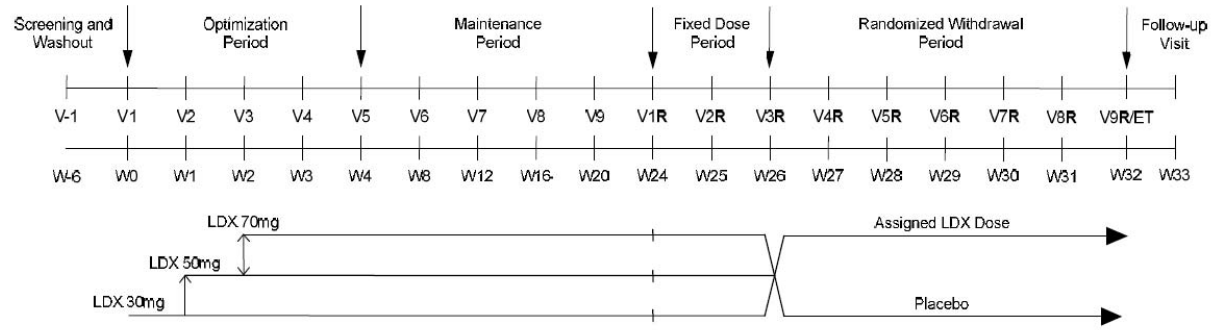
The study consisted of 4 periods (following 1-6 weeks of screening and washout for US subjects only):

1. Open-label Optimization Period (4 weeks): Eligible subjects started at SPD489 30mg and could be titrated in weekly increments of 20mg until an optimal dose was reached (up to a maximum of 70mg/day). Titration to a lower dose level was permitted in decrements of 20mg to a minimum dose of 30mg/day.
2. Open-label Maintenance Period (at least 20 weeks): Following titration to an optimal dose of SPD489, subjects continued daily morning treatment with SPD489 for a minimum of 20 weeks.
3. Open-label Fixed Dose Period (2 weeks): Subjects continued daily morning treatment with SPD489 for 2 weeks. Subjects were to be discontinued immediately if they required further dose adjustments, if they experienced unacceptable tolerability, or if ADHD-RS-IV Total Score was >22 or CGI-S score was $\geq$3.
4. Double-blind Randomized Withdrawal Period (6 weeks): Subjects who completed the Fixed Dose Period visits entered the double-blind Randomized Withdrawal Period. Subjects were randomized using a 1:1 ratio to either continue on their assigned dose of SPD489 or switch to placebo, which was maintained for 6 weeks.
   Subjects meeting the following relapse criteria at any time during this period were to be immediately discontinued from the study:

- Subject had a ≥50% increase in ADHD-RS-IV Total Score compared to the ADHD-RS-IV Total Score at randomization (Visit 3R), and
- The subject had a ≥2-point increase in CGI-S score relative to the CGI-S score at visit 3R.

See Figure 3 below (source: SPD489-326 Clinical Study Report, Figure 1, page 29).

Figure 3. SPD489-326 Study Design Flow Chart



Screening and washout were exclusively for US subjects who were directly enrolled into the study.

Inclusion Criteria

All sites required that a parent or guardian would be available to dispense the investigational product at approximately 7:00AM daily for the duration of the study. All subjects were required to have a satisfactory medical assessment, including history, physical exam, and laboratory test, as well as blood pressure measurements within the 95th percentile for age, sex, and height.

At European study sites, subjects were required to have participated in the antecedent study, SPD489-325. Male and female subjects ages 6-17 years, inclusive, at the time of consent for SPD489-325 were required to satisfy all entry criteria for the antecedent study, and complete a minimum of 4 weeks of double-blind treatment, reach Visit 4 and complete the 1-week post-treatment washout in the antecedent study without experiencing any clinically significant adverse events (AEs) that would preclude exposure to SPD489.

At US study sites, subjects were enrolled directly, without prior exposure to the study drug. Subjects were males and females, ages 6-17 years at the time of consent, with a primary diagnosis of ADHD based on psychiatric evaluation using DSM-IV-TR criteria. Additionally, subjects were required to have an ADHD-RS-IV score of ≥28 at Visit 1. Females of child-bearing potential (FOCP) were required to have a negative serum pregnancy test at Visit 1, and to be willing to comply with contraceptive guidelines.

Exclusion Criteria

If, in the opinion of the investigator, lisdexamfetamine would be contraindicated due to a subject's comorbid psychiatric illness, that subject was excluded. Other exclusionary criteria include Conduct Disorder (but not Oppositional Defiant Disorder), concurrent acute illness or unstable medical condition, suicide risk, pregnancy, glaucoma, seizures, cardiovascular disease or clinically significant ECG, or family history of sudden cardiac death. Subjects were also excluded for a recent (within 6 months) history of substance abuse or dependence.

At European sites, subjects terminated from the antecedent study due to non-compliance, adverse event, or serious adverse event were excluded.

At US sites, subjects who failed to respond to Concerta® and/or to more than one adequate course (dose and duration) of amfetamine therapy were excluded.

Assessments

Efficacy Measures

- Attention-deficit/Hyperactivity Disorder Rating Scale – IV
- Clinical Global Impressions (CGI) Scale

Efficacy Analyses
The primary efficacy measure of the study was the percentage of treatment failures at the end of the Randomized Withdrawal Period. A composite measure, treatment failure was defined as a ≥50% increase (worsening) in ADHD-RS-IV Total Score *and* ≥2 point increase in CGI-S score at any double-blind visit relative to the respective score at the end of the Fixed Dose Period.

The primary efficacy analysis was performed on the treatment failure rates at the end of the Double-blind Randomized Withdrawal Phase for the Randomized Full Analysis Set (FAS) using a Cochran-Mantel-Haenszel (CMH) test stratified by country. Subjects who withdrew during the Randomized Withdrawal Period and did not provide efficacy data at the Early Termination (ET) visit were considered treatment failures in the primary efficacy analysis.

There were no key secondary efficacy measures.

Determination of Sample Size
To detect treatment failure rates of 20% and 50% in the SPD489 and placebo groups, respectively, at a minimum 90% power and a significance level of 0.05 (2-sided) using a chi-square test with equal allocation to treatment groups, the sponsor calculated that it was necessary to assess the primary efficacy measure in at least 104 subjects (52

subjects in each of the SPD489 and placebo groups). The randomization was stratified by country.

Results

Demographics and Baseline Characteristics

In the Open-label Safety Population, subjects had a mean (standard deviation [SD]) age of 10.9 (2.82) years and were predominantly white (93.1%). The proportion of male subjects (76.8%) was greater than female subjects. The mean (SD) baseline weight was 44.32kg (15.943). There were no clinically relevant differences between the groups at baseline with regard to demographic and baseline characteristics. See Table 5 below (source: SPD489-326 Clinical Study Report, Table 10, pages 72-73).

Table 5. SPD489-326 Summary of Demographic Characteristics (Open-label Safety Population)

	Treatment Group in Antecedent Study (SPD489-325)			SPD489-325 Rollover (N=236)	Directly Enrolled (N=40)	Total (N=276)
	SPD489 (N=78)	Placebo (N=75)	CONCERTA (N=83)			
Sex n (%)						
Male	58 (74.4)	60 (80.0)	68 (81.9)	186 (78.8)	26 (65.0)	212 (76.8)
Female	20 (25.6)	15 (20.0)	15 (18.1)	50 (21.2)	14 (35.0)	64 (23.2)
Ethnicity n (%)						
Hispanic/Latino	1 (1.3)	0	1 (1.2)	2 (0.8)	13 (32.5)	15 (5.4)
Not Hispanic/Latino	77 (98.7)	75 (100.0)	82 (98.8)	234 (99.2)	27 (67.5)	261 (94.6)
Race n (%)						
White	75 (96.2)	73 (97.3)	79 (95.2)	227 (96.2)	30 (75.0)	257 (93.1)
Black/African American	1 (1.3)	0	0	1 (0.4)	9 (22.5)	10 (3.6)
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Asian	1 (1.3)	0	0	1 (0.4)	0	1 (0.4)
American Indian or Alaska Native	0	0	0	0	0	0
Other	1 (1.3)	2 (2.7)	4 (4.8)	7 (3.0)	1 (2.5)	8 (2.9)
Age (years)						
Mean (SD)	11.2 (2.90)	11.1 (2.93)	10.9 (2.57)	11.1 (2.79)	10.2 (2.90)	10.9 (2.82)
Median	11.0	11.0	11.0	11.0	10.0	11.0
Min, Max	6, 17	6, 17	6, 16	6, 17	6, 16	6, 17
Age group n (%)						
6-12 years	50 (64.1)	52 (69.3)	60 (72.3)	162 (68.6)	29 (72.5)	191 (69.2)
13-17 years	28 (35.9)	23 (30.7)	23 (27.7)	74 (31.4)	11 (27.5)	85 (30.8)
Height (cm)						
Mean (SD)	150.85 (17.784)	148.75 (16.496)	148.41 (16.570)	149.32 (16.920)	143.88 (15.129)	148.53 (16.757)
Median	152.50	148.00	146.60	148.35	142.24	147.75
Min, Max	119.0, 184.0	115.0, 180.0	118.1, 192.0	115.0, 192.0	115.6, 165.6	115.0, 192.0
Weight (kg)						
Mean (SD)	46.57 (18.779)	43.97 (15.008)	44.02 (15.131)	44.85 (16.366)	41.19 (12.907)	44.32 (15.943)
Median	45.10	40.90	38.90	43.00	37.06	41.85
Min, Max	23.0, 92.0	22.8, 79.0	22.8, 87.2	22.8, 92.0	23.8, 69.2	22.8, 92.0
BMI (kg/m^2)						
Mean (SD)	19.56 (3.943)	19.30 (3.499)	19.35 (3.237)	19.40 (3.552)	19.38 (2.900)	19.40 (3.461)
Median	18.62	18.52	18.63	18.59	18.50	18.56
Min, Max	13.9, 29.7	14.1, 27.3	14.3, 29.8	13.9, 29.8	14.8, 26.9	13.9, 29.8

Includes subjects at Site 24
Age is age at start of antecedent study (SPD489-325), or at time of informed consent into Study SPD849-326 for directly enrolled subjects.
Measurements are from the Screening Visit of the antecedent study (SPD489-325), or last assessment before first dose of investigational product for directly enrolled subjects.
Percentages are based on the number of subjects with data in each treatment group and total.

