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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Suppl. Number:	21-977/S-0016 (SDN124)
Drug Name(s):	Vyvanse® / lisdexamfetamine dimesylate / NRP104 / SPD489 Capsules
Indication(s):	Attention-Deficit Hyperactivity Disorder in Adolescents Aged 13 to 17 Years
Applicant:	Shire Development, Inc.
Submission Date:	January 14, 2010
Review Priority:	Standard

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Keywords: LOCF ANCOVA

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Results from Study SPD489-305 demonstrated the superiority of Vyvanse® (30mg, 50mg, and 70mg/day) over placebo in improving the ADHD symptoms of adolescents aged 13-17 years, based upon the change from baseline to endpoint in clinician-administered ADHD-RS-IV total score.

1.2 Brief Overview of Clinical Studies

The sponsor submitted a Phase III, 4-week, randomized, double-blind, multi-center, parallel-group, placebo-controlled, forced-dose titration study SPD489-305 to evaluate the efficacy of SPD489 capsules (30, 50, or 70mg/day) compared to placebo in adolescents aged 13-17 with ADHD. Study SPD489-305 consisted of 4 phases: (1) screening and washout; (2) baseline; (3) 4-week double-blind treatment; and (4) post-treatment safety Follow-up.

A total of 314 patients were enrolled and all were assigned to randomized treatment at 45 centers in the United States. Of these randomized patients, 79 were in the placebo group, and 78, 79, and 78 were in the SPD489 30mg group, the SPD489 50mg group, and the SPD489 70mg group, respectively. A total of 265 randomized patients completed the 4-week double-blind treatment.

The primary efficacy variable was the change from baseline to endpoint in ADHD-RS-IV total score and it was analyzed by an LOCF ANCOVA. The efficacy analysis set consisted of 299 randomized patients (placebo: 76; SPD489 30mg: 76; SPD489 50mg: 72; SPD489 70mg: 75) with at least one post-baseline ADHD-RS-IV measurement during the double-blind treatment phase. These patients had a mean age of 14.6 years at baseline, and were predominantly male (69.9%) and white (79.9%).

1.3 Statistical Issues and Findings

This reviewer confirmed the sponsor's finding that SPD489-305 (30mg, 50mg, and 70mg/day) was superior to placebo in improving the ADHD symptoms of adolescents aged 13-17 years, as demonstrated by the statistically significant difference in mean change from baseline to endpoint in the ADHD-RS-IV total score (adjusted p-values ≤ 0.0056).

Although this study was not designed to evaluate the dose-response relationship, the results showed that there seemed to be a dose-response in the change from baseline in ADHD-RS-IV total score (Figure 2), after taking into consideration the actual doses administrated for the SPD489 groups at each post-baseline visit. However, no additional benefit from the 70 mg dose over the 50mg dose was observed at Week 4.

In addition, this reviewer noticed that there seemed to be a dose-response trend in weight change, after taking into consideration the actual doses administrated for the SPD489 groups at each post-baseline visit. It appears that patients receiving higher dose tended to lose more weight (Table 12). At endpoint, patients in each SPD489 group seemed to be significant weight loss as compared with those in the placebo group (Table 13).

2. INTRODUCTION

2.1 Overview

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder characterized by developmentally inappropriate degrees of inattentiveness, impulsivity, and hyperactivity.

Lisdexamfetaime dimesylate (a.k.a. SPD489 and NRP104), a prodrug of dextroamphetamine (*d*-amphetamine), was developed for the once-daily treatment of ADHD with less potential for abuse. SPD489 capsules (30, 50, and 70mg), marketed as Vyvanse®, were approved by the Food and Drug Administration (FDA) for the treatment of ADHD in children aged 6-12 years in February 2007. Intermediate dose strengths of 20, 40, and 60 mg were approved for use in children aged 6 to 12 years in December 2007. SPD489 was approved for the treatment of ADHD in adults aged 18-55 years in April 2008. In Canada, SPD489 capsules (30 and 50mg) were approved for the treatment of ADHD in children aged 6-12 years in March 2009.

Shire is submitting a supplemental New Drug Application (sNDA) to meet the Pediatric Research Equity Act requirement with the submission of Study SPD489-305 and to seek the proposed indication for the treatment of ADHD in adolescent patients aged 13 to 17 years with Vyvanse®.

2.2 Data Sources

The submitted data and study report are located in the following directory (EDR location): \\cdsesub1\EVSPROD\NDA021977\0035.

The study report is:
\\cdsesub1\EVSPROD\NDA021977\0035\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\spd489-305\spd489-305-report-body.pdf.

The statistical analysis plan (SAP) is:
\\cdsesub1\EVSPROD\NDA021977\0035\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\spd489-305\spd489-305-sap.pdf.

The derived efficacy data and the sponsor's SAS codes are contained in
\\cdsesub1\EVSPROD\NDA021977\0035\m5\datasets\spd489-305\analysis.

3. STATISTICAL EVALUATION

There is one Phase III study (SPD489-305) only in this submission. The study was initiated on 08 October 2008 and ended on 06 April 2009.

3.1 Evaluation of Efficacy

3.1.1   Objectives

Table 1 summarizes the study objectives of study SPD489-316 and variable(s) relating to each objective.

Table 1: Study Objectives and Variable(s) Relating to Each Objective

Objectives	Measure(s)
Primary Objective: to evaluate the efficacy of SPD489 compared to placebo over the course of 4 weeks in the treatment of adolescents (13-17) with at least moderately symptomatic ADHD	Clinician-administered ADHD-RS-IV
Key Secondary Objective: to assess the efficacy of SPD489 compared to placebo	Clinical Global Impression – Global Improvement (CGI-I)
Other Secondary Objectives: • to assess subject perception on qualify of life of SPD489 compared to placebo • to evaluate the safety and tolerability of SPD489	Youth Quality of Life Instrument – Research Version (YQOL-R) occurrence of treatment-emergent adverse events, specific evaluation of blood pressure and pulse, ECG results, clinical laboratory test results, and physical examination findings

(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Section 2; page 0014)

3.1.2   Study Design

This was a Phase III, 4-week, randomized, double-blind, multi-center, parallel-group, placebo-controlled, forced dose-titration, safety and efficacy study. The study consisted of 4 phases (Figure 1): (1) screening and washout; (2) baseline; (3) 4-week double-blind treatment; and (4) post-treatment safety Follow-up. It was conducted at 45 investigative sites in the United States.

Figure 1: Study Design Flow Chart
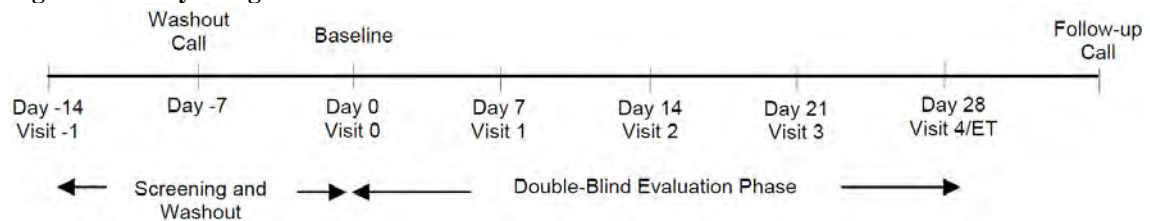
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Figure 1, page 0015)

Eligible ADHD adolescents were randomized in a 1:1:1:1 ratio to receive either SPD489 (30, 50, or 70mg/day) or placebo for a double-blind stepwise forced dose titration for 3 weeks followed by a 1-week Dose Maintenance Phase. As shown in Table 2, all subjects randomized to SPD489 started at a dose of 30mg/day. Subjects randomized to 30mg began dosing at 30mg per day during Week 1 and remained on that dose throughout the study; those randomized to 50mg were titrated to that dose over a 1-week period; and those randomized to 70mg were titrated to that dose over a 2-week period.

Table 2: Forced-Dose Titration Schedule

Treatment Group	Week 1 (Visit 0-1)	Week 2 (Visit 1-2)	Week 3 (Visit 2-3)	Week 4 (Visit 3-4)
SPD489 30mg	30mg	30mg	30mg	30mg
SPD489 50mg	30mg	50mg	50mg	50mg
SPD489 70mg	30mg	50mg	70mg	70mg
Placebo	Placebo	Placebo	Placebo	Placebo

(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 1, page 0015)

3.1.3 Sample Size Calculation and Power Consideration

The primary efficacy measure was the change from baseline to endpoint in the ADHD-RS-IV total score. Assuming a standardized effect size of at least 0.55 for the comparison between one SPD489 dose group and placebo, a total of 71 subjects per treatment group was required for 90% power at the significance level of 0.05 (two-sided) using a two-sample *t*-test with equal allocation to treatment groups. A total of 300 subjects (75 subjects in each treatment group) were to be randomized to account for an anticipated 5% of randomized subjects prematurely discontinuing without providing any post-baseline ADHD-RS-IV measurement.

