U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21-977
Supplement #:	27
Drug Name:	Vyvanse (SPD489)
Indication(s):	ADHD Maintenance in Children and Adolescents Aged 6-17
Applicant:	Shire Development Inc.
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Biometrics Division:	Division of Biometrics I
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1 EXECUTIVE SUMMARY

This review describes statistical findings about the sponsor's study report SPD489-326 supporting the request for a new indication for the maintenance of efficacy associated with long-term (at least 6 months) use of SPD489 in the treatment of ADHD in children and adolescents. This review also describe statistical findings about the sponsor's study report SPD489-325 supporting the request of adding study results of SPD489-325 in the Clinical Studies section of the labeling.

The review confirms 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. The result of logrank test on time to treatment failure was also statistically significant in favor of SPD489. The review also confirms sponsor's finding from SPD489-325 that SPD489 (administered once daily in 30, 50, and 70 mg) showed positive effect compared to placebo in reducing the ADHD-RS-IV total score from Baseline at Endpoint. SPD489 at these doses is statistically significantly superior to placebo in increasing the proportion of patients with improved CGI-I at the Endpoint.

2 INTRODUCTION

This supplemental New Drug Application (sNDA) is supported by a single study in children and adolescents (SPD489-326). In addition, a short tem precursor study (SPD489-325) to the maintenance of efficacy study in children and adolescents is provided to be included in the Clinical Studies section of the labeling. Both studies are reviewed.

2.1 Overview

Lisdexamfetamine dimesylate (SPD489) is a pharmacologically inactive prodrug that is converted primarily in the blood to l-lysine, a naturally occurring essential amino acid, and dextroamphetamine following oral administration. The latter is responsible for the drug's therapeutic activity. SPD489 is a capsule formulation designed for once a day oral administration. SPD489 is marketed in the United States (US) as VYVANSE® at dose strengths of 20, 30, 40, 50, 60, and 70mg.

SPD489 NDA 21-977 for Vyvanse was approved in the US in Feb 2007 for the treatment of ADHD in children aged 6-12, in April 2008 for the treatment of ADHD in adults, in November 2010 for the treatment of ADHD in adolescents aged 13-17, and in January 2012 for the maintenance treatment of ADHD in adults.

Both Studies SPD489-325 and SPD489-326 were initially developed as registration studies for a European Marketing Authorization Application. Therefore, the protocols for SPD489-325 and SPD489-326 were submitted under the IND 67482 in January 2009 and withdrawn in April 2009. To fulfill the EU's new requirement for the evaluation of the long-term maintenance of

efficacy in this population, Shire amended the design of SPD489-326 to include a double-blind withdrawal phase in order to evaluate the long-term maintenance of efficacy. Hence, the amended protocol SPD489-326 was re-submitted in April 2010. The Statistical Analysis Plans (SAP) for both studies were submitted in the final submission with the study reports. The randomized withdrawal study in children and adolescents (SPD489-326) was of similar design to the randomized withdrawal study in adults (SPD489-401) which was the basis for approved labeling changes (S-022).

Study SPD489-326 was originally designed as a long-term, open-label extension to Study SPD489-325. Under the original study design, subjects received open-label treatment with SPD489 daily for 52 weeks to evaluate the long-term safety and efficacy of SPD489 in the treatment of ADHD in children and adolescents. Seven subjects completed the study under this protocol design. The study was subsequently modified to evaluate long-term maintenance of efficacy in this population. As a result, the length of the open-label period was reduced from 52 weeks to (at least) 26 weeks and a 6-week, double-blind, randomized withdrawal period was added to evaluate long-term maintenance of efficacy and to assess the need for continuous treatment of ADHD in children and adolescents.

Study SPD489-325 was a Phase 3, randomized, double-blind, multicenter, parallel-group, dose-optimization safety and efficacy study. This study was placebo-controlled and also included OROS MPH as an active reference arm.

2.2 Data Sources

The sponsor submitted study reports, analysis datasets, raw datasets, and programs for both studies. The analysis datasets and raw datasets are located in the following directory of the CDER electronic document room (EDR): \\Cdsesub1\evsprod\NDA021977\0096\m5

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer finds the quality and integrity of the submitted data satisfying and acceptable for the review analysis.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study SPD489-326

This study was a Phase 3, double-blind, placebo-controlled, randomized withdrawal, multicenter, extension long term maintenance of efficacy study.

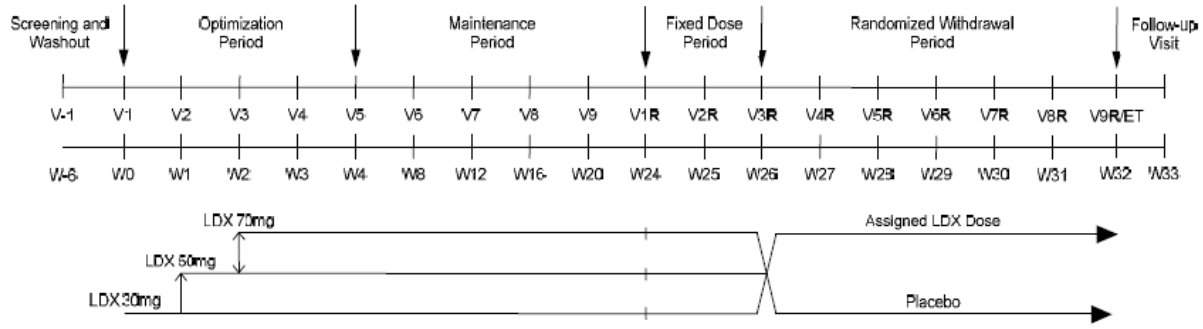
The SPD489-326 study was originally designed to evaluate the long-term safety and efficacy of SPD489 for the treatment of ADHD in children and adolescents as an open-label study. National scientific advice within the EU determined the requirement for the evaluation of the long-term maintenance of efficacy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

European children and adolescents (6-17 years of age inclusive at the time of consent for the antecedent study, SPD489-325) who had been exposed to double-blind test product for a minimum of 4 weeks, reached Visit 4, and completed the 1-week post-treatment washout during the antecedent study, SPD489-325, and were willing participate, were evaluated for study eligibility. To ensure that the sample size necessary to assess the primary efficacy measure was met, US children and adolescents (6-17 years of age inclusive) were also evaluated for direct entry into the study. In total, 276 children and adolescents were enrolled, 236 rollover subjects from Study SPD480-325 (EU subjects), and 40 directly enrolled subjects from sites in the US. Total of 157 patients (SPD489, 78 subjects; Placebo, 79 subjects) were randomized into the randomized withdrawal period. Randomization was stratified by country.