In the Randomized Safety Population, subjects had a mean (SD) age of 11.1 (2.60) years and were predominantly white (94.9%). The proportion of male subjects (78.3%) was greater than female subjects. The mean (SD) baseline weight was 45.88kg (16.656). There were no clinically relevant differences between the groups at baseline with regard to demographic and baseline characteristics. See Table 6 below (source: SPD489-326 Clinical Study Report, Table 11, pages 74-75).

Table 6. Summary of Demographic Characteristics (Randomized Safety Population)

	Randomized Treatment Group		
	SPD489 (N=78)	**Placebo (N=79)**	**Total (N=157)**
Sex n (%)			
Male	61 (78.2)	62 (78.5)	123 (78.3)
Female	17 (21.8)	17 (21.5)	34 (21.7)
Ethnicity n (%)			
Hispanic/Latino	5 (6.4)	4 (5.1)	9 (5.7)
Not Hispanic/Latino	73 (93.6)	75 (94.9)	148 (94.3)
Race n (%)			
White	74 (94.9)	75 (94.9)	149 (94.9)
Black/African American	1 (1.3)	2 (2.5)	3 (1.9)
Native Hawaiian or other Pacific Islander	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Other	3 (3.8)	2 (2.5)	5 (3.2)
Age (years)			
Mean (SD)	11.0 (2.63)	11.3 (2.58)	11.1 (2.60)
Median	11.0	12.0	11.0
Min, Max	6, 17	6, 17	6, 17
Age group n (%)			
6-12 years	55 (70.5)	50 (63.3)	105 (66.9)
13-17 years	23 (29.5)	29 (36.7)	52 (33.1)
Height (cm)			
Mean (SD)	149.30 (16.212)	149.93 (17.070)	149.62 (16.599)
Median	147.75	150.10	149.00
Min, Max	119.0, 192.0	118.4, 181.0	118.4, 192.0

Table 6 (con't.)

	Randomized Treatment Group		
	SPD489 (N=78)	**Placebo (N=79)**	**Total (N=157)**
Weight (kg)			
Mean (SD)	44.72 (16.199)	47.02 (17.122)	45.88 (16.656)
Median	41.00	47.63	44.80
Min, Max	22.8, 86.5	23.5, 92.0	22.8, 92.0
BMI (kg/m^2)			
Mean (SD)	19.44 (3.760)	20.17 (3.645)	19.80 (3.709)
Median	18.56	19.66	19.11
Min, Max	13.9, 29.8	14.2, 29.0	13.9, 29.8

Includes subjects at Site 24
Age is age at start of antecedent study (SPD489-325), or at time of informed consent into Study SPD489-326 for directly enrolled subjects.
Measurements are from the Screening Visit of the antecedent study (SPD489-325), or last assessment before first dose of investigational product for directly enrolled subjects.
Percentages are based on the number of subjects with data in each treatment group and total.

In the Open-label Safety Population, the mean (SD) baseline ADHD-RS-IV Total Score was 40.7 (6.86), the mean (SD) baseline ADHD-RS-IV hyperactivity/impulsivity subscale score was 18.8 (5.46), the mean (SD) baseline ADHD-RS-IV inattention subscale score was 21.9 (3.53), and the mean (SD) baseline CGI severity rating was 4.9 (0.80). See Table 7 below (source: SPD489-326 Clinical Study Report, Table 12, pages 76-77).

Table 7. SPD 489-326 Summary of Baseline Disease Characteristics (Open-label Safety Population)

	Treatment Group in Antecedent Study (SPD489-325)			SPD489-325 Rollover (N=236)	Directly Enrolled (N=40)	Total (N=276)
	SPD489 (N=78)	Placebo (N=75)	CONCERTA (N=83)			
Baseline ADHD-RS-IV Total Score						
n	77	75	82	234	40	274
Mean (SD)	40.6 (6.94)	40.5 (7.42)	40.2 (6.51)	40.4 (6.93)	42.5 (6.29)	40.7 (6.86)
Median	41.0	41.0	40.5	41.0	43.5	41.0
Min, Max	28, 54	28, 52	28, 54	28, 54	28, 53	28, 54
Baseline ADHD-RS-IV Hyperactivity/ Impulsivity Subscale Score						
n	77	75	82	234	40	274
Mean (SD)	18.2 (5.87)	18.9 (5.50)	18.5 (5.33)	18.5 (5.55)	20.7 (4.53)	18.8 (5.46)
Median	19.0	20.0	19.0	19.0	21.0	20.0
Min, Max	4, 27	8, 27	1, 27	1, 27	9, 27	1, 27
Baseline ADHD-RS-IV Inattention Subscale Score						
n	77	75	82	234	40	274
Mean (SD)	22.4 (3.31)	21.6 (3.76)	21.6 (3.51)	21.9 (3.54)	21.8 (3.55)	21.9 (3.53)
Median	23.0	22.0	21.5	22.0	23.0	22.0
Min, Max	13, 27	10, 27	15, 27	10, 27	14, 27	10, 27
Baseline CGI Severity Rating						
n	77	75	82	234	40	274
Mean (SD)	5.1 (0.78)	4.9 (0.85)	5.0 (0.82)	5.0 (0.82)	4.7 (0.64)	4.9 (0.80)
Median	5.0	5.0	5.0	5.0	5.0	5.0
Min, Max	4, 7	3, 7	3, 7	3, 7	4, 6	3, 7
ADHD Subtype n (%)						
n	78	75	83	236	40	276
Predominantly Inattentive	17 (21.8)	15 (20.0)	10 (12.0)	42 (17.8)	4 (10.0)	46 (16.7)
Predominantly Hyperactive/Impulsive	1 (1.3)	4 (5.3)	1 (1.2)	6 (2.5)	1 (2.5)	7 (2.5)
Combined	60 (76.9)	56 (74.7)	72 (86.7)	188 (79.7)	35 (87.5)	223 (80.8)
Time Since ADHD Diagnosis (years)						
n	78	75	83	236	40	276
Mean (SD)	2.49 (2.822)	2.20 (2.758)	2.26 (2.525)	2.32 (2.692)	2.08 (2.727)	2.28 (2.693)
Median	1.62	0.84	0.92	1.02	0.12	0.98
Min, Max	0.0, 10.9	0.0, 10.2	0.0, 9.0	0.0, 10.9	0.0, 9.4	0.0, 10.9

Includes subjects at Site 24
Baseline measurements are from the Screening Visit of the antecedent study (SPD489-325), or last assessment before first dose of investigational product for directly enrolled subjects.
Time from diagnosis calculated to time of informed consent in the antecedent study (SPD489-325), or Study SPD498-326 for directly enrolled subjects.
Percentages are based on the number of subjects with data in each treatment group and total.

In the Randomized Safety Population, the mean (SD) baseline ADHD-RS-IV Total Score was 41.0 (6.90), the mean (SD) baseline ADHD-RS-IV hyperactivity/impulsivity subscale score was 19.0 (5.21), the mean (SD) baseline ADHD-RS-IV inattention subscale score was 22.1 (3.45), and the mean (SD) baseline CGI severity rating was 5.1 (0.77). See Table 8 below (source: SPD489-326 Clinical Study Report, Table 13, pages 78-79).