Reviewer's Note: the study finally enrolled 314 subjects and only 15 (4.8%) subjects prematurely discontinued without providing any post-baseline ADHD-RS-IV measurement during the double-blind treatment phase. Of these 15 dropout patients, 4 were not dosed, and 10 were retrieved and were assessed at the early termination visit for a post-treatment ADHD-RS-IV measurement.

3.1.4 Efficacy Variables and Analyses

Primary efficacy variable: the change from baseline to endpoint in the clinician-administered ADHD-RS-IV total score.

The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV-TR^{TM} criteria. Each item is scored from a range of 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54. The 18 items may be grouped into two sub-scales:

hyperactivity/impulsivity (even number items 2-18) and inattentiveness (odd number items 1-17).

- **Primary Analysis**: LOCF ANCOVA on full analysis set in the double-blind treatment phase
  o Model: <u>factor</u>: treatment; <u>covariate</u>: baseline score.
  o Rank ANCOVA: would be used if the normality assumption for the ANCOVA model is not met based on diagnostic residual plots.

- **Multiplicity Adjustment:** Dunnett's test was used to control the family-wise Type I error rate at 0.05 (two-sided).

- **Sensitivity Analyses:**
  o Primary ANCOVA on per-protocol (PP) population
  o MMRM with unstructured covariance on observed data (<u>fixed effects</u>: treatment, visit, treatment-by-visit; <u>random effect</u>: subject; <u>covariate</u>: baseline score). The estimations of treatment effects and the comparisons between active doses and placebo were based on the **actual dose(s)** received at each post-baseline visit.

- **Subgroup analyses:** the ADHD-RS-IV total scores were analyzed separately for males, females, whites, non-whites, and age group (13-14 vs. 15-17).

- **Handling of missing data:** If more than 3 items had missing or invalid data, the total score would be set to missing. If 3 items or less were missing or invalid, the values for the missing items would be imputed using the mean of the non-missing items rounded to the nearest integer.

<u>**KEY secondary efficacy variable**</u>: the sponsor designated CGI-I as a key secondary efficacy variable.

- **Primary Analysis**: parametric ANCOVA on complete cases
  o Model: <u>factor</u>: treatment; <u>covariate</u>: baseline CGI-S scale.
  o Cochran-Mantel-Haenszel test: would be used for heavily skewed CGI-I data. This variable would be dichotomized as follows: 'very much improved' and 'much improved' are combined into one category (*improved*) and the remaining levels are combined into the other (*no improvement*).

- **Multiplicity Adjustment:** Dunnett's test was used to control the family-wise Type I error rate at 0.05 (two-sided).

- **Subgroup analyses:** the CGI-I scores were analyzed separately for males, females, whites, non-whites, and age group (13-14 vs. 15-17).

Reviewer's Note: Although the sponsor designated CGI-I as a key secondary efficacy variable, they did not pre-specify any multiplicity adjustment to control the study-wise Type I error rate for the two families of hypotheses associated with the primary and the

key secondary efficacy variables. They explained in their regulatory response (IND 67,482/SN211 dated 22 December 2008) that in previous ADHD studies, they had seen strong correlation between ADHD-RS-IV and CGI-I (Spearman ρ ranging from 0.8 to 0.9) at endpoint. They thought that this correlation could reduce the need to correct for Type I error across multiple outcomes. In addition, they used a model selection approach to select the better analysis (continuous or categorical) for CGI-I score using the same data, which could inflate the Type I error rate. Our comments regarding these two potential statistical issues were conveyed to the sponsor on 6 January 2010 but no further amendments to the SAP were identified. The sponsor's statistical analyses were performed following the SAP dated 19 December 2008.

3.1.5   Efficacy Results

3.1.5.1   Study Populations

- Enrolled Population: defined as all subjects who were dispensed study medication at the baseline visit.

- Safety Population: defined as all subjects who took at least one randomized dose of study medication during this study.

- Full Analysis Set (FAS): defined as all subjects who took at least one randomized dose of study medication during this study and had a valid baseline and at least one post-baseline follow-up assessment of the primary outcome measure.

- Per-Protocol (PP) Population: defined as all subjects in the FAS who completed the study as indicated on the CRF and were protocol compliant.

Reviewer's Note: Although the sponsor reports that "the primary efficacy analysis was performed … using the FAS", this reviewer found that the sponsor's primary analysis actually excluded 10 retrieved dropout patients (1 receiving placebo and 9 receiving SPD489) who were in the FAS but had one post-baseline ADHD-RS-IV measurement only AFTER the final dose of treatment (post-treatment assessment). In the following sections, this reviewer would use "FAS-DB" to denote the analysis set of the primary ANCOVA.

Table 3 summarizes the subject disposition. The treatment allocation was well-balanced among the four treatment groups, with 78 or 79 randomized patients per group. The dropout rate in the placebo group was 12.7%, numerically smaller than those in the SPD489 groups (30mg: 19.2%; 50mg: 16.5%; 70mg: 14.1%). The proportions of dropouts due to lack of efficacy in the placebo group (5.1%) and the SPD489 30mg group (5.1%) were numerically larger than those in the 50mg group (2.5%) and the 70mg group (0%). On the contrary, the proportion of dropouts due to adverse event(s) was only 1.3%

in the placebo group, which was numerically smaller than those in the SPD489 groups (30mg: 3.8%; 50mg: 3.8%; 70mg: 5.1%).

Table 3: Summary of Subject Disposition

	Placebo	SPD489 Assigned Treatment			SPD489	Overall
		30mg	50mg	70mg	All Doses	Enrolled
	N = 79	N = 78	N = 79	N = 78	N = 235	N = 314
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	79 (100.0)	78 (100.0)	79 (100.0)	78 (100.0)	235 (100.0)	314 (100.0)
Safety Pop.	77 (97.5)	78 (100.0)	77 (97.5)	78 (100.0)	233 (99.1)	310 (98.7)
Full Analysis Set (FAS)	77 (97.5)	78 (100.0)	76 (96.2)	78 (100.0)	232 (98.7)	309 (98.4)
FAS-DB[a]	76 (96.2)	76 (97.4)	72 (91.1)	75 (96.2)	223 (94.9)	299 (95.2)
Completers	69 (87.3)	63 (80.8)	66 (83.5)	67 (85.9)	196 (83.4)	265 (84.4)
Per-protocol Population	64 (81.0)	56 (71.8)	60 (75.9)	57 (73.1)	173 (73.6)	237 (75.5)
Early termination	10 (12.7)	15 (19.2)	13 (16.5)	11 (14.1)	39 (16.6)	49 (15.6)
Discontinuation Reason:						
Adverse event(s)	1 (1.3)	3 (3.8)	3 (3.8)	4 (5.1)	10 (4.3)	11 (3.5)
Protocol violations	3 (3.8)	2 (2.6)	2 (2.5)	0 (0.0)	4 (1.7)	7 (2.2)
Refused further participation	0 (0.0)	0 (0.0)	2 (2.5)	2 (2.6)	4 (1.7)	4 (1.3)
Lost to follow-up	1 (1.3)	1 (1.3)	1 (1.3)	3 (3.8)	5 (2.1)	6 (1.9)
Lack of efficacy	4 (5.1)	4 (5.1)	2 (2.5)	0 (0.0)	6 (2.6)	10 (3.2)
Other	1 (1.3)	5 (6.4)	3 (3.8)	2 (2.6)	10 (4.3)	11 (3.5)
Retrieved Dropouts[b]	1 (1.3)	4 (5.1)	5 (6.3)	6 (7.7)	15 (6.4)	16 (5.1)

These two rows were summarized by this reviewer:

a. FAS-DB: FAS patients who had at least one post-baseline assessment before they discontinued the double-blind (DB) treatment. This was actually the analysis set of the primary ANCOVA.

b. Retrieved Dropouts: FAS patients who discontinued the double-blind treatment and were retrieved to have a *post-treatment* ADHD-RS-IV measurement (assessment date > the final dose date).

(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 6, page 0036)

Table 4 summarizes the demographic and baseline characteristics for patients in the FAS-DB. These 299 subjects had a mean age of 14.6 years; 53.2% were 13-14 years old and 46.8% were 15-17 years old. They had a mean weight of 63.5 kg, and were predominantly male (69.9%) and white (79.9%). The proportions of males in the SPD489 30mg (76.3%) and 50mg (79.2%) groups were numerically larger than that in the SPD489 70mg group (56.0%). The mean baseline ADHD-RS-IV total score was 37.9. The majority of patients had the combined ADHD subtype (69.7% for the placebo group and 64.1% for the SPD489 groups). All others, with the exception of 2 patients treated with SPD489, had the predominantly inattentive subtype.

