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 Serial Number:	21-977 / S-022
Drug Name:	Vyvanse (SPD489)
Indication(s):	ADHD maintenance in adults
Applicant:	Shire Development Inc.
Date(s):	Initial submission date: 03/31/2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Keywords:
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1. EXECUTIVE SUMMARY

The reviewers confirm sponsor's findings that SPD489 (administered once-daily in 30 mg, 50 mg and 70 mg) was statistically significantly superior to placebo (Chi-squared test p-value less than 0.0001) in reducing the proportion of treatment failures at the end of the double-blind randomized 6 weeks withdrawal phase in adult patients with ADHD. The result of logrank test on time to treatment failure was also statistically significant in favor of SPD489.

[redacted] originally proposed by the sponsor were inappropriate for labeling inclusion because [redacted]

2. INTRODUCTION

2.1 Overview

Study SPD489-401 is a randomized withdrawal study conducted in adult ADHD patients in the United States (US) with a history of being on Vyvanse for 6 months before enrollment into the study, patients entered into dose optimization phase followed by a double-blind randomized withdrawal period.

Study SPD489-401 was developed as a registration study for a European Marketing Authorization Application. At the time, Shire did not intend to use the study to support a significant change in the US labeling for Vyvanse and the study met all of the criteria in 21 CFR 312.2 (b) for exemption. Therefore, the protocol and Statistical Analysis Plan (SAP) for Study SPD489-401 were not submitted under the IND 67,482. However, in recent months, Shire has reconsidered the clinical relevance this study may have for physicians treating ADHD adult patients. As a result, Shire has submitted a supplemental NDA (S-0022) with these data to update the US Prescribing Information for Vyvanse.

2.2 Data Sources

The sponsor's submitted data and program listings are available in the following directory of the CDER' electronic document room (EDR):
\\cdsesub1\EVSPROD\NDA021977\0075\m5\datasets\spd489-401\analysis

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. It is possible to reproduce the primary analysis dataset from the raw data and trace how the primary endpoint was derived.

3.2 Evaluation of Efficacy

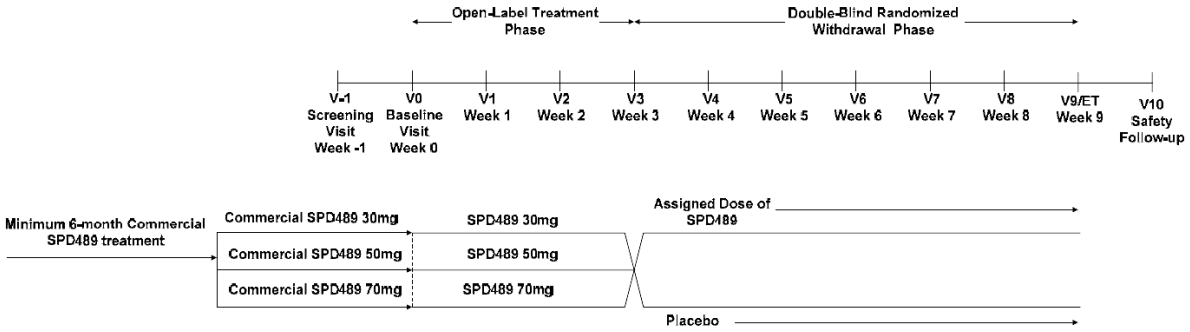
Objectives

The primary objective of the study was to evaluate the maintenance of efficacy, as measured by ADHD-RS (Rating Scale) with adult prompts and Clinical Global Impression – Severity (CGI-S) scores, through a randomized withdrawal design when subjects with ADHD have been on stable treatment with commercial SPD489 for a minimum of 6 month and are maintained on their dose of commercial SPD489.

Study Design and Endpoints

This was a Phase 4, double-blind, multi-center, US-only, placebo-controlled, randomized withdrawal safety and efficacy study in adults (18-55 years of age inclusive) diagnosed with ADHD. Subjects entered the study having been on stable treatment with commercial SPD489 (30, 50, or 70 mg) for a minimum of at least 6 months prior to the start of this study, defined as Visit 1. The study design is shown schematically in Figure 1.

Figure 1. Flow chart of the study design.



Source: Figure 1 (pg. 9) of the Clinical Study Report SPD489-401.