Table 8: SPD489-326 Summary of Baseline Disease Characteristics (Randomized Safety Population)

	Randomized Treatment Group		
	SPD489 (N=78)	Placebo (N=79)	Total (N=157)
Baseline ADHD-RS-IV Total Score			
n	77	79	156
Mean (SD)	41.9 (6.77)	40.2 (6.96)	41.0 (6.90)
Median	43.0	40.0	42.0
Min, Max	28, 54	28, 52	28, 54
Baseline ADHD-RS-IV Hyperactivity/ Impulsivity Subscale Score			
n	77	79	156
Mean (SD)	19.6 (5.45)	18.4 (4.93)	19.0 (5.21)
Median	20.0	18.0	19.0
Min, Max	7, 27	8, 27	7, 27
Baseline ADHD-RS-IV Inattention Subscale Score			
n	77	79	156
Mean (SD)	22.3 (3.30)	21.8 (3.58)	22.1 (3.45)
Median	23.0	23.0	23.0
Min, Max	13, 27	14, 27	13, 27
Baseline CGI-S Severity Rating			
n	77	79	156
Mean (SD)	5.1 (0.81)	5.0 (0.72)	5.1 (0.77)
Median	5.0	5.0	5.0
Min, Max	3, 7	4, 7	3, 7
ADHD Subtype n (%)			
n	78	79	157
Predominantly Inattentive	16 (20.5)	11 (13.9)	27 (17.2)
Predominantly Hyperactive/Impulsive	1 (1.3)	0	1 (0.6)
Combined	61 (78.2)	68 (86.1)	129 (82.2)
Time Since ADHD Diagnosis (years)			
n	78	79	157
Mean (SD)	2.87 (2.870)	2.46 (2.803)	2.67 (2.835)
Median	2.30	1.04	1.63
Min, Max	0.0, 9.4	0.0, 10.2	0.0, 10.2

Includes subjects at Site 24
Baseline measurements are from the Screening Visit of the antecedent study (SPD489-325), or last assessment before first dose of investigational product for directly enrolled subjects.
Time from diagnosis calculated to time of informed consent in the antecedent study (SPD489-325), or Study SPD498-326 for directly enrolled
subjects.
Percentages are based on the number of subjects with data in each treatment group and total.

Subject Disposition

In total, 276 children and adolescents were enrolled, 236 rollover subjects from Study SPD489-325 (EU subjects) and 40 directly enrolled subjects from sites in the US.

Children and adolescents were treated with SPD489 (30, 50, or 70mg/day) for at least 6 months prior to entering a 6-week double-blind randomized (SPD489 or placebo) withdrawal period. 157 children and adolescents were randomized; 78 to SPD489 and 79 to placebo.

Concomitant Medications

A summary of the most common (>2% subjects) concomitant medications taken during the Open-label Period is presented in Table 9 below (source: SPD489-326 Clinical Study Report, Table 16, page 84). In total, 135 subjects (48.9%) received concomitant medications during the Open-label Period, the most common of which were paracetamol (55 subjects, 19.9%) and ibuprofen (42 subjects, 15.2%). The administration of concomitant medications was slightly higher amongst directly enrolled subjects (26 subjects, 65.0%) as compared to rollover subjects (109 subjects, 46.2%).

Table 9. SPD489-326 Summary of Most Common (>2% Subjects) Concomitant Medications Taken During the Open-label Period (Open-label Safety Population)

	Treatment Group from Antecedent Study (SPD489-325)			SPD489-325 Rollover (N=236)	Directly Enrolled (N=40)	Total (N=276)
	SPD489 (N=78)	Placebo (N=75)	CONCERTA (N=83)			
	n (%)					
Any Concomitant Medications	38 (48.7)	35 (46.7)	36 (43.4)	109 (46.2)	26 (65.0)	135 (48.9)
Paracetamol	15 (19.2)	16 (21.3)	14 (16.9)	45 (19.1)	10 (25.0)	55 (19.9)
Ibuprofen	6 (7.7)	11 (14.7)	11 (13.3)	28 (11.9)	14 (35.0)	42 (15.2)
Cetirizine hydrochloride	1 (1.3)	3 (4.0)	2 (2.4)	6 (2.5)	5 (12.5)	11 (4.0)
Amoxicillin	2 (2.6)	1 (1.3)	2 (2.4)	5 (2.1)	4 (10.0)	9 (3.3)
Phenoxymethylpenicillin potassium	4 (5.1)	4 (5.3)	1 (1.2)	9 (3.8)	0	9 (3.3)
Salbutamol	1 (1.3)	1 (1.3)	4 (4.8)	6 (2.5)	3 (7.5)	9 (3.3)
Hydrocortisone	3 (3.8)	2 (2.7)	1 (1.2)	6 (2.5)	1 (2.5)	7 (2.5)
Acetylcysteine	2 (2.6)	1 (1.3)	3 (3.6)	6 (2.5)	0	6 (2.2)
Budesonide	1 (1.3)	3 (4.0)	2 (2.4)	6 (2.5)	0	6 (2.2)
Methylphenidate hydrochloride[a]	3 (3.8)	2 (2.7)	1 (1.2)	6 (2.5)	0	6 (2.2)

Includes subjects at Site 24
[a] Methylphenidate hydrochloride was taken on the date that investigational product was discontinued for 6 subjects
Percentages are based on the number of subjects in each treatment group and total.
Subjects could have received more than 1 medication.

A summary of the most common (>2% subjects) concomitant medications taken during the Randomized Withdrawal Period is presented in Table 10 below (source: SPD489-326 Clinical Study Report, Table 17, page 85). In total, 50 subjects (31.8%) received concomitant medications during the Randomized Withdrawal Period, of whom 39.7% were in the SPD489 group and 24.1% were in the placebo group. The most commonly administered concomitant medications during the Randomized Withdrawal Period were paracetamol (12 subjects, 7.6%) and ibuprofen (9 subjects, 5.7%).

Table 10. SPD489-326 Summary of Most Common (>2% Subjects) Concomitant Medications Taken During the Randomized Withdrawal Period (Randomized Safety Population)

	Randomized Treatment Group		
	SPD489 (N=78)	Placebo (N=79)	Total (N=157)
	n (%)		
Any Concomitant Medications	31 (39.7)	19 (24.1)	50 (31.8)
Paracetamol	8 (10.3)	4 (5.1)	12 (7.6)
Ibuprofen	5 (6.4)	4 (5.1)	9 (5.7)
Cetirizine hydrochloride	4 (5.1)	3 (3.8)	7 (4.5)

Includes subjects at Site 24
Percentages are based on the number of subjects in each treatment group and total.
Subjects could have received more than 1 medication.

Important Protocol Violations

There were no subjects who became pregnant during the study. Five placebo subjects in the Open-label Safety Population, and three active treatment subjects in the Randomized Withdrawal Population, were noted as having a deviation of abuse, misuse, or overdose of investigational product. Overall, approximately 50% of subjects reported major protocol deviations as defined in the Statistical Analysis Plan (SAP).

Table 11 below (source: SPD489-326 Clinical Study Report, Table 20, page 88) presents a summary of major protocol deviations for the Open-label Safety Population. A total of 147 subjects (53.3%) in the Open-label Safety Population had at least one major deviation from the protocol. The percentages of subjects with at least one major protocol deviation were 56.8 and 32.5% respectively for subjects entering from SPD489-325 and those directly enrolled.

Table 11. SPD489-326 Summary of Major Protocol Deviations (Open-label Safety Population)

	Treatment Group from Antecedent Study (SPD489-325)			SPD489-325 Rollover (N=236)	Directly Enrolled (N=40)	Total (N=276)
	SPD489 (N=78)	Placebo (N=75)	CONCERTA (N=83)			
	n (%)					
Subjects with major protocol deviation	48 (61.5)	40 (53.3)	46 (55.4)	134 (56.8)	13 (32.5)	147 (53.3)
Overall compliance <80% or >120% in Open-label Periods	4 (5.1)	3 (4.0)	7 (8.4)	14 (5.9)	7 (17.5)	21 (7.6)
Violation of in/exclusion criteria	44 (56.4)	35 (46.7)	43 (51.8)	122 (51.7)	5 (12.5)	127 (46.0)
Pregnancy	0	0	0	0	0	0
Abuse, misuse or overdose of study medication	0	5 (6.7)	0	5 (2.1)	0	5 (1.8)
Other	3 (3.8)	3 (4.0)	2 (2.4)	8 (3.4)	1 (2.5)	9 (3.3)

Includes subjects at Site 24
Percentages are based on the number of subjects in each treatment group and total.

The most frequently reported major protocol deviation was violation of inclusion/exclusion criteria. The most frequently reported inclusion criterion violation was subjects not satisfying the entry criteria in SPD489-325 including minimum required treatment duration and completion of the follow-up visit (inclusion criterion #4), subjects not having the required laboratory, pregnancy or ECG testing (inclusion criterion #5) at the time of enrollment, and blood pressure measurement >95th percentile for age, sex, and height (inclusion criterion #6). These deviations were reported for 26, 103, and 9 subjects respectively.

The sponsor noted that the root cause for the majority of these protocol deviations related to protocol-defined requirements that were operationally difficult to implement. For example, a subject who was enrolled in the antecedent study in violation of the protocol was allowed to continue in this study. However, the major protocol deviation was automatically repeated upon entry into this study. Secondly, sites operationally did not always repeat all of the required procedures upon entering a subject from the antecedent study with a >7 day gap between visits or repeated the parameters and did not have the second set available prior to enrollment. Finally, as in the antecedent study, site difficulties in the manual plotting of key coordinates such as, age and height; which was necessary to determine the BMI percentile or height percentile for a subject. Errors made in determining these requisite percentiles may also have impacted the determination of the maximum blood pressure level allowed at entry.

The major protocol deviations from these three inclusion/exclusion criteria were reviewed by a Shire physician prior to database lock and no significant safety issues were noted. The violations reviewed were judged to have no impact on the overall safety and efficacy conclusions.