A study design flow chart is presented in Figure 1. Study SPD489-326 consisted of the following periods:

- Screening and Washout (up to 6 weeks) (only applicable to directly enrolled subjects)
- Open-label (26 weeks), which included:
  - Optimization (4 weeks)
  - Maintenance (20 weeks)
  - Fixed Dose (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 ≥ 3.
- Randomized Withdrawal (6 weeks):
- Post-treatment Washout and Safety Follow-up (1 week).

Figure 1: Flow Chart of the Study Design for SPD489-326



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

Source: Sponsor's Figure 1 on Page 29 of Clinical Study Report SPD489-326.

The primary efficacy endpoint is the proportion of treatment failure at the end of the double-blind randomized withdrawal phase. In this study, treatment failure was defined as at least a 50% increase (worsening) in ADHD-RS-IV Total Score and at least a 2-point increase (worsening) in CGI-S score observed at any visit during the Randomized Withdrawal Period compared to Baseline (Visit 3R) of the Randomized Withdrawal Period.

There is no key secondary efficacy endpoint.

The design of the study is appropriate for the objectives of the study. The choice of the primary efficacy endpoint is not common for maintenance studies. The primary endpoint for long-term trials is typically based on time-to-relapse measure. However, the sponsor presented analysis results based on Time-to-failure in Section 9.2.1 "Primary Efficacy Results" of the study report.

Study SPD489-325

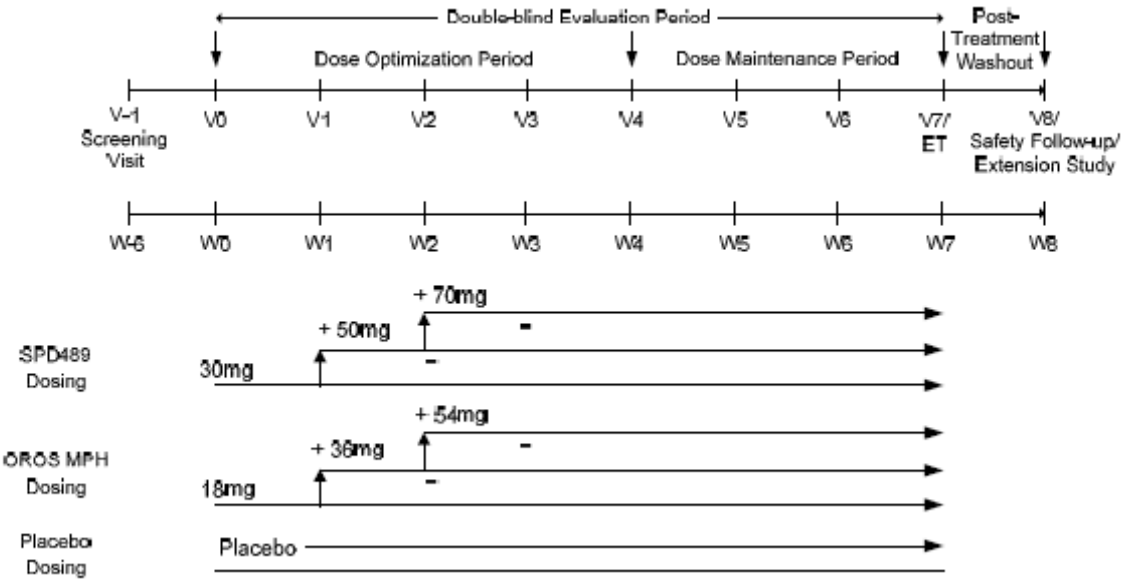
Study SPD489-325 was a Phase 3, randomized, double-blind, multicenter, parallel-group, dose-optimization safety and efficacy study. This study was placebo-controlled and also included OROS MPH as an active reference arm.

Children and adolescents (6-17 years of age, inclusive) diagnosed with ADHD were randomized to SPD489, OROS MPH, or placebo and treated for 7 weeks to evaluate safety and efficacy. A total of 336 subjects were enrolled and randomized (SPD489, 113 subjects; placebo, 111 subjects; OROS MPH, 112 subjects). The randomization was stratified by country and age group (6-12 years or 13-17 years).

The study consisted of the following periods (Figure 2):

- Screening and Washout (up to 6 weeks)
- Double-blind Evaluation (7 weeks), which included:
  - Dose Optimization (4 weeks)
  - Dose Maintenance (3 weeks)
- Post-treatment Washout and Safety Follow-up (1 week).

Figure 2: Flow Chart of the Study Design for SPD489-325



Source: Sponsor's Figure 1 on Page 19 of Clinical Study Report SPD489-325.

The primary efficacy endpoint is the change from Baseline score of the total score of the ADHD-RS-IV at Endpoint. The key secondary efficacy endpoint is the CGI-I at Endpoint. The sponsor included QOL variable as another key secondary endpoint. The protocol and the SAP were not reviewed by statisticians. We would like to refer to the clinicians about QOL variable.

The design of the study is appropriate for the objectives of the study. The choices of the primary efficacy endpoint and the key secondary efficacy endpoint, CGI-I, are appropriate.

3.2.2 Statistical Methodologies

Study SPD489-326

The primary efficacy analysis was performed on the proportion of treatment failures that accrued among subjects in the Randomized FAS during the Randomized Withdrawal Period, using CMH test stratified by country. All active doses of SPD489 were combined in the comparison against placebo because patients were randomized to either the drug arm (regardless of dosage) or the placebo arm. The primary test of the treatment effect was two-sided, and conducted at the significance level of 0.05.