The study consisted of 5 phases:

1) Screening (Visit -1 / Day -7),
2) Baseline (Visit 0 / Day 0),
3) 3-week open-label treatment phase on SPD489 (Visits 1–3 / Days 7, 14, 21),

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4) 6-week double-blind randomized withdrawal phase (Visits 4–9, ET*/ Days 28, 35, 42, 49, 56, 63),
5) Safety follow-up phone call (no visit / Days 70–72).

The *primary efficacy endpoint*, finalized in the amendment 1.0 of the protocol, is the proportion of treatment failures at the end of the Double-blind Randomized Withdrawal Phase. A subject was classed as a *treatment failure* if a 50% increase (worsening) in Adult ADHD-RS with prompts score is observed at any double-blind visit (Visits 4, 5, 6, 7, 8, or 9) relative to Visit 3 and a ≥2 point increase in CGI-S score relative to CGI-S at Visit 3 is observed at the corresponding double-blind visit.

The *secondary efficacy endpoints* include the time to treatment failure, the change from baseline of the ADHD-RS with adult prompts (total score) at each visit, and the CGI-S at each visit.

The original version of the protocol (Version 1.0) was dated 27 Jan 2009. There were 4 protocol amendments. The final version of the protocol (Version 5.0) is dated 12 Mar 2010. In brief:

- Amendment 4.0 (12 Mar 2010) added a secondary safety objective: "to monitor subject safety based on responses to the C-SSRS."
- Amendment 3.0 (16 Dec 2009) decreased the number of enrolled subjects from 163 to 145, updated text relating to treatment failures and study populations, removed a subgroup analysis by age, and added a sensitivity analysis
- Amendment 1.0 (31 Mar 2009) added an additional 2 weeks to the double-blind randomized withdrawal phase to bring the length of the double-blind randomized withdrawal phase to 6 weeks, updated the time period for aftercare to 9 months, and revised the primary efficacy endpoint to the proportion of treatment failures at the end of the double-blind randomized withdrawal phase.

The SAP was based on Version 5.0 of the protocol dated 12 Mar 2010, and the final eCRF, dated 06 Apr 2009. The following changes were made to the statistical methods described in the protocol version 5.0 (12 Mar 2010):

- The protocol (Sections 3.4 and 9.14) stated that the primary efficacy endpoint for each subject was "treatment failure *at the end of* the double-blind randomized withdrawal phase." The language describing the primary efficacy endpoint for each subject was changed to "treatment failure *accrued during* the double-blind randomized withdrawal phase."
- The protocol (Section 9.14) stated that the proportion of treatment failures *at each double-blind visit* would be assessed by applying the Chi-Square test to the observed data at each double-blind visit (Visits 4 to 9). The proportion of treatment failures was assessed by applying the Chi-Square test *only at endpoint*.
- The protocol (Section 9.14) described sensitivity testing for the primary efficacy analysis, including the classification of subjects who withdrew, but provided efficacy data at the ET visit. The protocol stated that any subjects who withdrew would be classified as a treatment failure. The SAP clarified this, indicating that any subject who withdrew *for any reason* would be classified as a treatment failure.

Patient Disposition, Demographic and Baseline Characteristics

* Subjects who withdrew from the study for any reason were asked to complete the early termination (ET). At least 3 documented attempts were made to contact any subject lost to follow-up at any time prior to the last scheduled visit.

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The sponsor pre-defined the following populations:

Enrolled Population – defined as all subjects who were dispensed investigational product at Baseline (Visit 0).

Safety Population – defined as all subjects who entered the open-label treatment phase of the study and took at least 1 dose of investigational product. One subject from the enrolled population was lost to follow-up prior to receiving investigational product.

Randomized Safety Population – defined as all subjects who were randomized to one of two treatment arm (stratified by the previously assigned SPD489 dose of 30 mg, 50 mg, or 70 mg at Visit 3, with 1:1 group allocation ratio) and took at least 1 dose of investigational product in the double-blind randomized withdrawal phase. Six subjects discontinued during the open-label phase treatment product due to the following reasons: adverse event (1 person), protocol non-adherence/subject non-compliance (3 persons), refused further participation in the study (1 person), other reasons (1 person).