Of the 147 subjects with at least one major protocol deviation, six subjects (4.1%) had a treatment-emergent SAE (Subject 04-001 cellulitis, Subject 12-016 syncope, Subject 13-017 wound, Subject 24-003 treatment noncompliance, Subject 26-003 abdominal pain, and Subject 55-001 aggression). The sponsor did not judge any of these SAEs to be plausibly related to the respective protocol deviation.

Excluding protocol deviations carried over from the preceding study, a total of 121 subjects (43.8%) reported major deviations. Of these, the most common was again violation of the in/exclusion criteria (34.4%). Deviations relating to compliance were reported by 21 subjects (7.6%). All other major deviations were reported by <5% of subjects.

Table 12 below (source: SPD489-326 Clinical Study Report, Table 21, page 89) presents a summary of major protocol deviations for the Randomized Safety Population. A total of 79 subjects (50.3%) in the Randomized Safety Population reported a major protocol deviation, the most common of which was a violation of the in/exclusion criteria

(46.5%), of whom 51.3% were randomized to SPD489 and 41.8% were randomized to placebo.

Table 12. SPD489-326 Summary of Major Protocol Deviations (Randomized Safety Population)

	SPD489 (N=78)	Placebo (N=79)	Total (N=157)
	n (%)		
Subjects with major protocol deviation	43 (55.1)	36 (45.6)	79 (50.3)
Overall compliance <80% or >120% in Randomized Withdrawal Period	3 (3.8)	3 (3.8)	6 (3.8)
Violation of in/exclusion criteria	40 (51.3)	33 (41.8)	73 (46.5)
Took prohibited medication for >2 consecutive days during Randomized Withdrawal Period	1 (1.3)	1 (1.3)	2 (1.3)
Pregnancy	0	0	0
Abuse, misuse or overdose of study medication	3 (3.8)	0	3 (1.9)
Other	1 (1.3)	4 (5.1)	5 (3.2)

Includes subjects at Site 24
Percentages are based on the number of subjects in each treatment group and total.

Excluding protocol deviations carried over from the preceding study, a total of 64 subjects (40.8%) reported major deviations. Of these, the most common was again violation of the in/exclusion criteria (35.7%). All other major deviations were reported by <5% of subjects.

Efficacy Findings

Two analysis sets were defined for efficacy: the Open-label FAS and the Randomized FAS. Each of these efficacy analysis sets excluded subjects from Site 24 (site excluded due to breach of Good Clinical Practice; see Section 3.2 above for details). However, a sensitivity analysis of the primary efficacy variable was performed that included data from Site 24.

The Open-label FAS included all subjects who received at least 1 dose of investigational product during the study. This population was used for assessing efficacy and Quality of Life information during the open-label periods of the study. The Randomized FAS included all subjects who were randomized and received at least 1 dose of investigational product during the Randomized Withdrawal Period. This population was used for assessing efficacy and QoL information during the Randomized Withdrawal Period of the study. The Open-label FAS and the Randomized FAS consisted of 262 subjects and 153 subjects, respectively.

The primary efficacy results are based on the proportion of treatment failures among subjects in the Randomized FAS during the Randomized Withdrawal Period. Treatment failure was defined as a 50% increase in ADHD-RS-IV Total Score and a ≥2 point increase in CGI-S score observed at any visit during the Randomized Withdrawal

Period compared to the respective scores at Baseline (Visit 3R). Subjects who withdrew from the Randomized Withdrawal Period and who did not provide efficacy data at the ET Visit were classed as treatment failures in the primary efficacy analysis.

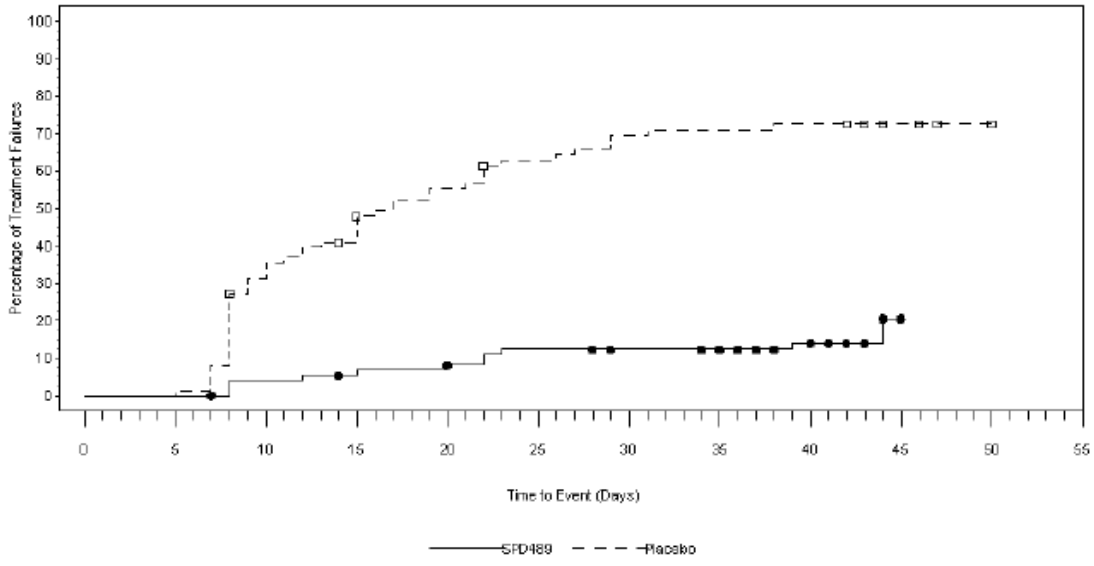
At Endpoint, 12/76 (15.8%) subjects who received SPD489 during the double-blind Randomized Withdrawal Period were categorized as treatment failures, compared to 52/77 (67.5%) of subjects who received placebo ($p<0.001$). See Figure 4 below for details regarding time to treatment failure (source: SPD489-326 Clinical Study Report, Figure 4, page 94).

Results of the sensitivity analysis of treatment failure, which includes subjects from Site 24, are similar to those obtained using the Randomized FAS. Among the 157 subjects in the Randomized FAS across all sites including Site 24 (SPD489, 78 subjects; placebo, 79 subjects), 13/78 (16.7%) subjects in the SPD489 group and 54/79 (68.4%) subjects in the placebo group met the criteria for treatment failure at Endpoint ($p<0.001$).

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

A number of secondary efficacy variables were listed, but none were identified as key secondaries.

Figure 4: Kaplan-Meier Plot of Time to Treatment Failure (Randomized Full Analysis Set)



6.1.3 Crosscutting Issues

Subgroup Analyses

Age

At Endpoint, regardless of age category, the majority of subjects in the placebo group met the criteria for treatment failure whereas the majority of subjects in the SPD489 group did not meet these criteria. Similar profiles were seen between the age groups.

Among the 103 subjects aged 6-12 in the Randomized FAS, 10/53 (18.9%) subjects in the SPD489 group and 34/50 (68.0%) subjects in the placebo group met the criteria for treatment failure at Endpoint ($p<0.001$). Among the 50 subjects aged 13-17 in the Randomized FAS, 2/23 (8.7%) subject in the SPD489 group and 18/27 (66.7%) subjects in the placebo group met the criteria for treatment failure at Endpoint ($p<0.001$).

Sex

At Endpoint, the majority of subjects in the placebo group met the criteria for treatment failure whereas the majority of subjects in the SPD489 group did not meet these criteria. Similar profiles were seen for males and females.

Among the 119 male subjects in the Randomized FAS, 10/59 (16.9%) subjects in the SPD489 group and 42/60 (70.0%) subjects in the placebo group met the criteria for treatment failure at Endpoint ($p<0.001$). Among the 34 female subjects in the Randomized FAS, 2/17 (11.8%) subjects in the SPD489 group and 10/17 (58.8%) subjects in the placebo group met the criteria for treatment failure at Endpoint ($p = 0.007$).

Race

Due to the small number of Non-white subjects compared to White subjects, no meaningful conclusion can be drawn for any effect of race on the proportions of treatment failure.

Region

Of the 9 countries that enrolled subjects in this study, treatment failure occurred in 8 countries (Belgium, France, Germany, Hungary, Italy, Poland, Sweden, and US). For each of these 8 countries, the proportion of treatment failure at Endpoint was consistently lower for subjects in the SPD489 group compared to the placebo group. When treatment failure occurred at any of Visits 4R through 7R, the proportion was consistently higher for placebo subjects than for SPD489 subjects, regardless of country.

One of the 9 countries (GB) did not have any treatment failures at Endpoint or at any study visit during the Randomized Withdrawal Period. However, this country only had 2

subjects (SPD489, 1 subject; placebo, 1 subject) enrolled in the Randomized Withdrawal Period.

A similar percentage of treatment failures were seen in subjects enrolled in the EU and US.