Subjects who withdrew from the Randomized Withdrawal Period and who did not provide efficacy data at the ET Visit were classed as treatment failure in the primary efficacy analysis.

An ad hoc analysis on time to treatment failure was performed in the Randomized FAS during the Randomized Withdrawal Period, using Wilcoxon test stratified by country with significance level of 0.05.

Two sensitivity analyses were performed on the primary efficacy endpoint. One counts all discontinued subjects as treatment failures. The other repeats the primary analysis including data from Site 24. GCP violations were found in Site 24. The GCP violations included the creation of efficacy data retrospectively.

As there is a single primary comparison at a single primary endpoint, adjustment of multiplicity is not needed for the primary efficacy test. There is no key secondary efficacy endpoint.

It is not clear the impact of classifying subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at the ET Visit as treatment failure. The reviewer classified subjects as treatment failure only if the definition of treatment failure is met during the randomized withdrawal period. The reviewer then repeated the pre-specified primary analysis. The common primary analysis for long-term trials, time-to-failure analysis, was also performed.

Study SPD489-325

The primary efficacy analysis was performed on total ADHD-RS-IV change from Baseline using the FAS. An ANOVA model with treatment group, Baseline score, and the factors age group (6-12 years or 13-17 years) and country was used to compare between the 3 treatment groups. The primary treatment comparison is SPD489 versus placebo. The differences in least square means between the active and placebo along with its 95% CI were presented.

An MMRM analysis was performed as a sensitivity analysis. The mixed-effect linear model includes the treatment group and the stratification factors age group (6-12 years or 13-17 years) and country as factors, baseline as a covariate, and a term for treatment group by visit interaction. An unstructured covariance matrix was used with a random subject effect.

The dichotomized CGI-I is the key secondary efficacy variable. The percentage of subjects who improved at the Endpoint was analyzed using a CMH test controlling for age group and country.

The overall Type I error, pre-specified at 0.05 (2-sided) in the protocol, is controlled using a hierarchical testing structure.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study SPD489-326

Two analysis sets were defined for efficacy: the Open-label FAS and the Randomized FAS. The sponsor excluded subjects from Site 24 (14 subjects) from both efficacy analysis sets because of GCP violations. The GCP violations included the creation of efficacy data retrospectively. 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 QoL 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.

A summary of subject disposition in the randomized withdrawal period is presented in Table 1.

Table 1: Summary of Subject Disposition in the Randomized Withdrawal Period (All Randomized Subjects) – SPD489-326

	Randomized Treatment Group		
	SPD489 (N=78)	Placebo (N=79)	Total (N=157)
	n (%)		
Subjects Who Were			
Randomized Safety Population[a]	78 (100.0)	79 (100.0)	157 (100.0)
Randomized Full Analysis Set[b]	76 (97.4)	77 (97.5)	153 (97.5)
Early Termination from Randomized Withdrawal Period	18 (23.1)	63 (79.7)	81 (51.6)
Completed Randomized Withdrawal Period to Visit 9R	60 (76.9)	16 (20.3)	76 (48.4)
Subjects Who Discontinued Randomized Withdrawal Period Due to:			
Met Relapse Criteria[c]	8 (10.3)	35 (44.3)	43 (27.4)
Adverse Event(s)	1 (1.3)	1[d] (1.3)	2[d] (1.3)
Protocol non-adherence/ subject non-compliance	2 (2.6)	1 (1.3)	3 (1.9)
Refused further participation in the study	1 (1.3)	7 (8.9)	8 (5.1)
Lost to Follow-up	0	0	0
Lack of Efficacy	5 (6.4)	18 (22.8)	23 (14.6)
Other	1 (1.3)	1 (1.3)	2 (1.3)

Includes subjects at Site 24

[a] Randomized Safety Population includes all subjects who received 1 dose of any investigational product during the Randomized Withdrawal Phase.

[b] Randomized Full Analysis Set includes all subjects who received 1 dose of any investigational product during the Randomized Withdrawal Phase (excluding Site 24).

[c] Relapse criteria was the category captured on the end of study form, and is based on the judgment of the investigator.

[d] Subject 32-006 had an AE leading to discontinuation which started in the Open-label Period but ended in the Randomized Withdrawal Period, and hence is included as withdrawing due to an AE in this table, but is not included in Section 14, Table 3.2.2.6.

Percentages are based on the number of randomized subjects in each treatment group.

Source: Sponsor's Table 7 on Page 67 of Clinical Study Report SPD489-326.

The patient's completion status during the double blind phase of the study is summarized in Table 2.

Table 2: Summary of Subject Completion Status by Visit (Randomized Safety Population) – SPD489-326

	Randomized Treatment Group		
	SPD489 (N=78)	Placebo (N=79)	Total (N=157)
	n (%)		
Completed Study to Visit 9R	60 (76.9)	16 (20.3)	76 (48.4)
Early Termination	18 (23.1)	63 (79.7)	81 (51.6)
Subjects Remaining in Study			
Visit 4R	78 (100.0)	79 (100.0)	157 (100.0)
Visit 5R	75 (96.2)	51 (64.6)	126 (80.3)
Visit 6R	70 (89.7)	35 (44.3)	105 (66.9)
Visit 7R	65 (83.3)	26 (32.9)	91 (58.0)
Visit 8R	61 (78.2)	17 (21.5)	78 (49.7)
Visit 9R	61 (78.2)	17 (21.5)	78 (49.7)

Includes subjects at Site 24
Percentages are based on the number of randomized subjects in each treatment group.
Note: Subjects 19-012 and 94-005 attended Visit 8R and then early terminated, they did not complete the study and hence do not appear in the first row. Their Early Termination Visit has been reassigned as Visit 9R, hence these subjects appear as remaining in the study at Visit 9R.

Source: Sponsor's Table 9 on Page 70 of Clinical Study Report SPD489-326.

Summary of the demographic and baseline physical characteristics is presented in Table 3.