Table 4: Demographic and Baseline Characteristics (FAS-DB)

		Placebo	SPD489 Assigned Treatment			SPD 489 All Doses	Overall
			30mg	50mg	70mg		
		N = 76	N = 76	N = 72	N = 75	N = 223	N = 229
Age (years)	Mean (SD)	14.5 (1.26)	14.6 (1.41)	14.7 (1.30)	14.4 (1.27)	14.6 (1.33)	14.6 (1.31)
13-14	N (%)	41 (54.0%)	42 (55.3)	34 (47.2%)	42 (56.0%)	118 (52.9%)	159 (53.2%)
15-17	N (%)	35 (46.0%)	34 (44.7)	38 (52.8%)	33 (44.0%)	105 (47.1%)	140 (46.8%)
Gender							
Male	N (%)	52 (68.4%)	58 (76.3%)	57 (79.2%)	42 (56.0%)	157 (70.4%)	209 (69.9%)
Female	N (%)	24 (31.6%)	18 (23.7%)	15 (20.8%)	33 (44.0%)	66 (29.6%)	90 (30.1%)
Race							
White	N (%)	65 (85.5%)	52 (68.4%)	61 (84.7%)	61 (81.3%)	174 (78.0%)	239 (79.9%)
Non-White	N (%)	11 (14.5%)	24 (31.6%)	11 (15.3%)	14 (18.7%)	49 (22.0%)	60 (20.1%)
Height (cm)	Mean (SD)	166.6 (10.09)	168.0 (9.48)	168.8 (8.87)	166.2 (8.43)	167.7 (8.97)	167.4 (9.26)
Weight (kg)	Mean (SD)	62.2 (13.35)	66.1 (15.07)	64.3 (12.71)	61.4 (10.30)	63.9 (12.95)	63.5 (13.05)
BMI (kg/m^2)	Mean (SD)	22.3 (3.65)	23.2 (3.97)	22.4 (3.12)	22.2 (3.05)	22.6 (3.42)	22.5 (3.48)
Baseline ADHD-RS-IV							
Total Score	Mean (SD)	38.3 (7.09)	38.5 (6.69)	37.4 (6.39)	37.3 (7.28)	37.8 (6.79)	37.9 (6.86)
Hyper/Imp*	Mean (SD)	15.6 (6.32)	15.9 (5.78)	14.8 (5.69)	15.3 (6.36)	15.3 (5.94)	15.4 (6.03)
Inattention	Mean (SD)	22.8 (3.02)	22.7 (3.40)	22.6 (3.26)	22.0 (3.44)	22.4 (3.37)	22.5 (3.28)
ADHD Subtype							
Inattentive	N (%)	23 (30.3)	21 (27.6)	30 (41.7)	27 (36.0)	78 (35.0)	101 (33.8)
Hyper/Imp*	N (%)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.3)	2 (0.9)	2 (0.7)
Combined	N (%)	53 (69.7)	55 (72.4)	41 (56.9)	47 (62.7)	143 (64.1)	196 (65.5)

*Hyperactiveity/Impulsive

(Source: Reviewer's Result using SAS 9.2, 2010)

There were 37 patients in the FAS-DB with major protocol deviations (Table 5). Of these patients, 23 did not meet washout specifications and 7 did not meet inclusion/exclusion criteria. Subject 042-002 failed to meet washout specifications. He also did not meet exclusion criteria (took excluded medication).

Table 5: Summary of Major Protocol Deviations by Treatment Group (FAS-DB)

	Placebo	SPD489 Assigned Treatment			SPD 489 All Doses	Overall
		30mg	50mg	70mg		
	N = 76	N = 76	N = 72	N = 75	N = 223	N = 299
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with major protocol deviations	5 (6.6)	11 (14.5)	10 (13.9)	11 (14.7)	32 (14.3)	37 (12.4)
Major protocol deviation:						
Failure to meet washout specifications	2 (2.6)	8 (10.5)	7 (9.7)	6 (8.0)	21 (9.4)	23 (7.7)
Did not meet inclusion criteria	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)	2 (0.7)
Did not meet exclusion criteria	0 (0.0)	2 (2.6)	1 (1.4)	2 (2.7)	5 (2.2)	5 (1.7)
Treatment compliance < 80% or > 120%	0 (0.0)	0 (0.0)	1 (1.4)	3 (4.0)	4 (1.8)	4 (1.3)
Overdose, abuse, or misuse of study med*	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pregnancy	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.4)	1 (0.3)
Other deviation	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.7)

*Subject 033-010 (placebo) inadvertently took 2 doses of study medication on the same day

(Source: Reviewer's Result using SAS 9.2, 2010)

3.1.5.2   Sponsor's Efficacy Results for Primary Efficacy Variable

The sponsor defined *Endpoint* as the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid score was obtained.

3.1.5.2.1   Primary Efficacy Analysis

Table 6 shows that efficacy was statistically demonstrated at endpoint for all 3 SPD489 groups (adjusted *p*-values ≤ 0.0056).

Table 6: Analysis of Change from Baseline to Endpoint in ADHD-RS-IV Total (FAS-DB, LOCF)

Endpoint	Baseline		Adjusted Change from Baseline						
FAS-DB (N = 299)	n	Mean (SD)	n	LS Mean (SE)	LS DIFF	95% CI	Effect Size	95% CI	*p*-value*
Placebo	76	38.3 (7.09)	76	-12.8 (1.25)					
SPD489 30mg	76	38.5 (6.69)	76	-18.3 (1.25)	-5.5	(-9.7, -1.3)	-0.5	(-0.8, -0.2)	0.0056
SPD489 50mg	72	37.4 (6.39)	72	-21.1 (1.28)	-8.3	(-12.5, -4.1)	-0.8	(-1.1, -0.4)	< 0.0001
SPD489 70mg	75	37.3 (7.28)	75	-20.7 (1.25)	-7.9	(-12.1, -3.8)	-0.7	(-1.1, -0.4)	< 0.0001

*adjusted *p*-value from Dunnett's test
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 14, page 0054)

The sponsor states that although the study was not designed to evaluate the dose-response relationship, there seemed to be a dose-response in the change from baseline in ADHD-RS-IV total score (Figure 2), after taking into consideration the actual doses administered for the SPD489 groups at each post-baseline visit (Table 2).

Dose-Response Relationship:
–   Week 1: Patients in all SPD489 groups received a 30mg daily dose. At the end of that treatment week (Visit 1), each of the three SPD489 groups (all receiving 30mg) had a similar improvement in ADHD-RSIV total score relative to placebo.

–   Week 2: The daily dose for the SPD489 50mg and 70mg groups was increased to 50mg. At the end of that treatment week (Visit 2), the SPD489 50mg and 70mg groups (both receiving 50mg) showed greater improvement relative to placebo in ADHD-RS-IV Total score than the SPD489 30mg group.

–   Week 3: The daily dose for the SPD489 70mg group was increased to 70mg. At the end of that treatment week (Visit 3), patients receiving SPD489 70mg showed greater improvement relative to placebo than patients receiving SPD489 50mg, who showed greater improvement than subjects receiving SPD489 30mg.

–   Week 4: The dose strengths remained constant. At the end of that treatment week (Visit 4), patients receiving SPD489 70mg and SPD489 50mg had similar improvement relative to placebo, but these subjects continued to have greater improvement in the ADHD-RS-IV total score relative to placebo than those receiving SPD489 30mg.