6.1.4 Conclusions Regarding Maintenance of Efficacy Claim

Lisdexamfetamine dimesylate has been shown to be efficacious in the maintenance treatment of ADHD in one randomized withdrawal study. In her review dated 4/14/13, statistical reviewer Jinglin Jong, PhD confirmed the sponsor's findings from SPD489-326 that SPD489 (administered once daily in 30 mg, 50 mg, and 70 mg) was statistically significantly superior to placebo (CMH test p-value less than 0.001) in reducing the proportion of treatment failures at the end of the double-blind randomized 6 weeks withdrawal phase in children and adolescents with ADHD. Further, she confirmed the finding from SPD489-325 that SPD489 (administered once daily in 30, 50, and 70 mg) showed positive effect compared to placebo in reducing the ADHDRS-IV total score from Baseline at Endpoint, and that SPD489 at these doses is statistically significantly superior to placebo in increasing the proportion of patients with improved CGI-I at the Endpoint.

7 Review of Safety

Safety Summary

In general, the safety profile of lisdexamfetamine dimesylate as demonstrated in study SPD489-325 is similar to the overall safety profile described in the original NDA review and in current labeling. In study SPD489-326 only subjects who tolerated the drug in the open-label phase were randomized into the double-blind withdrawal phase; thus, it is difficult to draw conclusions from the safety data generated by this study. However, the adverse events reported during study SPD489-326 are consistent with the known safety profile of lisdexamfetamine.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor submitted data from one randomized, double-blind, placebo-controlled trial (SPD489-325) and one study with an initial open-label phase followed by randomized withdrawal (SPD489-326). Given that the design of SPD489-326 precludes meaningful conclusions regarding the safety of lisdexamfetamine for the treatment of ADHD in children and adolescents, this safety review is focused on the safety data derived from study SPD489-325. In addition, information regarding adverse events at the more serious end of the spectrum (deaths, non-fatal serious adverse events, and adverse

events that led to dropout) from SPD489-326 was also examined. The safety population in each study and phase of study was defined as all subjects who received at least 1 dose of any investigational product during the study.

7.1.2 Categorization of Adverse Events

The JMP files for adverse events were reviewed with an emphasis on the verbatim to preferred term coding. In general, it appeared that most verbatim terms were appropriately coded to preferred terms.

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

See 7.1.1.

7.2 Adequacy of Safety Assessments

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

Lisdexamfetamine dimesylate is currently approved for the acute treatment of ADHD in children, adolescents, and adults, as well as the maintenance treatment of ADHD in adults in doses ranging from 30mg to 70mg daily. In this supplement, the sponsor is proposing to expand the approved indications for children and adolescents to include maintenance treatment.

SPD489-325
The mean (standard deviation [SD]) lengths of exposure were similar for the SPD489 and Concerta groups (6.05 [1.872 weeks] weeks and 6.13 [1.694] weeks) and were longer than placebo (5.07 [1.843] weeks). Overall, among subjects in the SPD489 and Concerta groups, the majority had 43-56 days of exposure to investigational product whereas, among placebo subjects, the majority had 22-35 or 43-49 days of exposure to investigational product. See Table 13 below for additional details (source: Summary of Clinical Safety, Table 1, page 10).

Table 13: Summary of Overall Drug Exposure (Safety Population)—Study SPD489-325

	SPD489 (N=111)	Placebo (N=110)	OROS MPH (N=111)	Total (N=332)
Length of Exposure (Weeks)				
n	111	110	111	332
Mean	6.05	5.07	6.13	5.75
SD	1.872	1.843	1.694	1.862
Min, Max	0.1, 7.9	0.6, 8.3	0.1, 8.6	0.1, 8.6
Length of Exposure Category (Days)	111	110	111	332
1-7 n (%)	5 (4.5)	3 (2.7)	3 (2.7)	11 (3.3)
8-14 n (%)	4 (3.6)	8 (7.3)	3 (2.7)	15 (4.5)
15-21 n (%)	3 (2.7)	4 (3.6)	2 (1.8)	9 (2.7)
22-28 n (%)	6 (5.4)	20 (18.2)	7 (6.3)	33 (9.9)
29-35 n (%)	8 (7.2)	24 (21.8)	10 (9.0)	42 (12.7)
36-42 n (%)	3 (2.7)	10 (9.1)	8 (7.2)	21 (6.3)
43-49 n (%)	60 (54.1)	32 (29.1)	52 (46.8)	144 (43.4)
50-56 n (%)	22 (19.8)	8 (7.3)	25 (22.5)	55 (16.6)
57-63 n (%)	0	1 (0.9)	1 (0.9)	2 (0.6)
>63 n (%)	0	0	0	0
Total Days Exposed				
Number of Days	4697	3904	4765	13366

Note: Length of Exposure = last dose date – first dose date + 1.
Note: Total number of days exposed is the total number of days over all subjects.
Note: Percentages are based on the number of subjects in Safety Population in each group.

SPD489-326

During the Open-label Period, the mean (SD) length of exposure across all SPD489 doses was 23.4 (11.78) weeks. When presented by dose level, the mean (SD) length of exposure to SPD489 was longer in the SPD489 50mg and 70mg groups compared to SPD489 30mg, with the respective durations of exposure being 11.4 (12.50) weeks and 15.5 (11.92) weeks compared to 6.6 (10.02) weeks. See Table 14 below for additional details (source: Summary of Clinical Safety, Table 3, page 15).

Table 14: Length of Exposure to Investigational Product During the Open-label Period (Open-label Safety Population)—Study SPD489-326

	SPD489 30mg (N=276)	SPD489 50mg (N=226)	SPD489 70mg (N=133)	All (N=276)
Length of Exposure (Weeks)				
Mean (SD)	6.6 (10.02)	11.4 (12.50)	15.5 (11.92)	23.4 (11.78)
Median	1.3	5.3	16.9	25.9
Min, Max	<1, 52	<1, 53	<1, 50	<1, 54
Total Days Exposed				
Number of Days	12665	18040	14432	45137
Length of Exposure Category During Open-label Period (Completed Days)				n (%)
At least 1 day				276 (100.0)
At least 29 days	(approximately 4 weeks)			249 (90.2)
At least 57 days	(approximately 8 weeks)			231 (83.7)
At least 85 days	(approximately 12 weeks)			222 (80.4)
At least 113 days	(approximately 16 weeks)			207 (75.0)
At least 141 days	(approximately 20 weeks)			198 (71.7)
At least 169 days	(approximately 24 weeks)			183 (66.3)
At least 197 days	(approximately 28 weeks)			46 (16.7)
At least 225 days	(approximately 32 weeks)			36 (13.0)
At least 253 days	(approximately 36 weeks)			32 (11.6)
At least 281 days	(approximately 40 weeks)			23 (8.3)
At least 309 days	(approximately 44 weeks)			16 (5.8)
At least 337 days	(approximately 48 weeks)			12 (4.3)
At least 365 days	(approximately 52 weeks)			3 (1.1)

Note: Length of Exposure = last dose date – first dose date +1.
Note: Total number of days exposed is the total number of days over all subjects.
Note: Percentages were based on the number of subjects in Open-label Safety Population in each group.
Note: The Open-label Period was originally planned to have a duration of 52 weeks.

Of the 276 subjects in the Open-label Safety Population, 183 subjects (66.3%) had at least 169 days of open-label treatment with SPD489; 46 subjects (16.7%) received at least 197 days of open-label treatment. This sharp reduction between the numbers of subjects receiving approximately 6 months of open-label treatment and those receiving more than 6 months of open-label treatment is due to the implementation of an amendment to the original protocol which decreased the number of weeks in the Open-label Period from 52 to 26 and added a 6-week double-blind Randomized Withdrawal Period. Some subjects continued to receive open-label treatment for up to 52 weeks

under the original protocol rather than entering the 6-week double-blind period of the study.

During the Randomized Withdrawal Period, the overall mean (SD) lengths of exposure to SPD489 and placebo were 5.2 (1.59) weeks and 2.8 (2.06) weeks, respectively. The shorter duration of exposure among placebo subjects compared to SPD489 was consistent with a higher dropout rate among placebo subjects compared to SPD489 (79.7% vs 23.1%, respectively). See Table 15 below for additional details (source: Summary of Clinical Safety, Table 5, page 18).

Table 15: Length of Exposure to Investigational Product During the Randomized Withdrawal Period (Randomized Safety Population)—Study SPD489-326

	Statistic	SPD489 (N=78)	Placebo (N=79)
Length of Exposure (Weeks)			
	Mean (SD)	5.2 (1.59)	2.8 (2.06)
	Median	5.9	2.0
	Min, Max	1, 7	<1, 8
Length of Exposure Category (Completed Days)			
At least 1 day	n (%)	78 (100.0)	79 (100.0)
At least 8 days	n (%)	74 (94.9)	56 (70.9)
At least 15 days	n (%)	71 (91.0)	38 (48.1)
At least 22 days	n (%)	65 (83.3)	26 (32.9)
At least 29 days	n (%)	62 (79.5)	19 (24.1)
At least 36 days	n (%)	62 (79.5)	18 (22.8)
At least 43 days	n (%)	16 (20.5)	9 (11.4)
Total Days Exposed			
Number of Days		2832	1556

Note: Length of Exposure = last dose date – first dose date +1.
Note: Total number of days exposed is the total number of days over all subjects.
Note: Percentages were based on the number of subjects in Randomized Safety Population in each group.

7.2.2 Explorations for Dose Response

Study SPD489-326 was an open-label, dose-optimization design and a dose response was therefore not interpretable.