Table 3: Summary of Demographic characteristics (Randomized Safety Population) – SPD489-326

		SPD489 (N=78)	Placebo (N=79)	Total (N=157)
Age (year)	Mean (SD)	11.0(2.63)	11.3(2.58)	11.1(2.60)
	Min-Max	6-17	6-17	6-17
6-12 years	Mean (SD)	55(70.5)	50(63.3)	105(66.9)
13-17	Mean (SD)	23(29.5)	29(36.7)	52(33.1)
Sex				
Male	n(%)	61(78.2)	62(78.5)	123(78.3)
Female	n(%)	17(21.8)	17(21.5)	34(21.7)
Race				
White	n(%)	74(94.9)	75(94.9)	149(94.9)
Black/African American	n(%)	1(1.3)	2(2.5)	3(1.9)
Other	n(%)	3(3.8)	2(2.5)	5(3.2)
Height (cm)	Mean (SD)	149.30(16.2)	149.93(17.1)	149.62(16.6)
	Min-Max	119.0-192.0	118.4-181.0	118.1-192.0
Weight (kg)	Mean (SD)	44.72(16.2)	47.02(17.1)	45.88(16.7)
	Min-Max	22.8-86.5	23.5-92.0	22.8-92.0
BMI (kg/m^2)	Mean (SD)	19.44(3.8)	20.17(3.6)	19.80(3.7)
	Min-Max	13.9-29.8	14.2-29.0	13.9-29.8

Includes subjects at Site 24.
Source: Sponsor's Table 11 on Page 74 of Clinical Study Report SPD489-326.

Study SPD489-325

All efficacy analyses were performed on FAS. The FAS includes all subjects who received at least 1 dose of investigational product excluding 15 subjects from Site 24. GCP violations were found in Site 24. The GCP violations included the creation of efficacy data retrospectively.

A summary of subject disposition is presented in Table 4.

Table 4: Summary of Subject Disposition (All Enrolled Subjects) – SPD489-325

	SPD489 (N=113) n (%)	Placebo (N=111) n (%)	CONCERTA (N=112) n (%)	Total (N=336) n (%)
Subjects who were:				
Randomized	113 (100.0)	111 (100.0)	112 (100.0)	336 (100.0)
Safety Population	111 (98.2)	110 (99.1)	111 (99.1)	332 (98.8)[a]
Full Analysis Set	104 (92.0)	106 (95.5)	107 (95.5)	317 (94.3)[b]
Study Completers[c,d]	80 (70.8)	42 (37.8)[e]	74 (66.1)	196 (58.3)
Early Termination[d]	33 (29.2)	68 (61.3)	38 (33.9)	139 (41.4)
Reason for Discontinuation:				
Adverse Event(s)	5 (4.4)	4 (3.6)	2 (1.8)	11 (3.3)
Protocol Non-adherence/ Subject Non-compliance	3 (2.7)	2 (1.8)	3 (2.7)	8 (2.4)
Refused further participation in the study	4 (3.5)	4 (3.6)	5 (4.5)	13 (3.9)
Lost to Follow-up	0	0	1 (0.9)	1 (0.3)
Lack of Efficacy	11 (9.7)	54 (48.6)	22 (19.6)	87 (25.9)
Other	10 (8.8)	4 (3.6)	5 (4.5)	19 (5.7)

[a] Four randomized subjects (Subjects 23-002 and 31-001 in the SPD489 group; Subject 20-002 in the placebo group; Subject 16-001 in the CONCERTA group) did not receive investigational product and were therefore excluded from the Safety Population.
[b] 19 randomized subjects were excluded from the FAS. These include 4 subjects who were not dosed (see Footnote 1) and 15 subjects from Site 24 (see Section 8).
[c] Defined as completing Visits 0 through 8.
[d] The categories of Study Completers and Early Termination include subjects enrolled at Site 24.
[e] Because Subject 10-002 (in the placebo group) had an incomplete end of study page, this subject's completion status could not be determined at time of database lock. Therefore, the number of completers + the number of early terminators is 1 less than the number randomized to placebo. However, subsequent to database lock it was determined that this subject was discontinued after the parent refused further participation in the study.
Note: The Safety Population is defined as all subjects who received at least 1 dose of investigational product during this study.
Note: The Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product. Subjects enrolled at Site 24 were excluded from the Full Analysis Set.
Note: Of the 336 subjects who were randomized, 3 subjects (Subjects 08-004 and 20-006 in the CONCERTA group and Subject 16-003 in the SPD489 group) attempted to take investigational product but were unable to swallow the capsules. Because these subjects attempted to take investigational product, they have a first dose date (even though the number of capsules taken was 0) and are therefore included in the Safety Population and the Full Analysis Set.
Note: Percentages are based on the number of enrolled subjects in each treatment group.

Source: Sponsor's Table 3 on Page 43 of Clinical Study Report SPD489-325.

The patients' completion status during the double-blind phase of the study is summarized in Table 5.

Table 5. Patients Completion Status of the Double Blind Phase (Safety Population) – SPD489-325

	Statistic	SPD489 (N=111)	Placebo (N=110)	Concerta (N=111)	Total (N=332)
Study Completers	n (%)	80 (72.1%)	42 (38.2%)	74 (66.7%)	196 (59.0%)
Early Termination	n (%)	31 (27.9%)	67 (60.9%)	37 (33.3%)	135 (40.7%)
Subjects Remaining in Study					
Visit 1 (Day 7)	n (%)	111 (100.0%)	110 (100.0%)	111 (100.0%)	332 (100.0%)
Visit 2 (Day 14)	n (%)	104 (93.7%)	106 (96.4%)	108 (97.3%)	318 (95.8%)
Visit 3 (Day 21)	n (%)	103 (92.8%)	99 (90.0%)	104 (93.7%)	306 (92.2%)
Visit 4 (Day 28)	n (%)	99 (89.2%)	91 (82.7%)	103 (92.8%)	293 (88.3%)
Visit 5 (Day 35)	n (%)	90 (81.1%)	65 (59.1%)	92 (82.9%)	247 (74.4%)
Visit 6 (Day 42)	n (%)	82 (73.9%)	44 (40.0%)	84 (75.7%)	210 (63.3%)
Visit 7 (Day 49)	n (%)	81 (73.0%)	43 (39.1%)	76 (68.5%)	200 (60.2%)
Visit 8 (Day 56)	n (%)	99 (89.2%)	95 (86.4%)	98 (88.3%)	292 (88.0%)
Follow-up Phone Call instead of Visit 8	n (%)	9 (8.1%)	9 (8.2%)	12 (10.8%)	30 (9.0%)