Full Analysis Set (FAS) – defined as all subjects who were randomized and received at least 1 dose of investigational product. The sponsor has also excluded the subjects from site 055 (6 patients) because of the GCP noncompliance discovered during the quality assurance audit performed by the Shire quality assurance auditor from 20 Jul – 22 Jul, 2010. The decision to exclude the data was made prior to database lock and unblinding, but after the SAP was completed (19 Mar, 2010). All 6 subjects were randomized and received at least 1 dose of investigational product. There were no clinically concerning safety results for any of these subjects. Dosing information and the disposition for the 6 subjects enrolled at site 055 are presented in Table 1.

Table 1. Dosing information and disposition of the site 055 patients,

Subject ID	Sex, Age, Race	Treatment Sequence	Date of the 1st dose	Date of the last dose	Completion status	Reason for early termination
055-0002	F/32/W	50 mg / 50 mg	25 Nov 2009	12 Jan 2010	Withdrew	Relapse crit. met
055-0004	M/31/W	50 mg / Placebo	09 Feb 2010	04 Mar 2010	Withdrew	Relapse crit. met
055-0005	F/31/F	50 mg / 50 mg	20 Feb 2010	23 Apr 2010	Completed	
055-0006	M/28/O	50 mg / Placebo	11 Mar 2010	19 Apr 2010	Withdrew	Relapse crit. met
055-0007	M/39/W	70 mg / 70 mg	16 Mar 2010	17 May 2010	Completed	
055-0008	M/28/W	70 mg / 70 mg	22 Mar 2010	12 May 2010	Withdrew	Relapse crit. met

Source: pg. 29 of the Clinical Study Report SPD489-401.

Among the inclusion criteria for subjects to be enrolled and randomized for the double-blind phase, this reviewer found it relevant to the review to emphasize the following ones:

1) Eligible subjects with Baseline (Visit 0) ADHD-RS with adult prompts total score of <22 will be enrolled in the open-label treatment phase (pg 18, protocol).
2) At Baseline (Visit 0), subject had an ADHD-RS with adult prompts total score of <22 and CGI-S score ≤3 (mildly ill). (pg 19, study report)
3) A minimum score of <22 using the Adult ADHD-RS with prompts is required at screening and at the Baseline Visit for inclusion (pg 49, protocol).
4) Subject will enter the study having been on stable treatment with commercial SPD489 (30, 50, or 70mg) for a minimum of 6 months preceding the Screening Visit (Visit -1) with acceptable tolerability (pg. 13, study report).

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Table 2. Patient disposition during the double-blind phase of the study.

n (%)	Placebo	SPD489				Total
		30 mg	50 mg	70 mg	All doses	
	N=60	N=6	N=23	N=27	N=56	N=116
Randomized subjects	60(100.0)	6(100.0)	23(100.0)	27(100.0)	56(100.0)	116(100.0)
Randomized safety population (took at least one dose)	60(100.0)	6(100.0)	23(100.0)	27(100.0)	56(100.0)	116(100.0)
Full Analysis Set (FAS)	60(100.0)	6(100.0)	23(100.0)	27(100.0)	56(100.0)	116(100.0)
Completed through Visit 9	13(21.7)	5 (83.3)	21(91.3)	24(88.9)	50(89.3)	63(54.3)
Early termination	47(78.3)	1 (16.7)	2 (8.7)	3(11.1)	6(10.7)	53(45.7)
Reasons for discontinuation						
Relapse criteria met	45(75.0)	1 (16.7)	1 (4.3)	3(11.1)	5(8.9)	50(43.1)
Adverse event	1 (1.7)	0	0	0	0	1(0.9)
Non-adherense/non-compliance	1 (1.7)	0	0	0	0	1(0.9)
Refused further participation	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Other	0	0	1 (4.3)	0	1(1.8)	1(0.9)

Source: Table 3 (pg. 36) of the Clinical Study Report SPD489-401.

Reviewer's Note: It appears that here and thereafter the sponsor provides the results for the randomized subjects and FAS excluding the six subjects from site 055. According to the definition of the Randomized Safety Population, there should be 122 patients, not 116.

The patients' completion status during the double blind phase of the study is summarized by visit in Table 3.