In Study SPD489-325, similar percentages of SPD489 subjects experienced at least one TEAE that began while receiving 30mg (55.0%) or 70mg (51.1%); 37.5% of subjects had at least one TEAE that began while receiving 50mg. These results should be interpreted with caution as this was a dose-optimization study.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Safety Measures in SPD489-325

- Medical and medication history – Visit -1 (Screening)
- Physical examination (including height and weight). A full physical examination was performed at Screening Visit, at Visit 7/ET (Day 49), and at Visit 8 (Day 56); and an abbreviated physical examination was to be performed at the Baseline Visit (Day 0) if more than 30 days had elapsed since the Screening Visit.
- Vital signs – Assessed at all visits
- Clinical laboratory evaluations. Clinical laboratory evaluations, including biochemistry, hematology, and urinalysis, were assessed at Screening and at Visit 7/ET (Day 49). Clinical laboratory tests were to be performed at the Baseline Visit (Day 0) if more than 30 days had elapsed since the Screening Visit.
- Pregnancy test. A serum beta HCG pregnancy test was performed on all FOCPs at Screening and Visit 7/ET (Day 49). A urine pregnancy test was performed at Baseline (Day 0), at Visit 4 (Day 28), and at Visit 8 (Day 56).
- Urine Drug Screen (UDS). Assessed at Screening and Visit 7/ET.
- Electrocardiogram. A 12-lead ECG was performed at each study visit. Three ECGs, approximately 10 minutes apart each, were preformed at the Baseline Visit (Day 0).
- Adverse Events. Adverse events were assessed throughout the study (i.e., from the time informed consent was signed up to and including the Follow-up Visit).
- Brief Psychiatric Rating Scale for Children. The BPRS-C was added to the protocol as a safety assessment per Amendment 1.0 (dated 22 Dec 2009) after the study had been initiated. The BPRS-C was to be completed at the Baseline Visit (Day 0), at Visit 4 (Day 28), and at Visit 7/ET (Day 49).
- Columbia-Suicide Severity Rating Scale. The C-SSRS was added to the protocol as a safety assessment per Amendment 1.0 (dated 22 Dec 2009) after the study had been initiated. Three versions of this scale were used: the “Baseline” version, the “Already Enrolled Subjects” version, and the “Since Last Visit” version.
  - For new subjects, the C-SSRS “Baseline” version was completed at the Baseline Visit (Day 0), and the C-SSRS “Since Last Visit” version was completed at all subsequent visits.
  - For ongoing subjects, the C-SSRS “Already Enrolled Subjects” version was completed at the next study visit and the C-SSRS “Since Last Visit” version was completed at all subsequent visits.
- Suitability of Subject to Remain in the Study. This assessment was added to the protocol per Amendment 1.0 (dated 22 December 2009) after the study had been initiated. The Suitability of Subject to Remain in the Study was assessed at each of Visits 1 (Day 7) through 7/ET (Day 49), inclusive. As part of this assessment, the subject was assessed for current potential for suicide, suicidal ideation, self-harm or

harm to others, as well as psychiatric disorders. The assessment was based on a clinical interview with the subject and by reviewing other relevant sources available, including results of the C-SSRS and BPRS-C.

Safety Measures in SPD489-326

- Medical and medication history – Visit -1 (Screening)
- Physical examination (including height and weight). A full physical examination was performed at Screening (Visit -1 for US subjects; Visit 8 of the antecedent study for rollover subjects), Visit 9R/ET and Safety Follow-up Visit.
- Vital signs – Assessed at all visits
- Clinical laboratory evaluations. Clinical laboratory evaluations, including biochemistry, hematology, and urinalysis, were assessed at Screening (Visit -1 for US subjects; Visit 7 of the antecedent study for rollover subjects), Visit 9, Visit 3R, and Visit 9R/ET
- Pregnancy test. A serum beta HCG pregnancy test was performed on all FOCPs at Screening (Visit-1 for US subjects; Visit 8 of the antecedent study for rollover subjects) and Visit 9R/ET. A urine pregnancy test was conducted at Visits 1, 7, 3R, and Safety Follow-up. Additional urine pregnancy tests were performed at the Investigator's discretion.
- Urine Drug Screen (UDS). Assessed at Screening (Visit -1 for US subjects; Visit 7 of the antecedent study for rollover subjects), Visit 3R, and 9R/ET.
- Electrocardiogram. A 12-lead ECG was performed at Screening (Visit -1 for US subjects; Visit 8 of the antecedent study for rollover subjects) and Visits 1 (US subjects only), 7, 3R, and 9R/ET.
- Adverse Events. Adverse events were assessed throughout the study (i.e., from the time informed consent was signed up to and including the Follow-up Visit).
- Brief Psychiatric Rating Scale for Children. The BPRS-C was added to the protocol as a safety assessment per Amendment 2.0 (dated 17 Dec 2009) after the study had been initiated. The BPRS-C was to be completed at Visits 1 (Visit 7 of the antecedent study for EU subjects), 5, 3R, and 9R/ET. However, for EU subjects the BPRS-C was completed only if completed at Baseline [Visit 0] of the antecedent Study SPD489-325.
- Columbia-Suicide Severity Rating Scale. The C-SSRS was added to the protocol as a safety assessment per Amendment 2.0 (dated 17 Dec 2009) after the study had been initiated. Three versions of this scale were used: the "Baseline" version, the "Already Enrolled Subjects" version, and the "Since Last Visit" version.
  - For US subjects, the C-SSRS "Baseline" version was completed at the Baseline Visit (Day 0), and the C-SSRS "Since Last Visit" version was completed at all subsequent visits.
  - For ongoing EU subjects, the C-SSRS "Already Enrolled Subjects" version was completed at the next study visit and the C-SSRS "Since Last Visit" version was completed at all subsequent visits.

7.2.5 Metabolic, Clearance, and Interaction Workup

None.

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

No further evaluations done.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during either SPD489-325 or SPD489-326.

7.3.2 Nonfatal Serious Adverse Events

SPD489-325
Eight subjects each had a single serious treatment-emergent adverse event (TEAE) during study SPD489-325 (SPD489: 3 subjects, 2.7%; placebo: 3 subjects, 2.7%; OROS MPH, 2 subjects, 1.8%). Of these 8 treatment-emergent SAEs, 1 event (overdose in the OROS MPH group) was considered by the Investigator to be related to investigational product.

The sponsor required any new onset of seizures, syncope, or loss of consciousness to be an important medical event and therefore to be reported as an SAE. Of the 8 subjects with SAEs, 2 subjects had syncope (SPD489, 1 subject; Concerta, 1 subject) and 1 subject (placebo) had loss of consciousness. These events were moderate in intensity and none were considered by the Investigator to be related to investigational product. Treatment with investigational product was interrupted for the placebo subject but dosing was not affected for the other 2 subjects. All events resolved.

Serious adverse events for the other 5 subjects were gastroesophageal reflux disease (SPD489, 1 subject), appendicitis (SPD489, 1 subject), hematoma, (placebo, 1 subject), clavicle fracture (placebo, 1 subject), and overdose (Concerta, 1 subject). Of these 5 treatment-emergent SAEs, 1 event (overdose) was considered related to investigational product. The subject (Concerta) with an SAE of overdose took 2 Concerta capsules (each capsule, 54mg) in one day. The event of overdose was mild and resolved without medical intervention.

SPD489-326
During the Open-label Period of SPD489-326, 12 subjects (4.3%) reported 14 SAEs, of which 13 events were treatment-emergent. Syncope and aggression were the only SAEs that were reported in more than 1 subject during the Open-label Period. No

subjects in the SPD489 group reported an SAE during the Randomized Withdrawal Period.

Syncope was reported as an SAE for 2 subjects. The syncopal episodes were single episodes and were not considered by the Investigator to be related to investigational product. Both events resolved without pharmacological intervention. For 1 subject, the event was mild and the investigational product was discontinued. For the other subject, the event was moderate and no action was taken with regard to investigational product; this subject also had abnormal behavior reported as an SAE that was severe in intensity and resolved 1 day prior to the onset of syncope.

Other than syncope, aggression was the only SAE reported for 2 subjects during the Open-label Period. Neither event of aggression was considered by the Investigator to be related to investigational product. For 1 subject, the event was mild and resolved with pharmacological treatment. For the other subject, the event was severe and resolved with pharmacological and non-pharmacological treatment; this subject also had dehydration reported as an SAE that was severe in intensity and resolved approximately 4 months prior to the onset of aggression.

Eight other subjects each had 1 SAE reported during open-label treatment; these SAEs included abdominal pain, vomiting, cellulitis, gastric infection, wound, anger, oppositional defiant disorder, and treatment noncompliance.

7.3.3 Dropouts and/or Discontinuations

SPD489-325
During SPD489-325, eleven subjects were discontinued from investigational product due to a total of 19 Treatment-Emergent Adverse Events (TEAEs) (SPD489: 5 subjects, 4.5%; placebo: 4 subjects, 3.6%; Concerta: 2 subjects, 1.8%). TEAEs within the SPD489 group that led to discontinuation of investigational product were vomiting and anorexia (each, 2 subjects); and decreased appetite, angina pectoris, tachycardia, weight decreased, and insomnia (each, 1 subject).