Note: Percentages are based on the number of subjects in each treatment group and total.
Note that subjects may have had a Visit 8 even if they did not complete the study, and hence the number at Visit 8 is higher than the number at Visit 7.
The number at each visit is the number attending each visit - so for example if a subject missed Visit 4 but came back for Visit 5, then they would not appear in the Visit 4 row.
Subject 10-002 had a missing end of study page, so the number of completers plus number of early terminators is 1 less than the number randomised.
Four subjects (09-003, 24-014, 24-016 and 33-001) attended all visits up to Visit 6, and then had an Early Termination Visit instead of Visit 7. The Early Termination visit is then re-assigned to Visit 7, and hence there 200 subjects remaining in the study at Visit 7, but 196 completers.

Source: Sponsor's Table 1.2.4 on Page 219 of Clinical Study Report SPD489-325.

Summary of the demographic and baseline physical characteristics is presented in Table 6.

Table 6: Summary of Demographics and Baseline Characteristics (Safety Population) – SPD489-325

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

[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.

Source: Sponsor's Table 4 on Page 46 of Clinical Study Report SPD489-325.

3.2.4 Results and Conclusions

Study SPD489-326

Sponsor's Results and Conclusions:

Based on the primary analysis results (Table 7) for the pre-specified primary endpoint, the sponsor concluded that the maintenance study for subjects treated with SPD489 for a minimum of 6 months was demonstrated by the significantly lower proportion of treatment failure (15.8%) compared to subjects receiving placebo (67.5%) in the 6 week double-blind randomized withdrawal phase of the study (p-value<0.001).

Table 7: Summary and Analysis of Treatment Failures at Endpoints (Randomized Full Analysis Set) – SPD489-326

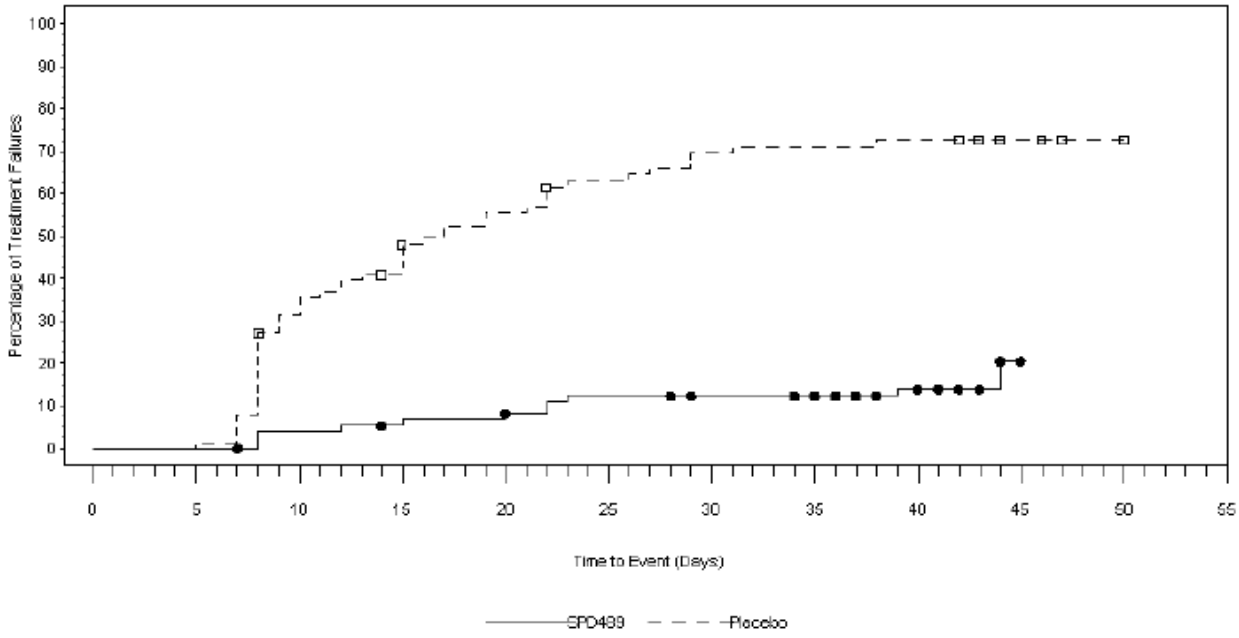
Treatment Failure	Statistic	SPD489 (N=76)	Placebo (N=77)	p-value[a]
No	n (%)	64 (84.2)	25 (32.5)	<0.001
Yes	*n (%)*	*12 (15.8)*	*52 (67.5)*	

Excludes subjects at Site 24.
[a]p-value is based on Cochran-Mantel-Haenszel statistic stratified by country comparing the 2 treatment groups. Endpoint is the last on-treatment post-Baseline Visit (Visit 3R) of the Randomized Withdrawal Period (Visits 4R-9R) with a non-missing assessment. Subjects without an Endpoint value are classed as Treatment Failures.
Source: Section 14, Table 2.1.1.1.

Source: Sponsor's Table 22 on Page 92 of Clinical Study Report SPD489-326.

The sponsor also performed an ad hoc analysis to compare the time to treatment failure between SP489 and placebo. The median time to treatment failure was not calculable for the SPD489 group and was 17.0 days (95% CI:12.0, 22.0) for the placebo group. The difference in time to treatment failure was statistically significant (p<0.001). See for a Kaplan-Meier plot of time to treatment failure for the Randomized FAS.

Figure 3: Kaplan-Meier Plot of Time to Treatment Failure (Randomized Full Analysis Set) – SPD489-326



Excludes subjects at Site 24
The symbols represent censored observations.
Source: Sponsor's Figure 4 on Page 94 of Clinical Study Report SPD489-326.