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Figure 2: LS Mean Change from Baseline in ADHD-RS-IV Total by Visit (FAS-DB)
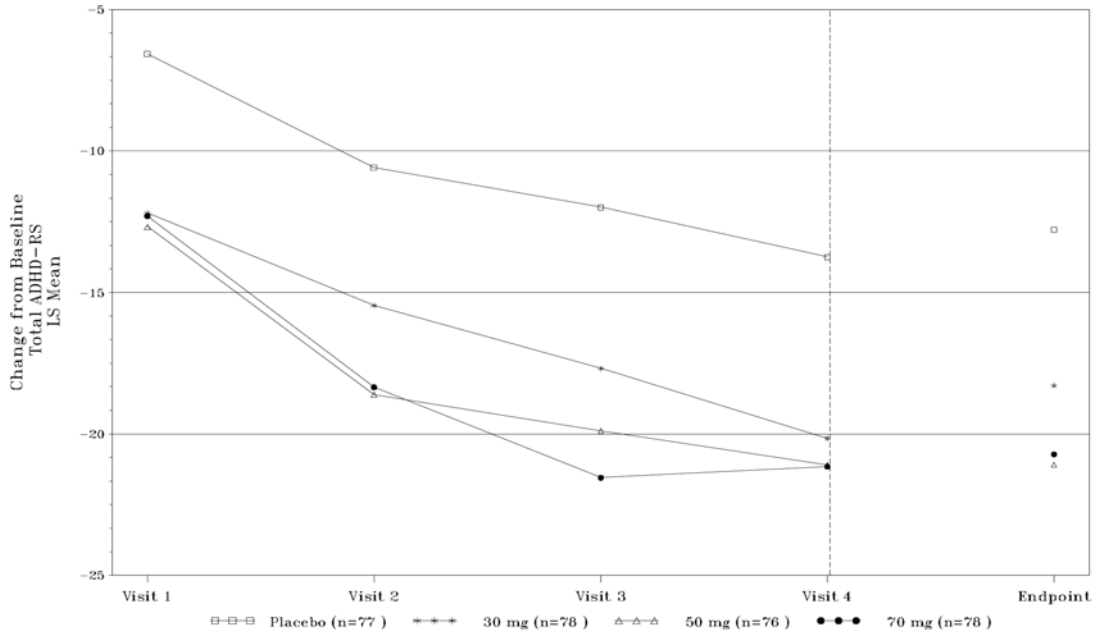
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Figure 4, page 0058)

FDA's Comments: This reviewer confirmed the sponsor's finding that each SPD489 group had a statistically significantly larger mean decrease from baseline to endpoint in ADHD-RS-IV total score than the placebo group (adjusted p-values ≤ 0.0056).

Two critical assumptions of ANCOVA appeared to be reasonable for the sponsor's primary ANCOVA: The homoscedasticity from the primary ANCOVA was examined by plot of residuals versus predicted values (Figure 3) and it apparently was not violated. The normality of residuals appeared to be supported by the Q-Q plot (Figure 4).

Figure 3: Plot of Residuals vs Predicted Values from Sponsor's Primary ANCOVA (FDA-DB, LOCF)

(Source: Reviewer's Result using SAS 9.2, 2010)

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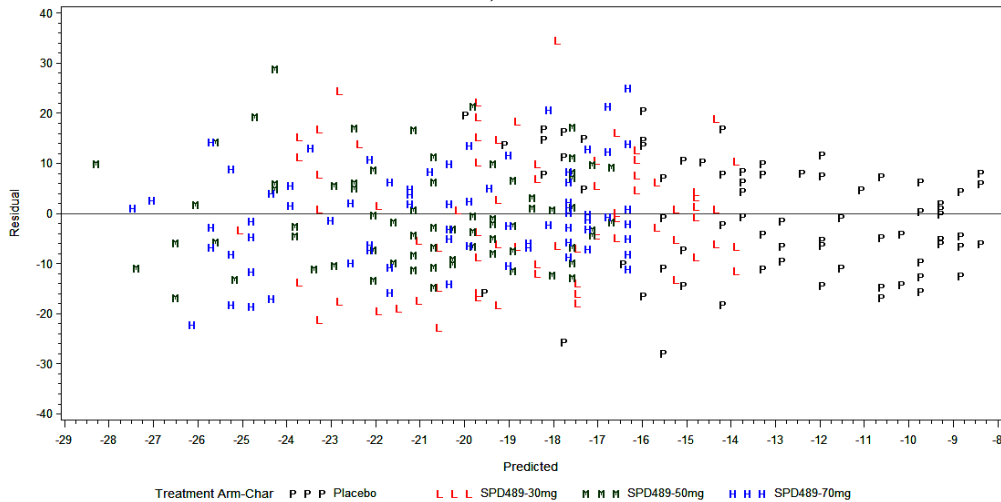
Figure 4: Q-Q Plot for Residuals from Sponsor's Primary ANCOVA (FDA-DB, LOCF)
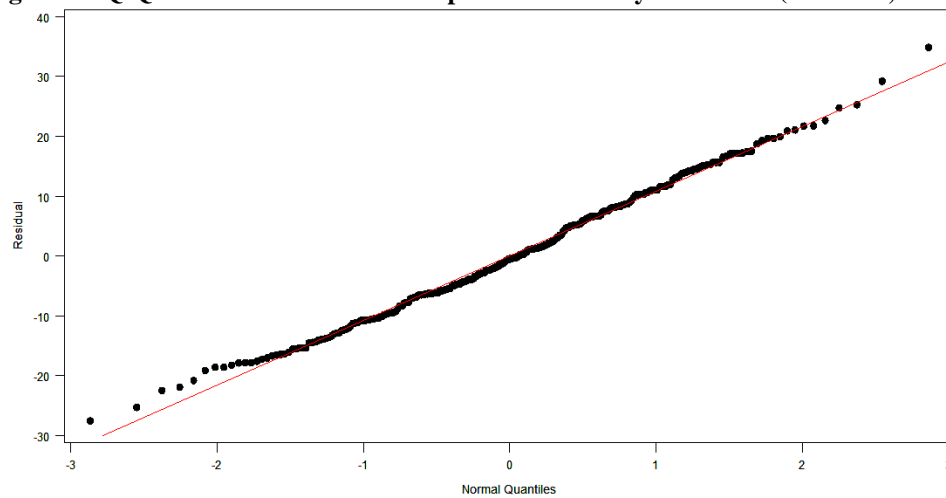
(Source: Reviewer's Result using SAS 9.2, 2010)

To assess the effect of ADHD-RS-IV baseline score-by-treatment interaction on the primary efficacy outcomes, this reviewer included this interaction term into the primary ANCOVA. Figure 5 showed the regression lines fitted using the model with interaction. Although these regression lines appeared to be not parallel, the observed mean reduction in each SPD489 group was consistently numerically greater than that in the placebo group over the observed range of baseline scores, which supported the efficacy of SPD489 capsules compared with placebo.

Figure 5: Baseline ADHD-RS-IV Total Score by Treatment Interaction – Scatter Plot of Endpoint Changes vs. Baseline Scores (FAS-DB, LOCF)

(Source: Reviewer's Result using SAS 9.2, 2010)

15
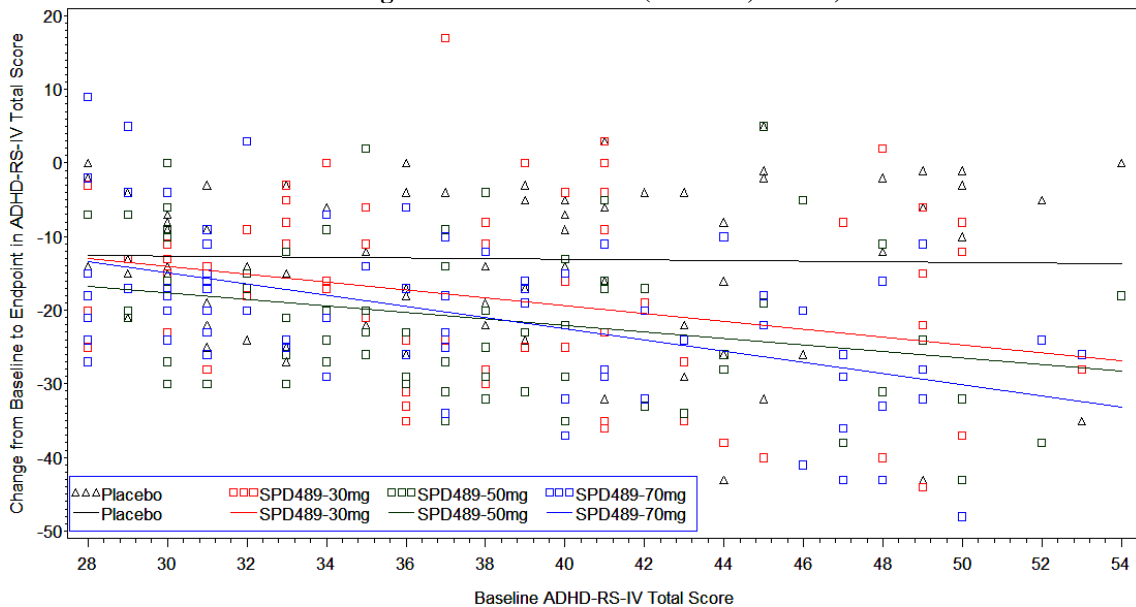
3.1.5.2.2 Sensitivity Analyses

As shown in
Table 7, the sponsor's ANCOVA results for the PP population were consistent with those
for the FAS-DB patients.