SPD489-326
During the Open-label Period of SPD489-326, 45 subjects (16.3%) were discontinued from investigational product due to a TEAE. The most common TEAEs leading to discontinuation were insomnia (8 subjects, 2.9%), aggression (5 subjects, 1.8%), decreased appetite, headache, and depressed mood (each in 4 subjects, 1.4%). No subjects in the SPD489 group were discontinued from investigational product during the Randomized Withdrawal Period due to a TEAE.

The majority of TEAEs leading to discontinuation were mild or moderate in intensity. Five subjects had TEAEs leading to discontinuation that were severe in intensity (insomnia in 1 subject; anorexia, asthenia, headache, and insomnia in 1 subject;

worsening of ADHD in 1 subject; aggression, agitation, and irritability in 1 subject; and explosive behavior in 1 subject). With the exception of explosive behavior, all events were considered by the Investigator to be related to investigational product.

Of the 45 subjects with TEAEs leading to discontinuation, 3 subjects had TEAEs leading to discontinuation that were serious (mild syncope, 1 subject; moderate abdominal pain, 1 subject; severe explosive behavior, 1 subject). The SAEs that led to discontinuation all resolved and none were considered by the Investigator to be related to investigational product.

7.3.4 Significant Adverse Events

Except as noted above, no other clinically significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

Cardiovascular effects are of concern with drugs in the stimulant class.

In SPD489-325, of the 332 subjects in the Safety Population, TEAEs associated with the System Organ Class Cardiac Disorders were reported for 6 subjects (SPD489: 3 subjects, 2.7%; placebo: 1 subject, 0.9%; Concerta: 2 subjects, 1.8%). Three TEAEs were associated with Cardiac Disorders—tachycardia (SPD489, 2 subjects; placebo, 1 subject; Concerta, 1 subject), palpitations (SPD489, 1 subject; placebo, 1 subject; Concerta, 1 subject), and precardiac pain (which was coded to the MedDRA preferred term of angina pectoris) (SPD489, 1 subject). No TEAE associated with Cardiac Disorders was serious. One subject (SPD489) was discontinued due to TEAEs of tachycardia and precardiac pain (angina pectoris). Both of these events resolved.

In SPD489-326, during open-label treatment with SPD489, the overall frequency of TEAEs associated with Cardiac Disorders was 1.8%. The most frequently reported Cardiac Disorders TEAE was palpitations, which was reported for 1.1% of subjects. All Cardiovascular Disorders TEAEs were mild or moderate in intensity.

No Cardiac Disorders were reported as SAEs. Two subjects (0.7%) reported TEAEs associated with Cardiac Disorders that led to discontinuation during open-label treatment. These TEAEs were palpitations (1 subject) and supraventricular tachycardia (1 subject).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common (>5.0% and 2X placebo) Treatment Emergent Adverse Events (TEAEs) in the SPD489 group of study SPD489-325 vs. placebo were decreased

appetite (25.2% vs. 2.7% in placebo), insomnia (14.4% vs. 0%), weight decreased (13.5% vs. 0%), nausea (10.8% vs. 2.7%), anorexia (10.8% vs. 1.8%), and sleep disorder (5.4% vs. 0.9%).

Study SPD489-325 included an active control arm of Concerta in addition to a placebo. The most common (>5.0% and 2X placebo) TEAEs in the Concerta group were decreased appetite (15.3% vs. 2.7% in placebo), insomnia (8.1% vs. 0%), nausea (7.2% vs. 7.2%), cough (7.2% vs. 0%), initial insomnia (6.3% vs. 0.9%), and anorexia (5.4% vs. 1.8%).

The AE profiles of both active treatments were consistent with the known effects of stimulant treatment as well as seasonal disorders commonly observed in long-term studies.

7.4.2 Laboratory Findings

No clinically meaningful trends were observed in clinical laboratory results over time for either Study SPD489-325 or SPD489-326.

7.4.3 Vital Signs

Overall, SPD489 was associated with modest mean increases in pulse, systolic blood pressure, and diastolic blood pressure, which are consistent with the known effects of stimulant treatment, and the labeled side effect profile of this product.

Vital signs data from SPD489-325 are presented in Table 16 below (source: SPD489-325 Clinical Study Report, Table 42, page 148).

Table 16: Summary of Vital Signs (Safety Population)—Study SPD489-325

	SPD489 (N=111)		Placebo (N=110)		CONCERTA (N=111)	
Variable/Visit	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Sitting Pulse (bpm)						
Baseline (Day 0)						
n	111		110		111	
Mean	75.0		77.5		76.6	
SD	11.70		11.48		10.20	
Median	75.0		76.0		76.0	
Min, Max	53, 136		54, 118		52, 109	
Endpoint						
n	106	106	108	108	108	108
Mean	80.2	5.5	77.0	-0.6	79.8	3.4
SD	14.04	13.19	9.71	10.63	12.68	13.19
Median	78.0	4.0	77.5	0.0	79.5	4.0
Min, Max	51, 124	-36, 52	54, 106	-46, 28	52, 124	-36, 32
Seated Systolic BP (mmHg)						
Baseline (Day 0)						
n	111		110		111	
Mean	107.4		107.8		107.1	
SD	10.40		10.41		9.94	
Median	105.0		106.5		106.0	
Min, Max	87, 138		84, 146		80, 140	
Endpoint						
n	107	107	108	108	108	108
Mean	108.7	1.0	108.6	1.0	107.1	0.3
SD	8.90	9.82	9.60	9.62	9.29	11.14
Median	108.0	0.0	110.0	0.0	105.0	0.0
Min, Max	89, 128	-21, 30	85, 137	-23, 30	90, 137	-40, 36
Seated Diastolic BP (mmHg)						
Baseline (Day 0)						
n	111		110		111	
Mean	68.3		66.1		65.0	
SD	9.92		9.05		9.46	
Median	70.0		65.5		65.0	
Min, Max	46, 98		42, 87		33, 85	
Endpoint						
n	107	107	108	108	108	108
Mean	68.7	0.2	67.1	1.2	66.8	1.7
SD	8.31	9.64	9.08	8.67	9.52	9.85
Median	70.0	0.0	68.0	0.0	67.0	2.0
Min, Max	45, 90	-27, 26	40, 93	-20, 30	40, 98	-24, 34

In the Open-label period of Study SPD489-326, mean (SD) values for vital signs parameters were:

- Sitting pulse was 77.3bpm (10.78) at Baseline and 83.3bpm (12.47) at Open-label Endpoint.
- Sitting systolic blood pressure was 107.8mmHg (9.91) at Baseline and 109.5mmHg (9.22) at Open-label Endpoint.
- Sitting diastolic blood pressure was 67.1mmHg (9.37) at Baseline and 69.4mmHg (8.21) at Open-label Endpoint.

Vital sign data from the Randomized Withdrawal Period of SPD489-326 are listed in Table 17 below (source: SPD489-326 Clinical Study Report, Table 63, page 191).

Table 17: Summary of Vital Signs by Actual Dose in the Randomized Withdrawal Period—Observed Values (Randomized Safety Population)—Study SPD489-326

Variable / Visit	Statistic	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Total
Sitting Pulse (bpm)						
Baseline						
Observed	n	79	19	27	32	78
	Mean	75.7	79.5	78.5	75.5	77.5
	SD	10.17	13.49	14.11	9.88	12.33
	Min, Max	54, 102	60, 104	60, 136	57, 96	57, 136
Endpoint						
Observed	n	75	18	27	32	77
	Mean	79.8	80.6	83.9	84.3	83.3
	SD	10.78	8.85	13.03	12.72	11.99
	Min, Max	52, 103	64, 98	64, 120	60, 120	60, 120
Change from Baseline	n	75	18	27	32	77
	Mean	4.2	0.4	5.4	8.8	5.6
	SD	10.30	13.14	19.83	11.83	15.52
	Min, Max	-16, 28	-32, 25	-72, 31	-24, 37	-72, 37
Sitting Systolic Blood Pressure (mmHg)						
Baseline						
Observed	n	79	19	27	32	78
	Mean	108.4	110.3	109.9	105.0	108.0
	SD	9.03	9.72	8.75	10.05	9.73
	Min, Max	90, 140	95, 126	98, 138	86, 125	86, 138

Table 17 (con't.)

Variable / Visit	Statistic	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Total
Endpoint						
Observed	n	75	18	27	32	77
	Mean	107.5	107.1	109.8	109.9	109.2
	SD	8.89	10.60	8.28	11.55	10.22
	Min, Max	85, 130	90, 130	94, 130	95, 140	90, 140
Change from Baseline	n	75	18	27	32	77
	Mean	-0.6	-2.3	-0.1	4.9	1.5
	SD	9.66	8.21	11.12	13.32	11.79
	Min, Max	-20, 25	-19, 10	-33, 20	-15, 35	-33, 35
Sitting Diastolic Blood Pressure (mmHg)						
Baseline						
Observed	n	79	19	27	32	78
	Mean	66.9	67.3	71.2	63.5	67.1
	SD	9.27	8.65	9.83	9.19	9.78
	Min, Max	35, 90	50, 85	55, 98	42, 80	42, 98
Endpoint						
Observed	n	75	18	27	32	77
	Mean	66.8	68.3	70.8	66.4	68.4
	SD	8.13	8.00	6.40	8.66	7.92
	Min, Max	45, 90	60, 81	60, 80	48, 82	48, 82
Change from Baseline	n	75	18	27	32	77
	Mean	-0.1	1.2	-0.4	2.9	1.4
	SD	8.12	10.88	11.81	11.16	11.27
	Min, Max	-20, 20	-20, 20	-34, 20	-18, 25	-34, 25

Includes subjects at Site 24
Baseline is Baseline Visit from the antecedent study (SPD489-325) or Visit 1 of Study SPD489-326 for directly enrolled subjects.
Endpoint is the last valid vital sign value obtained after Visit 3R.
bpm=beats per minute

7.4.4 Electrocardiograms (ECGs)

In SPD 489-326, a 12-lead ECG was obtained at Visit 1 (Day 0), Visit 7 (Day 84), Visit 3R/ET, and 9R/ET. For this study, QTcF was used; the sponsor noted that this was thought to be the more relevant QT correction because subjects receiving stimulant therapy may have increased heart rates.