The Sponsor repeated the above two analysis including subjects from site 24. The efficacy results are very similar whether removing the site or not. The sponsor also repeated the above two analysis counting all discontinued subjects as treatment failures. The results are similar.

Reviewer's Results and Conclusions:

The sponsor's analysis classified subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at the ET Visit as treatment failure in the primary efficacy analysis. It is not clear the impact of this classification. This reviewer started from raw data and classified subjects as treatment failure only if the definition of treatment failure is observed during the Randomized Withdrawal Period. The reviewer's results of the primary analysis on FAS are summarized in Table 8.

Table 8: Summary of Reviewers' Primary Analysis Results for the Primary Endpoint – SPD489-326

Treatment Failure	Statistics	SPD489 (N=74)	Placebo(N=77)	pvalue
No	n(%)	64 (86.49)	24 (31.17)	<0.001
Yes	n(%)	10 (13.51)	53 (68.83)	

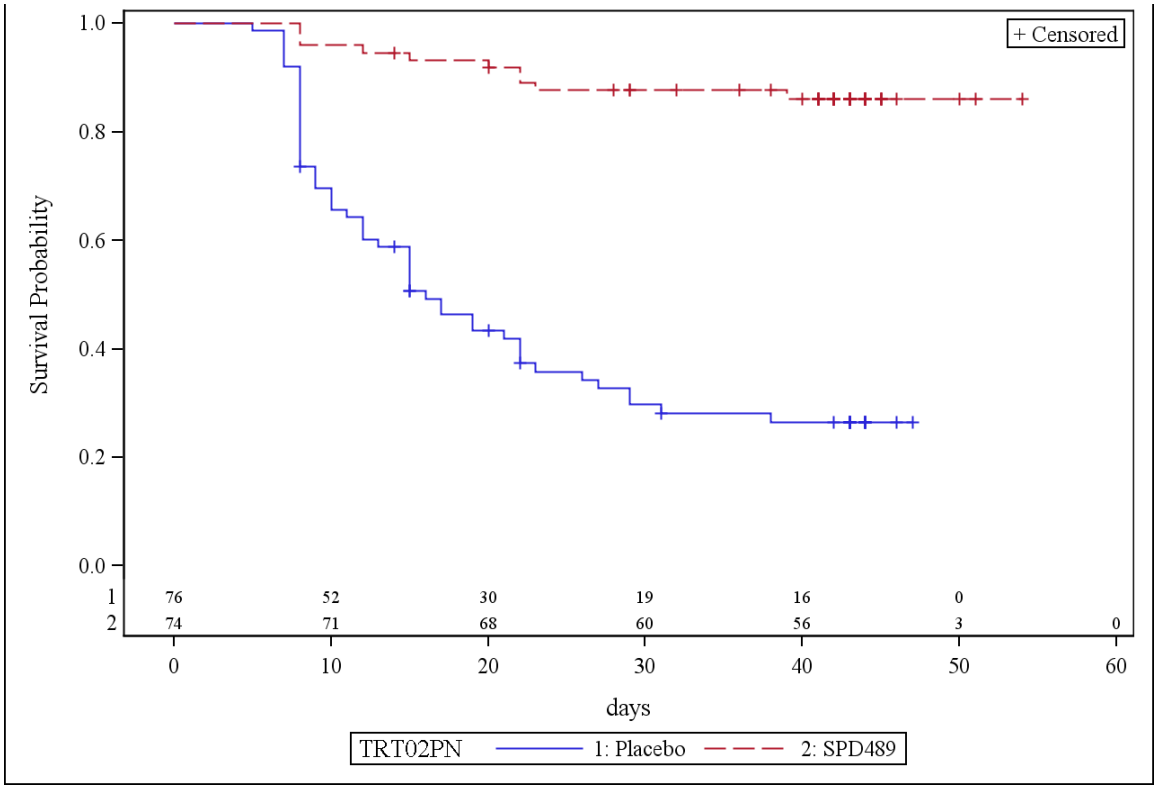
Exclude subjects at Site 24.
p-value is based on CMH statistics stratified by country.

Source: Reviewer's analysis.

The primary endpoint for long-term trials is typically based on a time-to-failure measure. Based on logrank test applied to the FAS excluding site 24, there was a statistically significant difference in favor of SPD489 with respect to the time to the treatment failure ($p<0.0001$). That is, the time to the treatment failure was generally longer in the SPD489 group compared with the placebo group through out the random withdrawal period.

The following figure displays the Kaplan-Meier estimates of the reliability (survival) function. The survival curve of SPD489 is consistently higher than the survival curve of the placebo.

Figure 4: The Estimate of the Reliability (Survival) Function for SPD489 and Placebo – SPD489-326



Source: Reviewer's analysis.

Study SPD489-325

Sponsor's Results and Conclusions:

The primary analysis results for the pre-specified primary endpoint are presented in Table 9. The differences from Baseline at Endpoint in LS mean changes between SPD489 and Placebo (-18.6) and between OROS MPS and Placebo (-13.0) were statistically significant ($p<0.001$) for both comparisons, with respective effect size of 1.804 and 1.263.

Table 9: Analysis of Change from Baseline at Endpoint in ADHP-RS-IV Total Score (Full Analysis Set) –SPD489-325

Treatment	Baseline		Change from Baseline at Endpoint[a]					p-value
	N	Mean (SD)	N	LS Mean Change	LS Means Diff.	95% CI	Effect Size[b]	
SPD489	102	40.7 (7.31)	98	-24.3	-18.6	(-21.5, -15.7)	1.804	<0.001
Placebo	105	41.0 (7.14)	104	-5.7				
OROS MPH	106	40.5 (6.72)	103	-18.7	-13.0	(-15.9,-10.2)	1.263	<0.001

[a] LS Mean, Effect Size and p-value are based on type III sum of squares from an analysis of covariance model for the change from baseline, including treatment group, country, and age groups as fixed effects and baseline value as a covariate.
[b] The effect size was calculated as the difference in LS means between active and placebo divided by the root mean square error.
Note: A negative difference in LS Mean (Active - Placebo) indicates a positive effect of the active treatment over placebo.
CI=confidence interval;

Source: Sponsor's Table 2 on Page 21 of Summary of Clinical Efficacy.