Table 7: Analysis of Change from Baseline to Endpoint in ADHD-RS-IV Total Score (PP, LOCF)

Endpoint	Baseline		Adjusted Change from Baseline						
PP (N = 237)	n	Mean (SD)	n	LS Mean (SE)	LS DIFF	95% CI	Effect Size	95% CI	*p*-value*
Placebo	64	38.5 (7.41)	64	-13.2 (1.31)					
SPD489 30mg	56	38.3 (6.60)	56	-20.5 (1.40)	-7.3	(-11.8, -2.8)	-0.7	(-1.1, -0.3)	0.0005
SPD489 50mg	60	36.7 (5.96)	60	-21.9 (1.35)	-8.7	(-13.1, -4.2)	-0.8	(-1.2, -0.5)	< 0.0001
SPD489 70mg	57	36.8 (7.38)	57	-20.7 (1.38)	-7.5	(-12.0, -2.9)	-0.7	(-1.1, -0.3)	0.0004

*adjusted *p*-value from Dunnett's test
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 2.1.2.2, page 0172)

The sponsor performed an MMRM analysis on the FAS-DB to assess the treatment
effects of the *actual doses* at each post-baseline visit. As shown in Table 8, the results
were consistent with those from the primary efficacy findings.

Table 8: MMRM Analysis of Change from Baseline in ADHD-RS-IV Total Score (FAS-DB, OC)

Visit		Placebo N= 77	SPD489 30 mg N= 78	SPD489 50 mg N= 76	SPD489 70 mg N= 78
				Assigned Treatment	
Visit 1	n LS Mean (SE) change[a] Diff (95% CI) p-value[b]	76 -6.48 (1.005)	223 -12.37 (0.587) -5.89 (-8.18, -3.60) <0.0001[c]		
Visit 2	n LS Mean (SE) change[a] Diff (95% CI) p-value[b]	75 -10.48 (1.125)	73 -15.30 (1.134) -4.82 (-7.96, -1.68) 0.0027	142 -18.47 (0.814) -7.99 (-10.73, -5.26) <0.0001[d]	
Visit 3	n LS Mean (SE) change[a] Diff (95% CI) p-value[b]	75 -11.92 (1.179)	69 -17.67 (1.204) -5.75 (-9.07, -2.44) 0.0007	70 -19.95 (1.214) -8.03 (-11.36, -4.70) <0.0001	70 -21.39 (1.207) -9.47 (-12.79, -6.15) <0.0001
Visit 4	n LS Mean (SE) change[a] Diff (95% CI) p-value[b]	67 -13.14 (1.273)	62 -19.20 (1.304) -6.06 (-9.64, -2.47) 0.0010	65 -21.19 (1.305) -8.04 (-11.63, -4.45) <0.0001	65 -21.00 (1.299) -7.86 (-11.44, -4.28) <0.0001

[a] LS Mean (SE) computed from a mixed effects linear model for repeated measures.
[b] p-value is from the comparison of active dose to placebo at each visit. A negative difference (Diff) in LS Mean (Active - Placebo) indicates a positive effect of the active treatment over the placebo.
[c] Estimated from subjects in the three SPD489 arms vs. Placebo.
[d] Estimated from subjects in SPD489-50mg and -70mg arms vs. Placebo.
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 15, page 0056)

Reviewer's Note: The sponsor's MMRM analysis results in Table 8 were obtained using
their SAS program \\cdsesub1\EVSPROD\NDA021977\0035\m5\datasets\spd489-
305\analysis\programs\rtadhdse.txt. This reviewer identified three places in this program

that need to be corrected or improved (Table 9). The results based on the revised SAS program were different but consistent with the sponsor's MMRM analysis results.

Table 9: Reviewer's Corrections or Improvements of Sponsor's SAS Program for MMRM Analysis

	Sponsor's Program rtadhdse.txt	Reviewer's Correction/Improvement
1. The analysis set was FDA-DB	Used the mean baseline ADHD-RS-IV total score across patients in the FAS	Used the mean baseline ADHD-RS-IV total score across patients in the FAS-DB
2. One patient (ID: 039-006) assigned to the 50mg group did not take any SPD489 capsules at Visit 1. This patient was in the FAS-DB but not in the PP population.	Counted Patient 039-006 as taking SPD489 30mg at Visit 1.	Excluded the efficacy data of Patient 039-006 at Visit 1 from the MMRM analysis
3. At Visit 1, the numbers of patients receiving 30mg in the three SPD489 groups were different	Assigned equal weights (1/3:1/3:1/3) to three SPD489 groups when comparing SPD489 30mg (actual dose) and placebo	Corrected the weights so that they were proportional to the numbers of patients receiving 30mg in the three SPD489 groups.

(Source: Reviewer's Results)

3.1.5.3 Sponsor's Efficacy Results for Secondary Efficacy Variables

3.1.5.3.1 Change from Baseline to Endpoint in ADHD-RS-IV Subscale Scores

<u>ADHD-RS-IV Hyperactivity/Impulsivity Score</u>

Consistent with the primary efficacy results, the sponsor's ANCOVA results for change from baseline at Endpoint in ADHD-RS-IV Hyperactivity/Impulsivity subscale score supported the efficacy of SPD489 capsules compared with placebo (Table 10).

Table 10: Analysis of Change from Baseline to Endpoint in ADHD-RS-IV Hyperactivity/Impulsivity Subscale Score (FAS-DB, LOCF)

Endpoint	Baseline		Adjusted Change from Baseline						
FAS-DB (N = 299)	n	Mean (SD)	n	LS Mean (SE)	LS DIFF	95% CI	Effect Size	95% CI	*p*-value*
Placebo	76	15.6 (6.32)	76	-5.3 (0.61)					
SPD489 30mg	76	15.9 (5.78)	76	-7.9 (0.61)	-2.5	(-4.6, -0.5)	-0.5	(-0.8, -0.2)	0.0099
SPD489 50mg	72	14.8 (5.69)	72	-8.6 (0.63)	-3.3	(-5.3, -1.2)	-0.6	(-0.9, -0.3)	0.0007
SPD489 70mg	75	15.3 (6.36)	75	-8.6 (0.61)	-3.3	(-5.3, -1.2)	-0.6	(-0.9, -0.3)	0.0005

*adjusted *p*-value from Dunnett's test
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 17, page 0062)

<u>ADHD-RS-IV Inattention Score</u>

Consistent with the primary efficacy results, the sponsor's ANCOVA results for change from baseline at Endpoint in ADHD-RS-IV Inattention Score subscale score supported the efficacy of SPD489 capsules compared with placebo (Table 11).

Table 11: Analysis of Change from Baseline to Endpoint in ADHD-RS-IV Inattention Subscale Score (FAS-DB, LOCF)

Endpoint	Baseline		Adjusted Change from Baseline						
FAS-DB (N = 299)	n	Mean (SD)	n	LS Mean (SE)	LS DIFF	95% CI	Effect Size	95% CI	*p*-value*
Placebo	76	22.8 (3.02)	76	-7.4 (0.73)					
SPD489 30mg	76	22.7 (3.40)	76	-10.4 (0.73)	-3.0	(-5.4, -0.6)	-0.5	(-0.8, -0.1)	0.0109
SPD489 50mg	72	22.6 (3.26)	72	-12.4 (0.75)	-5.0	(-7.5, -2.6)	-0.8	(-1.1, -0.5)	< 0.0001
SPD489 70mg	75	22.0 (3.44)	75	-12.2 (0.74)	-4.8	(-7.2, -2.3)	-0.8	(-1.1, -0.4)	< 0.0001

*adjusted *p*-value from Dunnett's test

(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 19, page 0067)

3.1.5.3.2   *Clinical Global Impression – Global Improvement*

Figure 6 displays the dichotomous summary of CGI-I scores by treatment group at each post-baseline visit and at endpoint. The percentage of patients considered "improved" (rated either 'much improved' or 'very much improved') in each treatment group appeared to follow an increasing trend from Visit 1 through Visit 4. At endpoint, 39.5% of placebo-treated patients were considered "improved". This proportion was numerically smaller than those in the SPD489 groups (30mg: 57.9%; 50mg: 73.6%; 70mg: 76.0%). The sponsor states that there seemed to be a dose-response trend in the dichotomous CGI-I result (Figure 6), after taking into consideration the actual doses administered for the SPD489 treatment groups at each post-baseline visit (Table 2).