Table 3. Patients' completion status of the double-blind phase (FAS without site 055 data).

n (%)	Placebo	SPD489				Total
	N = 60	30 mg N = 6	50 mg N = 23	70 mg N = 27	All doses N = 56	N = 116
Completed study	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)	63 (54.3)
Early termination	47 (78.3)	1 (16.7)	2 (8.7)	3 (11.1)	6 (10.7)	53 (45.7)
Subjects remained in study at:						
Visit 4 (Day 28)	32 (53.3)	5 (83.3)	22 (95.7)	25 (92.6)	52 (92.9)	84 (72.4)
Visit 5 (Day 35)	22 (36.7)	5 (83.3)	22 (95.7)	25 (92.6)	52 (92.9)	74 (63.8)
Visit 6 (Day 42)	17 (28.3)	5 (83.3)	21 (91.3)	25 (92.6)	51 (91.1)	68 (58.6)
Visit 7 (Day 49)	15 (25.0)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)	65 (56.0)
Visit 8 (Day 56)	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)	63 (54.3)
Visit 9 (Day 63)	13 (21.7)	5 (83.3)	21 (91.3)	24 (88.9)	50 (89.3)	63 (54.3)

Source: Table 5 (pg. 38) of the Clinical Study Report SPD489-401.

Summary of the demographic and baseline physical characteristics is presented in Table 4.

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Table 4. Demographic and baseline characteristics during the double-blind phase (FAS without site 055 data).

		SPD489 N = 56	Placebo N = 60	Total N = 116
Age (years)	Mean (SD)	36.5 (10.95)	35.1 (11.39)	35.8 (11.15)
	Min – Max	18 – 55	18 – 55	18 – 55
Sex				
Male	n (%)	24 (42.9)	26 (43.3)	50 (43.1)
Female	n (%)	32 (57.1)	34 (56.7)	66 (56.9)
Race/Ethnicity				
White	n (%)	50 (89.3)	56 (93.3)	106 (91.4)
Black/African American	n (%)	0	2 (3.3)	2 (1.7)
Asian	n (%)	2 (3.6)	2 (3.3)	4 (3.4)
Hispanic/Latino	n (%)	7 (12.5)	2 (3.3)	9 (7.8)
Non-Hispanic or Latino	n (%)	49 (87.5)	58 (96.7)	107 (92.2)
Other	n (%)	4 (7.1)	0	4 (3.4)
Height (cm)	Mean (SD)	169.9 (10.12)	171.5 (10.25)	170.7 (10.18)
	Min – Max	152 – 191	147 – 196	147 – 196
Weight (kg)	Mean (SD)	75.4 (16.81)	76.5 (19.66)	76.0 (18.27)
	Min – Max	48 – 123	47 – 137	47 – 137
Body Mass Index (kg/m^2)	Mean (SD)	26.0 (4.66)	25.8 (5.28)	25.9 (4.97)
	Min – Max	19 – 38	19 – 40	19 – 40
Baseline ADHD-RS with adult prompts (total score)	Mean (SD)	10.6 (4.96)	10.6 (4.82)	10.6 (4.87)
	Min – Max	0 – 21	1 – 20	0 – 21
Baseline CGI-S	Mean (SD)	2.1 (0.8)	2.2 (0.78)	2.1 (0.79)
	Min – Max	1 – 3	1 – 4	1 – 4

Source: Table 1.2.3 (pg. 109) of the Clinical Study Report SPD489-401.

Statistical Methodologies

The primary efficacy endpoint (treatment failure at the end of the Double-blind Randomized Withdrawal Phase) was defined as a 50% increase (worsening) in Adult ADHD-RS with prompts score at any double-blind visit (Visits 4, 5, 6, 7, 8, or 9) relative to Visit 3 and a more than 2-point-increase in CGI-S score relative to CGI-S at Visit 3 at the corresponding double-blind visit.

The **primary efficacy analysis** was performed on the treatment failure proportions at the end of the Double-blind Randomized Withdrawal Phase for the FAS, using a Chi-Square test. In the primary analysis, 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 treatment effect was two-sided, and conducted at the significance level of 0.05.

The **sensitivity of the primary efficacy analysis** was assessed by repeating the primary efficacy analysis with all withdrawals for any reason classified as treatment failures.

Statistical Analyses Plan (SAP) also specifies **the analysis** for the secondary efficacy variable time to treatment failure (pg. 28) using Wilcoxon test for the FAS.

The first key secondary efficacy variable proposed by the sponsor: The analysis was performed on the Adult ADHD-RS-IV prompts change score at endpoint, defined as the last post-randomization treatment

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week (i.e., Visits 4 through 9) for which a valid ADHD-RS score was obtained, from Visit 3, using an ANCOVA model. The ANCOVA model included treatment group (the effect of interest), as a factor, and the corresponding Baseline score as a covariate. The alpha level of 0.05 was set for the type I error rate.