A sensitivity analysis using a mixed model repeated measures analysis was done on the primary variable. The results of this analysis confirmed the primary analysis.

The primary analysis on the key secondary efficacy endpoint, CGI-I, was performed on dichotomized CGI-I results (ie. "Improvement" (which included very much improved and much improved) vs "no improvement" (which included minimally improved, no change, minimally worse, much worse, and very much worse)). The results are presented in Table 10. The percentages of improved subjects in SPD489 group and OROS MPH group are statistically significantly higher than that of Placebo group.

Table 10: Summary and Analysis of Dichotomized CGI-I (Full Analysis Set) – SPD489-325

Visit	CGI-I	SPD489 (N=104)	Placebo (N=106)	Concerta (N=107)
Endpoint	n	100	104	104
	Improvement n (%)	78 (78.0)	15 (14.4)	63 (60.6)
	No Improvement n (%)	22 (22.0)	89 (85.6)	41 (39.4)
	Difference in Improvement vs Placebo (95% CI)	63.6 (53.0, 74.1)		46.2 (34.6, 57.7)
	Comparison to Placebo p-value	<0.001		<0.001

Note: p-value is based on Cochran Mantel Haenszel test controlling for country and age group.
Source: Sponsor's Table 16 on Page 84 of Clinical Study Report SPD489-325.

Reviewer's Results and Conclusions:

The reviewer started from raw data and repeated the sponsor's primary analysis on the primary efficacy variable and the key secondary efficacy variable, CGI-I. The results are presented in Table 11 and Table 12. The results are similar to the sponsor's results and the conclusions are the same.

Table 11: Reviewer's Analysis on Change from Baseline at Endpoint in ADHD-RS-IV Total Score – SPD489-325

		Baseline	Change from Baseline at Endpoint			
Treatment	n	Mean (SD)	LS Mean Change	LS mean Diff	95% CI	pvalue
SPD489	105	40.8(7.29)	-27.2	-17.4	(-20.8, -14.0)	<0.001
Placebo	107	40.9(7.14)	-9.9			
OROS MPH	108	40.5(6.69)	-22.1	-12.2	(-15.5, -8.8)	<0.001

Source: Reviewer's results.

Table 12: Reviewer's Analysis Results on Dichotomized CGI-I – SPD489-325

Visit	CGI-I	SPD489 (N=105)	Placebo (N=107)	Concerta (N=108)
Endpoint	n	105	107	107
	Improvement n (%)	76 (72.4)	15 (14.0)	62 (57.9)
	No Improvement n (%)	29 (27.6)	92 (86.0)	45 (42.1)
	Comparison to Placebo p-value	<0.001		<0.001

Source: Reviewer's results.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS OF STUDY

4.1 Gender, Race, Age, and Geographic Region

Study SPD489-326

Based on sponsor's results which are summarized in Table 13, all the subgroup analyses performed are in favor of SPD489. The subgroup analysis stratified by race was omitted because the majority of the population (94.9%) was white.

Table 13: Summary of Treatment Failures for Subgroups at Endpoints (Randomized FAS) – SPD489-326

Subgroup	Treatment Failure	SPD489 N(%)	Placebo N(%)	pvalue
FAS	No	64(84.2%)	25 (32.5%)	<0.001
	Yes	12 (15.8%)	52 (67.5%)	
6-12 Years	No	43 (81.1%)	16 (32.0%)	<0.001
	Yes	10 (18.9%)	34 (68.0%)	
13-17 Years	No	21 (91.3%)	9 (33.3%)	<0.001
	Yes	2 (8.7%)	18 (66.7%)	
Male	No	49 (83.1%)	18 (30.0%)	<0.001

	Yes	10 (16.9%)	42 (70.0%)	
Female	No Yes	15 (88.2%) 2 (11.8%)	7 (41.2%) 10 (58.8%)	0.007
European Sites	No Yes	56 (84.6%) 10 (15.2%)	21 (31.8%) 45 (68.2%)	<0.001
US Sites	No Yes	8 (80.0%) 2 (20.0%)	4 (36.4%) 7 (63.6%)	0.049

Sources: Sponsor's Tables 22, 24, 25, 2.1.1.11, and 2.1.1.12 of Clinical Study Report SPD489-326.

The reviewer used Cox-proportional hazard model on the time to treatment failure for the FAS subgroup populations by age group, gender and region. The results are presented below. All the subgroup analyses performed are consistently in favor of SPD489.

Table 14: Reviewer's Summary of Hazard Ratio and 95% CI for Subgroups – SPD489-326

Subgroup	h-ratio(95%CI) (Placebo/SPD489)
FAS	8.40(4.25, 16.63)
6-12 Years	7.11(3.27, 15.43)
13-17 Years	12.91(2.96, 56.35)
Male	7.81(3.77, 16.18)
Female	14.28(1.81, 112.4)
European Sites	9.72(4.55, 20.77)
US Sites	4.18(0.86, 20.24)

Source: Computed by the reviewer.

Study SPD489-325

The sponsor reported analysis results on subgroups of age group and gender in Table 15 and Table 16. The effectiveness of SPD489 compared to placebo was maintained regardless of age category (6-12 years, 13-17 years) or sex. The subgroup analysis stratified by race was omitted because the majority of the population (96.4%) was white.