Figure 6: CGI-I Improvement by Treatment Group at Each Visit and at Endpoint (FAS-DB)
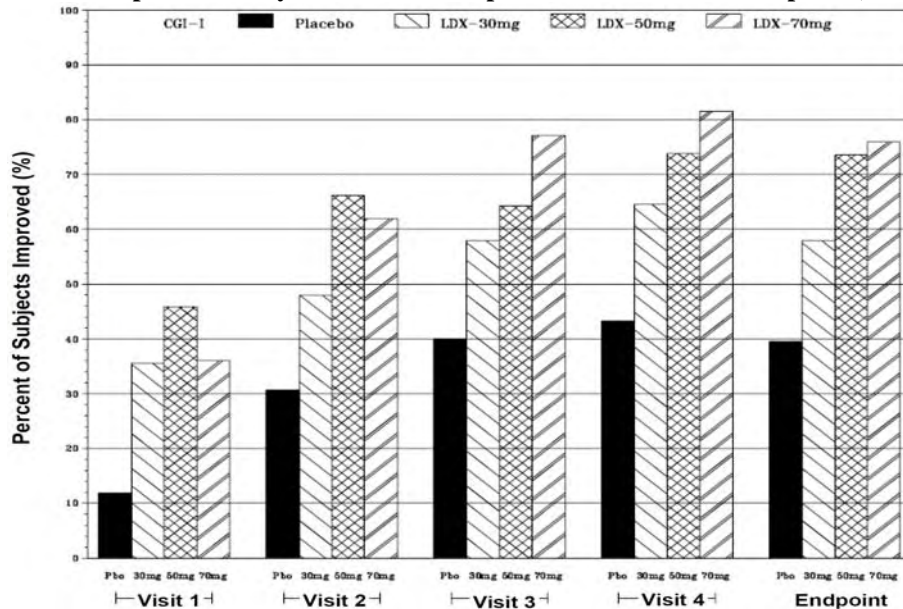
(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Figure 6, page 0076)

The sponsor's ANCOVA results and CMH test results for CGI-I score consistently supported the efficacy of SPD489 capsules compared with placebo, with *p*-values from Dunnett's test smaller than 0.0001 at endpoint.

3.1.5.4   Statistical Reviewer's Findings and Comments

3.1.5.4.1   *Cumulative Distribution Functions of Primary Efficacy Variable*

This reviewer confirmed the sponsor's findings for all efficacy variables and concluded that Study 489-305 demonstrated statistically significant treatment effect of SPD489 capsules over placebo in improving ADHD symptoms of adolescents based on the primary efficacy variable.

Figure 7 displays the cumulative distribution function (CDF) curves of the primary efficacy variable (LOCF) for the placebo and the three SPD489 groups. Considering that the dropout rates appeared to be balanced across the treatment groups and were all smaller than 20% (Table 3), the comparison of the CDF curves based on the LOCF data should be reliable to reveal the difference in percentiles for the primary efficacy variable among the treatment groups. These CDF curves supported the efficacy of SPD489 compared with placebo by showing that, for any given value of change from baseline to endpoint in ADHD-RS-IV total score (horizontal axis) within the range [-40, 0], the proportion of patients whose ADHD-RS-IV change was less than or equal to that value (vertical axis) in the placebo group was almost consistently smaller than those in the three SPD489 groups. There were only 2 placebo-treated patients and 9 SPD489-treated patients (30mg: 4; 50mg: 2; 70mg: 3) whose endpoint changes in the ADHD-RS-IV total score were positive. This suggests that the ADHD symptoms seemed to be improved from baseline for the majority of the FAS-DB patients at endpoint, even for those receiving placebo.

Figure 7: Cumulative Distribution Function Curves of Change from Baseline to Endpoint in ADHD-RS-IV Total Score by Treatment Group (FAS-DB, LOCF)
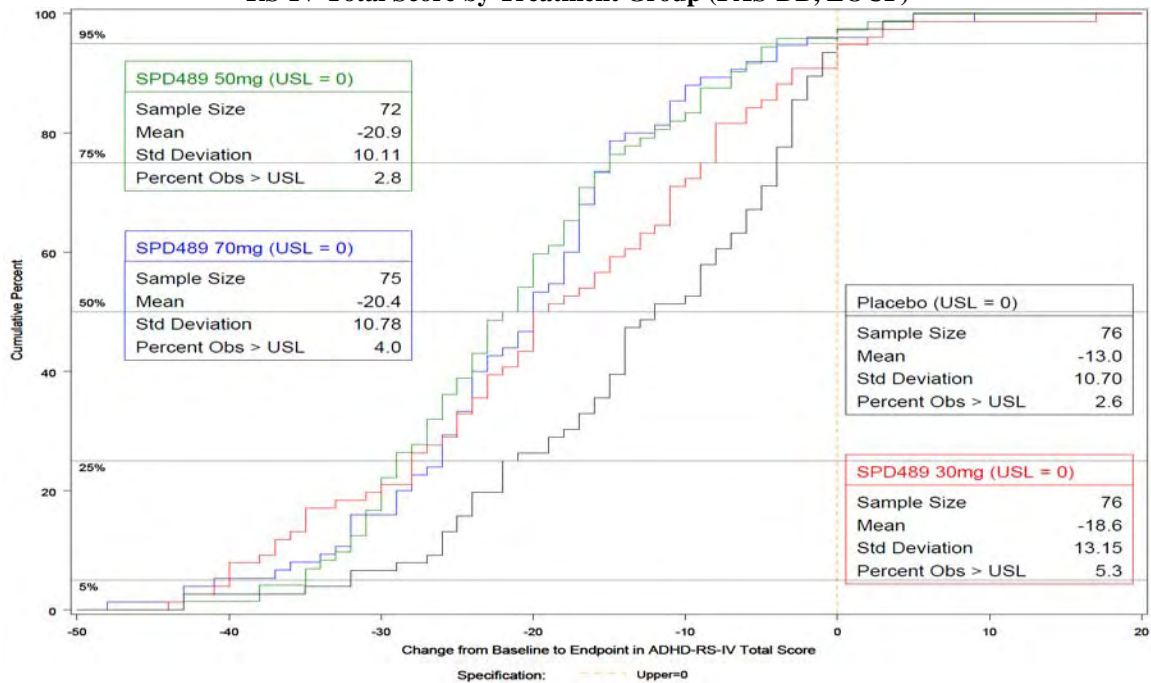
(Source: Reviewer's Result using SAS 9.2, 2010)

3.1.5.4.2   Response Profiles of Dropouts

As shown in Table 3, there were a total of 49 randomized patients (Placebo: 10; SPD489: 39) who discontinued the double-blind treatment. The dropout rate in the SPD489-treated patients (16.6%) was numerically larger than that in the placebo-treated patients (12.7%). Of those 49 dropouts, 5 did not have any post-baseline assessment and 16 were retrieved dropouts, who were retrieved to have a post-treatment ADHD-IV-RS measurement at the early termination visit. Only 1 retrieved dropout was receiving placebo.

This reviewer explored the response profiles of the 49 dropouts by treatment (Figure 8). Most of these patients discontinued the study after one or two weeks' treatment. It appears that the FAS dropouts in the placebo group had less improvement on average in ADHD symptoms than those in the SPD489 groups at Visits 1-3, as measured by the raw mean change in ADHD-RS-IV total score. This was consistent with the primary efficacy findings.

Figure 8: Observed Changes from Baseline in ADHD-RS-IV Total Score for Dropouts (FAS, OC)
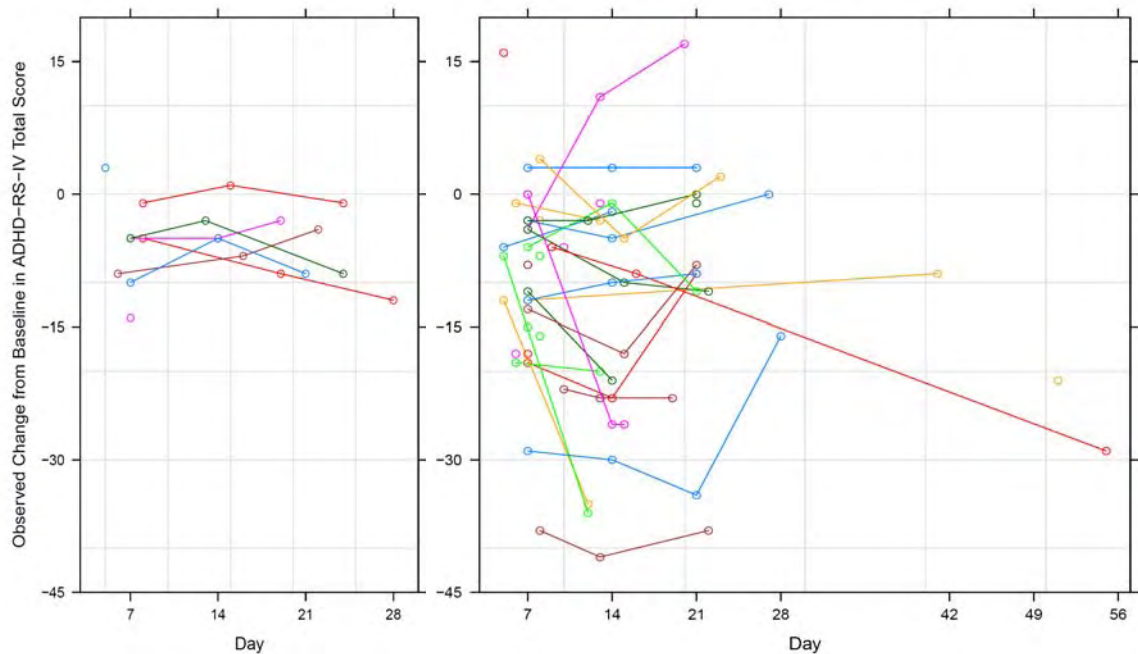
*Per the protocol of Study 489-305, visit windows were ±2 days throughout the double-blind evaluation period (Weeks 1-4).
Note: Ten (10) FAS dropouts only had post-baseline assessment(s) after terminating the double-blind treatment and were excluded from the primary analysis.