The key second secondary efficacy variable proposed by the sponsor: The analysis was performed on the CGI-S change score at endpoint, defined as the last post-randomization treatment week (i.e., Visits 4 through 9) for which a valid CGI-S score is obtained, from Visit 3, using an ANCOVA model. The ANCOVA model included treatment group (the effect of interest) as a factor and the corresponding baseline CGI-S (at Visit 3) as a covariate. The protocol also specified that in case of a heavily-skewed distribution of CGI-S data, i.e., with only a few levels populated, the Chi-square test should be used to examine treatment effects at that endpoint.

As there is a single primary comparison at a single primary endpoint, adjustment of multiplicity was not needed for the primary efficacy test.

Sponsor's Efficacy Results

Based on the primary analysis 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 (<9%) compared to subjects receiving placebo (75%) in the 6- week double-blind randomized withdrawal phase of the study (p-value <0.0001). See Table 5.

Table 5. Summary of results of the primary and sensitivity analyses for the primary endpoint (FAS without site 055 data).

Analysis	Definition of the endpoint	SPD489 n (%)	Placebo n (%)	p-value (χ^2 test)
Primary analysis	Treatment failure No treatment failure Total	5 (8.9) 51 (91.1) 56	45 (75.0) 15 (25.0) 60	< .0001
Sensitivity analysis	Withdrawal of any type No failure or withdrawal Total	6 (10.7) 50 (89.3) 56	47 (78.3) 13 (21.7) 56	< .0001

Source: Table 3.1.1.1 and Table 3.1.2.1 of the Clinical Study Report SPD489-401.

The sponsor performed two secondary efficacy analyses: ANCOVA with ADHD-RS change from baseline, and the Cochran Mantel Haenszel (CMH) Chi-Square test (since only few levels of the outcome variable were populated). The results are summarized in Table 6 and Table 7.

Table 6. The ANCOVA results of the first key secondary endpoint (ADHD-RS total score) using FAS without site 055 data.

Treatment Assigned	N	Baseline (Visit 3)	Adjusted change from the baseline (recorded at the last post-baseline visit of randomized phase)			
		Mean (SD)	LS Mean (SE)	Difference (95% CI)	Effect Size (95% CI)	p-value
SPD489	56	10.6 (4.96)	1.6 (1.39)	-15.23 (-19.1, -11.4)	-1.5 (-1.9, -1.1)	<.0001
Placebo	60	10.6 (4.82)	16.8 (1.35)			

Source: Table 17 (pg. 53) of the Clinical Study Report SPD489-401.

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Table 7. The CMH Chi-square test's results of the second key secondary endpoint (CGI-S) using FAS without site 55 data.

Categorical SGI-S	SPD489 (N=56)		Placebo (N = 60)	
	Baseline n(%)	Endpoint n (%)	Baseline n (%)	Endpoint n (%)
Normal, not at all ill	16 (28.6)	18 (32.1)	12 (20.0)	3 (5.0)
Borderline mentally ill	21 (37.5)	20 (35.7)	25 (41.7)	7 (11.7)
Mildly ill	19 (33.9)	10 (17.9)	22 (36.7)	7 (11.7)
Moderately ill	0	4 (7.1)	1 (1.7)	20 (33.3)
Markedly ill	0	4 (7.1)	0	21 (35.0)
Severely ill	0	0	0	2 (3.3)
p-value (CMH χ^2 test)	<.0001			

Source: Table 18 (pg. 54) of the Clinical Study Report SPD489-401.

The results of these two secondary endpoints support the efficacy findings of the primary efficacy analysis (statistically significant difference between placebo and SPD489) by resulting in statistically significant p-value (<0.0001). The applicability of these analyses and validity of their results are discussed at the end of the following section.

Reviewer's Results and Comments

The sponsor's efficacy analysis was performed using FAS excluding the data from the site 055 (6 patients). This decision was made by sponsor after conducting its own audit during 20 Jul – 22 Jul, 2010, i.e., before the data was locked and unblinded, but after the SAP was completed (19 Mar, 2010).

The sponsor reported that the audit observations included, but were not limited to, the following:

- Source documentation confirming stable treatment of commercial SPD489 for a minimum of 6 months prior to Screening (Visit -1; an inclusion criterion) was not obtained until after randomization for at least 2 subjects.
- For some subjects, scores on the ADHD-RS with adult prompts rating scale which would have been exclusionary appeared to have been adjusted to make the subjects eligible for the study.
- ADHD-RS with adult prompts and CGI assessments were signed by an unapproved rater who was identified as a "trainee." The notes to file written to explain the situation were contradictory.