At baseline, the mean (SD) PR interval was 140.4msec (18.78), heart rate was 75.9bpm (10.34), QRS interval was 85.6msec (7.86), QT interval was 351.2msec (22.94), QTcF was 377.8msec (15.41), and QTcB was 392.2msec (17.01).

Overall, mean changes in ECG parameters were small and consistent with the effect of stimulant therapy. Mean changes in ECG parameters generally occurred between Baseline and the first on-treatment ECG measurement at Visit 7 (Day 84); thereafter ECG parameters were relatively stable with the exception of heart rate which demonstrated a small increase over time.

For the overall Safety Population, the mean (SD) changes from baseline were:

- At Visit 7 (Day 84): PR interval -4.5msec (12.80), heart rate 7.3bpm (14.25), QRS interval 0.6msec (4.92), QT interval -11.3msec (23.50), QTcF -1.1msec (15.43), and QTcB 4.7msec (21.15).
- At Visit 3R: PR interval -5.2msec (12.36), heart rate 6.4bpm (12.18), QRS interval 0.1msec (4.50), QT interval -11.4msec (20.03), QTcF -2.8msec (13.33), and QTcB 2.2msec (17.69).
- At Open-label Endpoint: PR interval -5.3msec (12.25), heart rate 7.8bpm (12.46), QRS interval 0.5msec (4.62), QT interval -12.0msec (21.14), QTcF -1.2msec (14.85), and QTcB 5.0msec (19.34).

In the Randomized Withdrawal Period, mean changes in ECG parameters were also small and consistent with the effects of stimulant therapy. For the Randomized Safety Population, the mean (SD) changes from baseline were:

- At Visit 3R:
  − SPD489: PR interval 133.5msec (21.30), heart rate 83.7bpm (15.03), QRS interval 86.7msec (8.25), QT interval 340.3msec (24.67), QTcF 377.8msec (16.33), and QTcB 398.5msec (20.85).
  − Placebo: PR interval 134.3msec (15.21), heart rate 81.6bpm (13.78), QRS interval 85.4msec (8.36), QT interval 340.1msec (22.78), QTcF 374.6msec (15.50), and QTcB 393.5msec (20.57).
- At Endpoint:
  − SPD489: PR interval 132.1msec (18.60), heart rate 82.4bpm (14.45), QRS interval 86.3msec (9.28), QT interval 340.2msec (25.49), QTcF 375.7msec (16.77), and QTcB 395.3msec (20.43).
  − Placebo: PR interval 134.6msec (13.32), heart rate 78.2bpm (12.33), QRS interval 84.5msec (8.91), QT interval 346.0msec (22.00), QTcF 376.1msec (16.23), and QTcB 392.4msec (20.81).

No clinically concerning trends in ECG intervals associated with dose strength were observed in either study phase. There did not appear to be a clear relationship between dose strength and mean change in QT intervals, however this study was not designed to elicit dose-relationship information.

At Endpoint (determined as the last non-missing assessment obtained after Visit 1 including both the Open-label and Randomized Withdrawal Periods), 1 subject (0.6%) had an ECG that was considered by the Investigator to be clinically significant. For details, see Table 18 below (source: SPD489-326 Clinical Study Report, Figure 69, page 205). For the majority of subjects, the Investigator assessed ECG at Open-label Endpoint as either normal (68.9%) or not clinically significant (29.4%).

Table 18: Qualitative Change in Investigator's Interpretation of Electrocardiogram from Baseline to Endpoint in Both the Open-label and Randomized Withdrawal Periods for All Active Treatments (Open-label Safety Population)

		Endpoint				
		Normal n (%)	Not Clinically Significant n (%)	Clinically Significant n (%)	Unable to Evaluate n (%)	Total n (%)
Baseline	Normal	84 (47.5)	20 (11.3)	0	2 (1.1)	106 (59.9)
	Not Clinically Significant	37 (20.9)	32 (18.1)	1 (0.6)	0	70 (39.5)
	Clinically Significant	0	0	0	0	0
	Unable to evaluate	1 (0.6)	0	0	0	1 (0.6)
	Total	122 (68.9)	52 (29.4)	1 (0.6)	2 (1.1)	177 (100.0)

Includes subjects at Site 24
Baseline is the worst ECG evaluation at Baseline Visit from the antecedent study (SPD489-325) or Visit 1 of Study SPD489-326 for directly enrolled subjects.
Endpoint is the last non-missing assessment obtained after Visit 1. If there were multiple assessments at the last visit, the worst case was taken as Endpoint.
ECG=electrocardiogram

7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies were conducted to support this supplement.

7.4.6 Immunogenicity

No evaluations of immunogenicity were reported under this supplement. In SPD489-326, no subjects experienced AEs in the skin and subcutaneous tissue disorders SOC.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No analysis was conducted.

7.5.2 Time Dependency for Adverse Events

No analysis was conducted.

7.5.3 Drug-Demographic Interactions

No analysis was conducted.

7.5.4 Drug-Disease Interactions

No analysis was conducted.

7.5.5 Drug-Drug Interactions

No analysis was conducted.

7.6 Additional Safety Evaluations

None.

7.6.1 Human Carcinogenicity

Not included in this submission.

7.6.2 Human Reproduction and Pregnancy Data

Not included in this submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not included in this submission.

7.7 Additional Submissions / Safety Issues

Not applicable.

7.7.1 Suicidality and Other Psychiatric Adverse Events

During SPD489-325, one subject (SPD489) responded “yes” to the following items on the C-SSRS: wish to be dead, non-specific active suicidal thoughts, and active suicidal ideation with any methods without intent to act. An additional subject (SPD489) answered “yes” to the following suicide behavior: non-suicidal self injurious behavior. No other subject in any treatment group had a “yes” response to any parameter of the C-SSRS during the on-treatment period.

No subject had a suicide attempt, interrupted suicide attempt, or aborted suicide attempt while on treatment. No subject had suicidal ideation or suicidal thoughts reported as a TEAE.

8 Postmarket Experience

SPD489 was first approved for the treatment of ADHD in children aged 6-12 years of age on 23 Feb 2007 in the US. SPD489 is currently marketed in 3 countries (US, Canada, and Brazil). Post-marketing safety data have been accumulated during 4 years of commercial use.

As of Jan 2012, (b) (4) patients filled (b) (4) prescriptions, resulting in (b) (4) person-years of exposure since Vyvanse was launched in the US in June 2007. Review of post-marketing data confirms the safety profile of Vyvanse as presented in the periodic Safety Update Reports. The safety information as expressed in the current US Prescribing Information adequately reflects the known safety profile for Vyvanse.

9 Appendices

9.1 Literature Review/References

The published literature search used to support this supplement (S-027) was performed on 6 March 2012 and subsequently submitted as part of the Vyvanse NDA Annual Report on 20 April 2012 (Sequence Number 0092, Module 5.4 Published Clinical Trials Information). The 41 literature publications were identified through a literature search conducted by Genevieve Stoudt, MSLIS, Senior Electronic Resources Search Specialist, Shire Development LLC using the search criteria as noted in the Annual Report. Each of the articles was reviewed in its entirety by Maria Gasior, MD, Senior Clinical Medicine Director, Shire Development LLC. This review of published literature revealed no new potential adverse safety findings associated with Vyvanse and as such, the current benefit-risk profile of Vyvanse remains unchanged.

9.2 Labeling Recommendations

Complete labeling recommendations will be provided to the Review Team in a separate Word document using track changes. In Section 14, Clinical Studies, references to Concerta in the description of SPD489-325 were replaced by the term “active control” based on FDA’s “Guidance for the Clinical Studies section of Labeling for Human Prescription Drug and Biological Products – Content and Format. In the description of Study SPD489-326, the statement (b) (4) was deleted from the sponsor’s proposed language in Clinical Studies, (b) (4) Some additional

editorial changes were made to the sponsor's proposed language in Clinical Studies describing the child and adolescent maintenance study and the additional short-term study. In general, other labeling changes proposed by the sponsor are deemed acceptable.

9.3 Advisory Committee Meeting

Not applicable.

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

/s/

TIFFANY R FARCHIONE
03/22/2013

NI A KHIN
03/22/2013
I concur that this supplement be approved. See CDTL memo for additional comments.