(Source: Reviewer's Result using SAS 9.2 and S-Plus, 2010)

3.2 Evaluation of Safety

Table 12 summarizes the weight (kg) and the weight change from baseline (kg) by visit and actual dose. This reviewer noticed that there seemed to be a dose-response trend in weight change.

Table 12: Summary of Weight and Weight Change by Visit and Actual Dose (Safety Population)

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

(Source: Sponsor's Report Body; Study SPD489-305 Module 5; Table 41, page 0114)

This reviewer performed an ANCOVA (factor: treatment; covariate: baseline weight) for the FAS-DB patients to assess the treatment effect of SPD489 compared to placebo on weight change (kg) at endpoint. Dunnett's test was used to control the family-wise Type I error rate at 0.05 (two-sided). As shown in Table 13, there was strong evidence that each SPD489 group had statistically significant weight reduction as compared to the placebo group.

Table 13: Reviewer's Analysis of Weight Change (kg) at Endpoint (FAS-DB, LOCF)

Endpoint	Baseline		Adjusted Change from Baseline				
FAS-DB (N = 299)	n	Mean (SD)	n	LS Mean (SE)	LS DIFF	95% CI	p-value*
Placebo	76	62.2 (13.35)	76	0.9 (0.17)			
SPD489 30mg	76	66.1 (15.07)	76	-1.2 (0.17)	-2.1	(-2.7, -1.5)	< 0.0001
SPD489 50mg	72	64.3 (12.71)	72	-1.9 (0.18)	-2.8	(-3.4, -2.2)	< 0.0001
SPD489 70mg	75	61.4 (10.30)	75	-2.2 (0.17)	-3.1	(-3.6, -2.5)	< 0.0001

*p-value was adjusted by Dunnett's test

(Source: Reviewer's Result using SAS 9.2, 2010)

The sponsor reported that a total of 16 patients had potentially clinically important changes in weight. Two (2) patients (028-004 receiving placebo, 015-001 receiving SPD489 30mg) had ≥ 7% increase in weight. Fourteen (14) patients had ≥ 7% decrease in weight (range -6.4 to -3.9 kg). A total of 22 patients reported "weight decreased" as a treatment-emergent adverse event (TEAE). The sponsor's study report stated that the majority of those TEAEs were mild and no patient had a clinically notable change in weight during the study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This reviewer replicated the sponsor' subgroup analysis results and confirmed that the mean decreases from baseline to endpoint in ADHD-RS-IV total score for patient in each SPD489 group were consistently larger than those in the placebo group across various subgroup categories (gender, age [13-14 or 15-17], race [white or non-white]). This reviewer also explored the treatment differences in ADHD-RS-IV total score across other subgroup categories (geographic region, and ADHD subtype).

4.1 Gender, Race and Age

4.1.1 Gender

A total of 146 (69.9%) FAS-DB patients were males. As shown in Table 14, the raw mean changes to endpoint in ADHD-RS-IV total score consistently supported the efficacy of SPD489 over placebo for both males and females, while male patients in the SPD489 groups seemed to have greater improvement in ADHD symptoms.

Table 14: Baseline Mean and Raw Mean Change at Endpoint in ADHD-RS-IV Total Score by Gender (FAS-DB, LOCF)

Gender	Male (N = 209)				Female (N = 90)			
P-value* of Interaction: 0.2956	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
	N = 52	N = 58	N = 57	N = 42	N = 24	N = 18	N = 15	N = 33
Baseline: Mean (SD)	38.8 (7.26)	37.4 (6.19)	37.3 (6.17)	37.1 (7.99)	37.4 (6.77)	42.2 (7.08)	38.0 (7.39)	37.5 (6.37)
Endpoint: Mean (SD)	-12.3 (10.37)	-19.1 (13.54)	-21.2 (10.18)	-21.6 (11.49)	-14.4 (11.48)	-17.0 (12.03)	-19.5 (10.09)	-18.9 (9.76)

*p-value from ANCOVA model with gender-by-treatment interaction; only for exploratory purposes
(Source: Reviewer's Result using SAS 9.2, 2010)

4.1.2 Race

The majority (79.9%) of the FAS-DB patients were white. The subgroup analysis results by race (Table 15) were consistent with the primary efficacy findings.

Table 15: Baseline Mean and Raw Mean Change at Endpoint in ADHD-RS-IV Total Score by Race (FAS-DB, LOCF)

Race	White (N = 239)				Non-White (N = 60)			
P-value* of Interaction: 0.8517	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
	N = 65	N = 52	N = 61	N = 61	N = 11	N = 24	N = 11	N = 14
Baseline: Mean (SD)	38.1 (7.16)	37.6 (6.27)	37.5 (6.60)	37.0 (7.46)	39.6 (6.83)	40.6 (7.22)	37.3 (5.35)	38.6 (6.50)
Endpoint: Mean (SD)	-12.9 (10.57)	-17.9 (13.03)	-21.5 (10.41)	-20.1 (11.03)	-13.2 (11.98)	-20.0 (13.57)	-17.5 (7.83)	-21.9 (9.82)

*p-value from ANCOVA model with race-by-treatment interaction; only for exploratory purposes
(Source: Reviewer's Result using SAS 9.2, 2010)

4.1.3   Age

Age at enrollment ranged from 13 to 17 years for the FAS-DB set, which was categorized into two age subgroups: 13-14 years and 15-17 years. The subgroup analysis results by age category (Table 16) were consistent with the primary efficacy findings.

Table 16: Baseline Mean and Raw Mean Change at Endpoint in ADHD-RS-IV Total Score by Age Category (FAS-DB, LOCF)

Age Category		13-14 Years (N = 159)				15-17 Years (N = 140)			
P-value* of Interaction: 0.1260		Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
		N = 41	N = 42	N = 34	N = 42	N = 35	N = 34	N = 38	N = 33
Baseline:	Mean (SD)	39.1 (7.41)	39.4 (6.47)	37.9 (6.95)	36.4 (7.11)	37.5 (6.70)	37.4 (6.89)	37.0 (5.90)	38.4 (7.46)
Endpoint:	Mean (SD)	-13.5 (11.27)	-19.4 (14.89)	-22.1 (9.34)	-17.3 (10.13)	-12.3 (10.12)	-17.6 (10.75)	-19.7 (10.76)	-24.5 (10.34)

**p*-value from ANCOVA model with race-by-treatment interaction; only for exploratory purposes
(Source: Reviewer's Result using SAS 9.2, 2010)

4.2 Other Special/Subgroup Populations

4.2.1   Geographic Regions

There were 45 U.S. centers in total. The center size (#randomized patients) ranged from 1 to 16 (median = 7). This reviewer categorized these centers into 6 regions based on their center sizes and geographic locations: Western, Southwestern, Midwestern, Florida, Southeastern (Other), and Northeastern. The pooling algorithm is shown in Table 17.

Table 17: Reviewer's Pooling Algorithm for Subgroup Analysis by Geographic Region

Region	State in Study 489-305	Center ID	Region Size
Western	CA, NV, OR, WA	9, 10, 19, 23, 25, 27, 30, 41, 42	59
Southwestern	OK, TX	4, 6, 15, 17, 43	25
Midwestern	IL, IN, KS, MI, ND, OH	14, 18, 22, 24, 26, 31, 37, 44	61
Florida	FL	11, 21, 28, 29, 32, 33, 38	65
Southeastern (Other)	AR, GA, KY, LA, NC, TN, VA	1, 2, 3, 7, 8, 13, 16, 34, 39*, 40	70
Northeastern	NJ, NY, PA, VT	5, 12, 20, 35, 36, 45	34

*Two FAS-DB patients receiving SPD489 30mg and 1 receiving SPD489 70mg had a deduction from baseline ≥ 43 points at Visit 4.
(Source: Reviewer's Result using SAS 9.2, 2010)

Table 18 summarizes the subgroup analysis results by geographic region. The mean baseline ADHD-RS-IV total scores in the Southeastern regions (Florida and Southeastern - Other) were numerically larger than those in the Western and the Southwestern regions. Consistent with the primary efficacy findings, the negative mean changes to endpoint in ADHD-RS-IV total score consistently supported the efficacy of SPD489 relative to placebo for all the regions except the Northeastern region, which included only 30 FAS-DB patients. The raw mean changes at endpoint in ADHD-RS-IV total score by region are displayed in Figure 9.