Typically we do not remove observations from the pre-specified analysis dataset just because of reasons such as violation of inclusion criteria. Nevertheless, the efficacy results were very similar whether removing the site from analysis or not.

The demographic and baseline physical characteristics of all the subjects in the FAS without excluding the data from site 055 (Table 8) are very similar to those computed by the sponsor with the data from site 055 excluded (Table 4).

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Table 8. Demographic and baseline characteristics during the double-blind phase (FAS)

		SPD489 N = 60	Placebo N = 62	Total N = 122
Age (years)	Mean (SD) Min – Max	36.2 (10.67) 18 – 55	35.0 (11.25) 18 – 55	35.56 (10.94) 18 – 55
Sex				
Male	n (%)	26 (43.3)	28 (45.2)	54 (44.3)
Female	n (%)	34 (56.7)	34 (54.8)	68 (55.7)
Race/Ethnicity				
White	n (%)	54 (90)	57 (91.9)	111 (91.0)
Black/African American	n (%)	0	2 (3.2)	2 (1.6)
Asian	n (%)	2 (3.3)	2 (3.2)	4 (3.3)
Hispanic/Latino	n (%)	7 (11.7)	2 (3.2)	9 (7.4)
Non-Hispanic or Latino	n (%)	53 (83.3)	60 (96.8)	113 (92.6)
Other	n (%)	4 (6.7)	1 (1.6)	4 (3.3)
Height (cm)	Mean (SD) Min – Max	170.1 (10.25) 152 – 191	171.9 (10.34) 147 – 196	171.1 (10.29) 147 –196
Weight (kg)	Mean (SD) Min – Max	75.2 (17.29) 45 – 123	77.6 (20.26) 47 –137	76.4 (18.82) 45 – 137
Body Mass Index (kg/m^2)	Mean (SD) Min – Max	25.8 (4.72) 19 – 38	26.0 (5.34) 19 – 40	25.9 (5.03) 19 – 40
Baseline ADHD-RS with adult prompts (total score)	Mean (SD) Min – Max	10.7 (5.22) 0 – 21	10.8 (4.85) 1 – 20	10.7 (5.02) 0 – 21
Baseline CGI-S	Mean (SD) Min – Max	2.1 (0.79) 1 – 3	2.2 (0.78) 1 – 4	2.2 (0.78) 1 – 4

Source: Computed by the reviewer.

The reviewer confirms that efficacy was demonstrated based on the primary efficacy endpoint pre-specified by the sponsor, although the choice of the primary efficacy measure was not common for maintenance studies. The reviewer's results of the primary efficacy analysis (Chi-square of the proportion of the treatment failures) and its sensitivity analysis (Chi-square test based on the proportion of withdrawals for any reason) using entire FAS (i.e., without excluding the data from site 055) are summarized in Table 9.

Table 9. Summary of results of the primary and sensitivity analyses for the primary endpoint (FAS)

Analysis	Definition of the endpoint	SPD489 n (%)	Placebo n (%)	p-value (χ^2 test)
Primary analysis	Treatment failure No treatment failure Total	7 (11.7) 53 (83.3) 60	47 (75.8) 15 (24.2) 62	< .0001
Sensitivity analysis	Withdrawal of any type No failure or withdrawal Total	8 (13.3) 52 (86.7) 60	49 (79.0) 13 (21) 62	< .0001

Source: Computed by the reviewer.

The primary endpoint for long-term trials is typically based on a time-to-relapse measure. Based on logrank test applied to the FAS without removing any site, 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 Vyvanse group compared with the placebo group throughout the double-blind treatment period.