Table 15: Summary of Mean Change from Baseline at Endpoint in ADHD-RS-IV Total Score Presented by Age Category and Sex – SPD489-325

	6-12 Years			13-17 Years		
Visit	SPD489 (N=74)	Placebo (N=76)	OROS MPH (N=79)	SPD489 (N=30)	Placebo (N=30)	OROS MPH (N=28)
Baseline (Day 0)						
n	72	75	78	30	30	28
Mean (SD) Change	40.9 (7.70)	41.5 (7.33)	41.2 (6.62)	40.4 (6.40)	39.7 (6.58)	38.5 (6.72)
Endpoint						
n	69	74	75	29	30	28
Mean (SD) Change	-23.5 (10.76)	-6.1 (10.10)	-20.6 (13.25)	-27.5 (8.01)	-6.9 (9.95)	-14.3 (10.89)
	Males			Females		
	SPD489 (N=81)	Placebo (N=88)	OROS MPH (N=86)	SPD489 (N=23)	Placebo (N=18)	OROS MPH (N=21)
Baseline (Day 0)						
n	79	87	85	23	18	21
Mean (SD) Change	41.3 (7.31)	41.1 (7.48)	40.7 (6.97)	38.7 (7.09)	40.6 (5.37)	39.6 (5.70)
Endpoint						
n	76	87	83	22	17	20
Mean (SD) Change	-24.7 (10.17)	-6.5 (10.31)	-19.4 (12.16)	-24.5 (10.34)	-5.5 (8.56)	-17.0 (15.90)

Source: Sponsor's Table 3 on Page 22 of Summary of Clinical Efficacy.

Table 16: Summary of Dichotomized CGI-I Presented by Age Category and Sex – SPD489-325

		6-12 Years			13-17 Years		
Visit (CGI-I Category)		SPD489 (N=74)	Placebo (N=76)	OROS MPH (N=79)	SPD489 (N=30)	Placebo (N=30)	OROS MPH (N=28)
Visit 1 (Day 7)							
n		74	76	79	30	30	28
Improvement[a]	n (%)	28 (37.8)	8 (10.5)	14 (17.7)	12 (40.0)	4 (13.3)	4 (14.3)
No Improvement	n (%)	46 (62.2)	68 (89.5)	65 (82.3)	18 (60.0)	26 (86.7)	24 (85.7)
Endpoint							
n		71	74	76	29	30	28
Improvement	n (%)	53 (74.6)	9 (12.2)	49 (64.5)	25 (86.2)	6 (20.0)	14 (50.0)
No Improvement	n (%)	18 (25.4)	65 (87.8)	27 (35.5)	4 (13.8)	24 (80.0)	14 (50.0)
		Males			Females		
		SPD489 (N=81)	Placebo (N=88)	OROS MPH (N=86)	SPD489 (N=23)	Placebo (N=18)	OROS MPH (N=21)
Visit 1 (Day 7)							
n		81	88	86	23	18	21
Improvement[a]	n (%)	32 (39.5)	12 (13.6)	16 (18.6)	8 (34.8)	0	2 (9.5)
No Improvement	n (%)	49 (60.5)	76 (86.4)	70 (81.4)	15 (65.2)	18 (100.0)	19 (90.5)
Endpoint							
n		78	87	84	22	17	20
Improvement	n (%)	59 (75.6)	12 (13.8)	53 (63.1)	19 (86.4)	3 (17.6)	10 (50.0)
No Improvement	n (%)	19 (24.4)	75 (86.2)	31 (36.9)	3 (13.6)	14 (82.4)	10 (50.0)

[a] Improvement included very much improved and much improved and No Improvement included all other assessed categories.

Source: Sponsor's Table 5 on Page 26 of Summary of Clinical Efficacy.

The reviewer repeated the subgroup analyses on primary and key secondary efficacy endpoints. The results are summarized in Table 17 and Table 18. The results are similar to the sponsor's results. All the subgroup analyses performed are consistently in favor of SPD489.

Table 17: Reviewer's Summary of Change from Baseline at Endpoint in ADHD-RS-IV in Subgroups– SPD489-325

	SPD489		PLACEBO		CONCERTA	
Subgroup	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)
13 - 17 years	30	-26.3(10.84)	30	-6.7(10.04)	28	-13.9(11.51)
6 - 12 years	75	-22.1(11.96)	77	-5.6(9.86)	80	-18.9(14.36)
Female	23	-23.5(11.04)	18	-4.9(8.66)	21	-15.6(15.41)
Male	82	-23.2(12.02)	89	-6.2(10.14)	87	-18.1(13.43)

Source: Reviewer's results.

Table 18: Reviewer's Summary of CGI-I Results in Subgroups– SPD489-325

	SPD489	PLACEBO	CONCERTA

Subgroup	Improved	n (%)	n (%)	n (%)
13 - 17 years	N	6(20.0%)	24(80.0%)	14(50.0%)
	Y	24(80.0%)	6(20.0%)	14(50.0%)
6 - 12 years	N	23(30.7%)	68(88.3%)	31(39.2%)
	Y	52(69.3%)	9(11.7%)	48(60.8%)
Female	N	4(17.4%)	15(83.3%)	11(52.4%)
	Y	19(82.6%)	3(16.7%)	10(47.6%)
Male	N	25(30.5%)	77(86.5%)	34(39.5%)
	Y	57(69.5%)	12(13.5%)	52(60.5%)

Source: Reviewer's results.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues for both studies.

5.2 Collective Evidence

Study SPD489-326

The reviewer confirms sponsor's findings that SPD489 (administered once-daily in 30, 50 and 70 mg) was statistically significantly superior to placebo 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. The result of logrank test on time to treatment failure was also statistically significant.

Study SPD489-325

The reviewer confirms sponsor's findings that SPD489 was statistically significantly superior to placebo in reducing the ADHD-RS-IV total score from Baseline at Endpoint. SPD489 was statistically significantly superior to placebo in the proportion of patients with improved CGI-I at the Endpoint.

5.3 Conclusions and Recommendations

Study SPD489-326

Once-daily administered Vyvanse (30, 50, and 70 mg) showed positive effect compared to placebo in reducing the proportion of treatment failures in children and adolescents with ADHD.

Study SPD489-325

Once daily administrated Vyvanse (30, 50, and 70 mg) showed positive effect compared to placebo in reducing the ADHD-RS-IV total score from Baseline at Endpoint. SPD489 was statistically significantly superior to placebo in the proportion of patients with improved CGI-I at the Endpoint.

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

/s/

JINGLIN ZHONG
03/14/2013

PEILING YANG
03/14/2013
I concur with the review.

HSIEN MING J HUNG
03/14/2013