Table 18: Baseline Mean and Raw Mean Change at Endpoint in ADHD-RS-IV Total Score by Geographic Region (FAS-DB, LOCF)

Region		Western (N = 57)				Southwestern (N = 24)			
P-value* of Interaction: 0.3879		Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
		N = 15	N = 19	N = 11	N = 12	N = 4	N = 6	N = 8	N = 6
Baseline:	Mean (SD)	35.3 (4.88)	35.5 (5.48)	37.0 (6.21)	34.1 (4.34)	36.3 (9.95)	38.3 (9.29)	35.4 (8.38)	34.2 (7.68)
Endpoint:	Mean (SD)	-11.5 (8.71)	-15.8 (10.74)	-20.1 (10.90)	-15.00 (10.85)	-4.75 (6.40)	-26.3 (9.16)	-18.3 (11.36)	-23.5 (6.22)
		Midwestern (N = 58)				**Florida (N = 62)**			
		Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
		N = 14	N = 13	N = 17	N = 14	N = 22	N = 14	N = 13	N = 13
Baseline:	Mean (SD)	39.5 (6.80)	38.0 (5.64)	34.2 (4.44)	34.8 (6.20)	39.0 (8.59)	40.1 (7.90)	39.5 (6.15)	41.9 (8.62)
Endpoint:	Mean (SD)	-15.9 (12.22)	-19.5 (13.99)	-19.8 (10.56)	-20.1 (13.38)	-13.8 (11.98)	-23.9 (12.38)	-22.8 (8.08)	-22.0 (9.85)
		Southeastern (Other) (N = 68)				**Northeastern (N = 30)**			
		Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
		N = 14	N = 19	N = 12	N = 23	N = 7	N = 5	N = 11	N = 7
Baseline:	Mean (SD)	39.6 (6.97)	41.5 (6.19)	43.1 (6.37)	38.1 (6.78)	39.3 (4.89)	36.2 (4.71)	35.8 (3.63)	39.0 (8.47)
Endpoint:	Mean (SD)	-10.5 (9.88)	-16.1 (16.34)	-23.1 (10.66)	-23.4 (10.43)	-17.1 (9.46)	-11.8 (4.21)	-20.5 (10.80)	-15.0 (7.79)

*p-value from ANCOVA model with region-by-treatment interaction; only for exploratory purposes

(Source: Reviewer's Result using SAS 9.2, 2010)

Figure 9: Raw Mean Change at Endpoint in ADHD-RS-IV Total Score by Region (FAS-DB, LOCF)
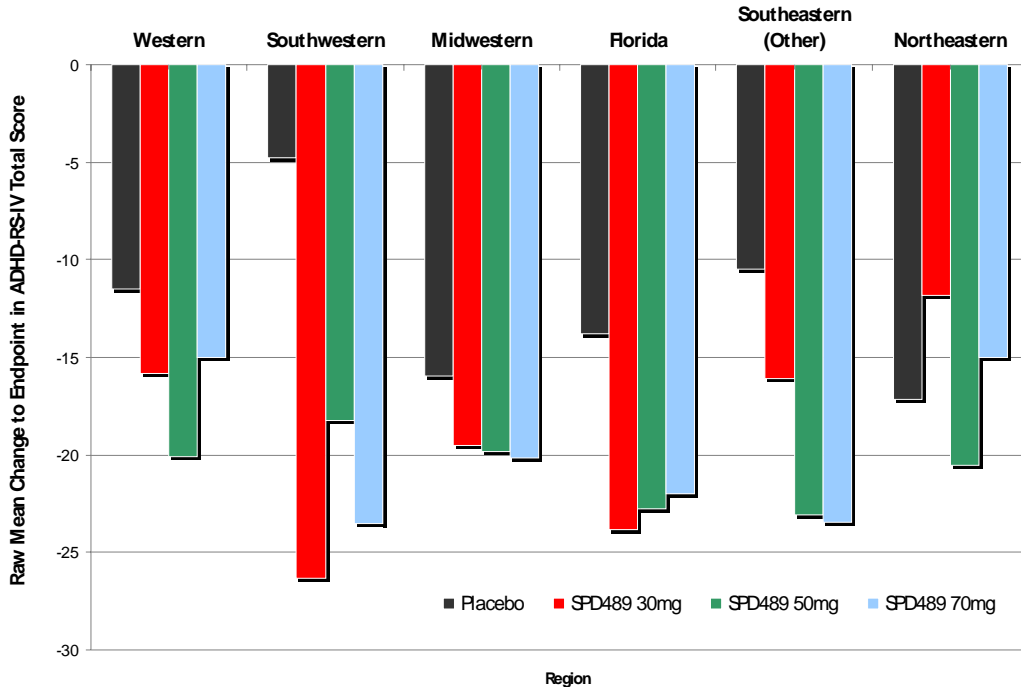
(Source: Reviewer's Result using Excel 2007)

4.2.2   ADHD Subtype

Of the 299 FAS-DB subjects, 2 (0.7%) had the hyperactive-impulsive subtype, 101 (33.8%) had the inattentive subtype, and 196 (65.5%) had the combined subtype. The baseline mean scores of ADHD-RS-IV total in the inattentive subtype group were numerically smaller than those in the combined subtype group. Consistent with the primary efficacy findings, the raw mean changes to endpoint in ADHD-RS-IV total score consistently supported the efficacy of SPD489 over placebo for both the inattentive and the combined subtype groups (Table 19).

Table 19: Baseline Mean and Raw Mean Change at Endpoint in ADHD-RS-IV Total Score by ADHD Subtype (FAS-DB, LOCF)

ADHD Subtype		Inattentive (N = 101)				Combined (N = 196)			
P-value* of Interaction: **0.0311**		Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg	Placebo	SPD489 30mg	SPD489 50mg	SPD489 70mg
		N = 23	N = 21	N = 30	N = 27	N = 53	N = 55	N = 41	N = 47
Baseline:	Mean (SD)	33.2 (4.03)	35.5 (6.35)	34.4 (4.47)	33.6 (5.39)	40.6 (7.00)	39.7 (6.50)	39.6 (6.80)	39.3 (7.52)
Endpoint:	Mean (SD)	-15.3 (8.23)	-19.3 (11.39)	-21.6 (8.06)	-17.6 (8.91)	-11.9 (11.53)	-18.3 (13.85)	-20.1 (11.49)	-21.8 (11.50)

*p-value from ANCOVA model with ADHD subtype-by-treatment interaction; two patients with hyperactive-impulsive subtype ADHD were excluded from the analysis set; only for exploratory purposes

(Source: Reviewer's Result using SAS 9.2, 2010)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This reviewer confirmed the sponsor's finding that SPD489-305 (30mg, 50mg, and 70mg/day) was superior to placebo in improving the ADHD symptoms of adolescents aged 13-17 years, as demonstrated by the statistically significant difference in mean change from baseline to endpoint in the ADHD-RS-IV total score (adjusted p-values ≤ 0.0056).

Although this study was not designed to evaluate the dose-response relationship, the results showed that there seemed to be a dose-response in the change from baseline in ADHD-RS-IV total score (Figure 2), after taking into consideration the actual doses administrated for the SPD489 groups at each post-baseline visit. However, no additional benefit from the 70 mg dose over the 50mg dose was observed at Week 4.

In addition, this reviewer noticed that there seemed to be a dose-response trend in weight change, after taking into consideration the actual doses administrated for the SPD489 groups at each post-baseline visit. It appears that patients receiving higher dose tended to lose more weight (Table 12). At endpoint, patients in each SPD489 group seemed to be significant weight loss as compared with those in the placebo group (Table 13).

5.2 Conclusions and Recommendations

Results from Study SPD489-305 demonstrated the superiority of Vyvanse® (30mg, 50mg, and 70mg/day) over placebo in improving the ADHD symptoms of adolescents aged 13-17 years, based upon the change from baseline to endpoint in clinician-administered ADHD-RS-IV total score.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21977	SUPPL-16	SHIRE DEVELOPMENT INC	VYVANSE (LISDEXAMFETAMINE DIMESYLATE)

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/s/

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05/21/2010

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