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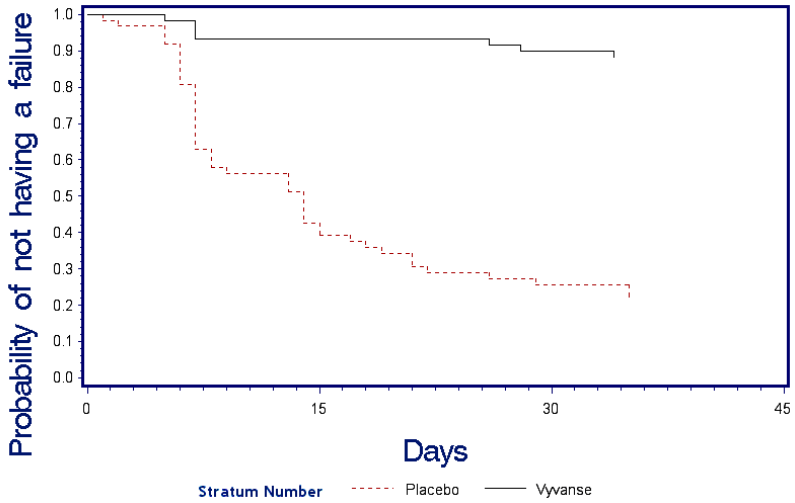
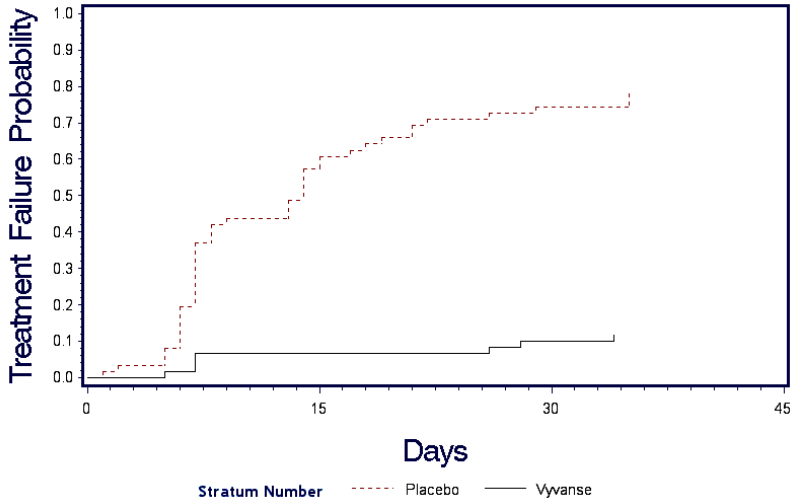
The following figures displays the Kaplan-Meier estimates of the reliability (survival) function and the cumulative probability of the treatment failure for the SPD489 treatment arm and placebo (Figure 2 and Figure 3). These two figures summarize the data from different perspectives. Generally speaking, while Figure 3 estimates the proportion of patients in each treatment arm who had a treatment failure by a given day after randomization, Figure 2 estimates the proportion of patients who had not developed a treatment failure by a given day which appears to support the efficacy of Vyvanse.

Figure 2. The estimate of the reliability (survival) function for Vyvanse (SPD489) and placebo (FAS).



Source: Computed by the reviewer.

Figure 3. Estimate of the cumulative probability of the treatment failure for Vyvanse (SPD489) and placebo (FAS).



Source: Computed by the reviewer.

The key secondary variables proposed by the sponsor can only be exploratory or at most supportive because patients were removed from trial as soon as they experienced the treatment failure. Thus, censoring is likely to be informative because the Adult ADHD-RS (total score) and CGI-S can be correlated with patient discontinuation, and the trial was not designed to reduce the kind of bias.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This section contains the reviewer's results of the exploratory analysis using Cox-proportional hazard model on the time to treatment failure for the FAS subgroup populations by gender, race, with and without the data from site 055 (see Table 10). These subgroup analyses results suggest a consistent trend in favor of SPD 489.

Table 10. The results of the Cox-proportional hazard analysis of the time to treatment failure by subgroups of gender, race, with and without site 055 data.

Subgroup	Number of patients	Excluding site 055			FDA (i.e., Including site 055)		
		SPD489 n (%)	Placebo n (%)	h-ratio (95%CI) (Placebo/SPD489)	SPD489 n (%)	Placebo n (%)	h-ratio (95%CI) (Placebo/SPD489)
FAS	Failed Total	5(8.93) 56	45(75.00) 60	14.14 (5.56,35.90)	7(11.67) 60	47(75.81) 62	11.43 (5.12,25.53)
Male	Failed Total	1(4.17) 24	19(73.08) 26	27.21 (3.62,204.67)	2(7.69) 26	21(75.00) 28	16.54 (3.83,71.34)
Female	Failed Total	4(12.50) 32	26(76.47) 34	10.49 (3.61,30.47)	5(14.71) 34	26(76.47) 34	9.09 (3.44,24.02)
White	Failed Total	4(8.00) 50	42(75.00) 56	16.19 (5.76,45.54)	6(11.11) 54	43(75.44) 57	12.23 (5.15,29.03)
Non-white	Failed Total	1(16.67) 6	3(75.00) 4	5.10 (0.52,49.71)	5(83.33) 6	1(20.00) 5	5.95 (0.65,54.31)

Source: Computed by the reviewer.

The subgroup analysis stratified by age was omitted because the entire population was under the age of 65.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The reviewers confirm sponsor's findings that SPD489 (administered once-daily in 30 mg, 50 mg and 70 mg) was statistically significantly superior to placebo (Chi-squared test p-value less than 0.0001) in reducing the proportion of treatment failures at the end of the double-blind randomized 6 weeks withdrawal phase in adult patients with ADHD. The result of logrank test on time to treatment failure was also statistically significant.

[redacted] (b) (4)) proposed by the sponsor were inappropriate for labeling inclusion because [redacted] (b) (4) (b) (4)

5.2 Conclusions and Recommendations

Once-daily administered Vyvanse at a fixed dose of 30 mg, 50 mg, and 70 mg showed positive effect compared to placebo in reducing the proportion of treatment failures in adult patients with ADHD.

APPENDICES

Table 11. Patient disposition during the double-blind phase of the study (with site 055 data).

n (%)	Placebo	SPD489				Total
		30 mg	50 mg	70 mg	All doses	
	N=62	N=6	N=25	N=29	N=60	N=122
Randomized subjects	62(100.0)	6(100.0)	25(100.0)	29(100.0)	60(100.0)	122(100.0)
Randomized safety population (took at least one dose)	62(100.0)	6(100.0)	25(100.0)	29(100.0)	60(100.0)	122(100.0)
Full Analysis Set (FAS)	62(100.0)	6(100.0)	25(100.0)	29(100.0)	60(100.0)	122(100.0)
Completed through Visit 9	13(21.0)	5 (83.3)	22(88.0)	25(86.2)	52(86.7)	65(53.3)
Early termination	49(79.0)	1 (16.7)	3 (12.0)	4(13.8)	8(13.3)	57(46.7)
Reasons for discontinuation						
Relapse criteria met	47(75.8)	1 (16.7)	2 (8.0)	4(13.8)	7(11.7)	54(44.3)
Adverse event	1 (1.6)	0	0	0	0	1(0.8)
Non-adherense/non-compliance	1 (1.6)	0	0	0	0	1(0.8)
Refused further participation	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Other	0	0	1 (4.0)	0	1(1.7)	1(0.8)

Source: Computed by the reviewer.

Table 12. Patients' completion status of the double-blind phase (FAS with site 055 data).

n (%)	Placebo	SPD489				Total
		30 mg	50 mg	70 mg	All doses	
	N = 62	N = 6	N = 25	N = 29	N = 60	N = 122
Completed study	13 (21.0)	5 (83.3)	22 (88.0)	25 (86.2)	52 (86.7)	65 (53.3)
Early termination	49 (79.0)	1 (16.7)	3 (12.0)	4 (13.8)	8 (13.3)	57 (46.7)
Subjects remained in study at:						
Visit 4 (Day 28)	34 (54.8)	5 (83.3)	24 (96.0)	27 (93.1)	56 (93.3)	90 (73.8)
Visit 5 (Day 35)	23 (37.1)	5 (83.3)	24 (96.0)	27 (93.1)	56 (93.3)	79 (64.8)
Visit 6 (Day 42)	18 (29.0)	5 (83.3)	23 (92.0)	27 (93.1)	55 (91.7)	73 (59.8)
Visit 7 (Day 49)	15 (24.2)	5 (83.3)	23 (92.0)	26 (89.7)	54 (90.0)	69 (56.6)
Visit 8 (Day 56)	13 (21.0)	5 (83.3)	22 (88.0)	26 (89.7)	53 (88.3)	66 (54.1)
Visit 9 (Day 63)	13 (21.0)	5 (83.3)	22 (88.0)	25 (86.2)	52 (86.7)	65 (53.3)

Source: Computed by the reviewer.

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ANDREJUS PARFIONOVAS
10/11/2011

PEILING YANG
10/11/2011
I concur.

HSIEN MING J J HUNG
10/11/2011