CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-037

STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-037 / N_000
Drug Name:	SPD503 (guanfacine)
Indication(s):	Attention Deficit Hyperactivity Disorder.
Applicant:	Shire
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Biometrics Division:	Division of Biometrics I (HFD-710)
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Keywords: ANCOVA.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Guanfacine in doses 1 mg/day, 2 mg/day, 3 mg/day and 4 mg/day demonstrated statistically significant treatment effect in the pre-specified primary efficacy endpoint.

1.2 Brief Overview of Clinical Studies

The sponsor submitted findings of two fixed dose studies SPD503-301 and SPD503-304 (hereafter referred to as 301 and 304) on the safety and efficacy of guanfacine in the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents. These studies were multi-center, randomized, double-blind, placebo-controlled Phase III studies conducted in the United States. Patients enrolled in all studies were from 6 to17 years of age presenting with ADHD as defined by DSM-IV-TR Criteria.

Study 301 was a fixed dose study with three guanfacine treatment arms (2 mg/day, 3 mg/day and 4 mg/day) and 8-week acute therapy phase: 5 weeks of fixed dose escalation and 3 weeks of downward dose tapering. The study was performed in 48 study centers in the United States and involved 345 patients. Study 304 was a fixed dose US study with guanfacine treatment arms: 1 mg/day, 2 mg/day, 3 mg/day and 4 mg/day and 9 week treatment period. There were 324 patients involved in the study. The primary efficacy variable for both studies was change in ADHD-RS-IV total score from baseline to endpoint visit.

1.3 Statistical Issues and Findings

Study 301 has demonstrated that guanfacine in doses 2 mg/day, 3 mg/day and 4 mg/day was effective in the treatment of attention deficit/hyperactivity disorder in the overall intent-to-treat population. Study 304 has demonstrated that guanfacine in doses 1 mg/day, 2 mg/day, 3 mg/day and 4 mg/day was effective in the overall intent-to-treat population. However, for both studies patients in the age group 13-17 did not show numerical difference between the placebo group and almost all guanfacine dose groups (refer to Section 4.1).

2. INTRODUCTION

2.1 Overview

The clinical development program for guanfacine in the treatment of ADHD included two randomized, double-blind, placebo-controlled studies. The studies were conducted in the United States. Table 1 lists an overview of the studies.

Table 1. Reviewer's overview of the randomized studies

Study	Treatment Duration	Guanfacine Doses (mg/day)	Comparator(s)
SPD503-301-US	8 weeks	Fixed 2, 3 and 4	Placebo
SPD503-301-US	9 weeks	Fixed 1, 2, 3 and 4	Placebo

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for this submission is listed below:
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Description of Studies 301, 304

3.1.1.1 Objectives of the Studies

Primary Objective: To evaluate efficacy and safety of guanfacine hydrochloride compared with placebo in the treatment of children and adolescents (aged 6-17 years) attention deficit/ hyperactivity disorder (ADHD) as measured by the ADHD-RS-IV change from baseline score at endpoint visit. For study SPD503-301 the targeted doses of guanfacine were 2, 3 and 4 mg once daily. In Study SPD503-304, four doses of guanfacine (1mg, 2mg, 3mg and 4mg/daily) were compared with placebo.

Secondary Objectives: To assess the duration of effect of guanfacine. In study 301, parent and teaching rating scales were used. In study 304, the duration of effect was assessed by parent rating scales. To compare safety and tolerability of the guanfacine treatment groups with placebo. To assess the effect of guanfacine on global impressions of ADHD severity and improvement from the clinician and parent or caregiver. To assess the effect of guanfacine on

self-esteem, mental health, and family functioning based on the parent and child versions of the Child Health Questionnaire.

3.1.1.2 Design of the Studies

Both studies were multi-center, randomized, double-blind, placebo-controlled Phase III studies. Patients of age 6 to 17 inclusive who met criteria for ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV-TR) were eligible to participate in the studies.

Study 301

Study SPD503-301 was designed to assess the safety and efficacy of 2, 3 and 4 mg/day doses of guanfacine in the treatment of attention deficit/hyperactivity disorder.
The study consisted of three periods: Screening, Washout and Double-blind Treatment periods. Visits were scheduled 7 days (+-2 days) apart during the three periods. The Double-blind treatment period consisted of 8 weeks: 5 weeks of dose escalation and 3 weeks of downward tapering. There were 345 patients enrolled in the study at Baseline visit. Subjects' doses were escalated in 1mg increments on a weekly basis beginning at 1mg/day at Week 1. Although the amount of time a subject was maintained at the randomized fixed dose varied depending on the dose, subjects were to be maintained at the randomized fixed dose for a minimum of 2 weeks. The highest dose occurred during Weeks 4 and 5 when subjects in the 4 mg group received 4mg/day. Starting Week 6, subjects began to taper off SPD503. Doses were reduced in 1 mg decrements on weekly basis until subjects reached 2mg/day.

Table 2. Study 301 Drug Dosing Regimen

	Double-blind Period							
	Titration					Tapering		
SPD503 Dose	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
2mg	1mg	2mg	2mg	2mg	2mg	2mg	2mg	1mg
3mg	1mg	2mg	3mg	3mg	3mg	3mg	2mg	1mg
4mg	1mg	2mg	3mg	4mg	4mg	3mg	2mg	1mg

Source: Table 5 of Clinical Study 301 Report (pg. 48).

Study 304

Study SPD503-304 was designed to assess the efficacy of 1, 2, 3 and 4 mg/day doses of guanfacine. There were 324 patients randomized to the four guanfacine groups and placebo group. Patients had 12 planned study visits over the course of the 16-week study, which consisted of a Screening period (up to 2 weeks), Washout/Baseline period (1 week), a Double-blind Treatment period (9 weeks), and a Follow-up period (two visits). With reference to the Baseline visit, visits were scheduled seven days apart, +- two days, during the Double-blind Treatment period of the study. The design was a titration to a fixed randomized dose followed by dose tapering. The Double-blind Treatment period consisted of nine weeks: three weeks of dose escalation (Days 1-21), three weeks of dose maintenance (Days 22-42), and three weeks of dose

tapering (Days 43-63). All subjects randomized to the 1mg dose group remained at 1mg/day for Days 1-63. Subjects in the 2mg group received the following doses: 1mg/day from Days 1-21, 2mg/day from Days 22-56; and a 1mg/day for Days 57-63. Subjects in the 3mg group received the following doses: 1mg/day from Days 1-7; 2mg/day for Days 8-21; 3mg/day for Days 22-49; 2mg/day for Days 50-56; and 1mg/day for Days 57-63. Subjects in the 4mg group received the following doses: 1mg/day for Days 1-7; 2mg/day for Days 8-14; 3mg/day for Days 15-21; 4mg/day for Days 22-42; 3mg/day for Days 43-49; 2mg/day for Days 50-56; and 1mg/day for Days 57-63.

Table 3. Study 304 Drug Dosing Regimen

SPD503	Dose Titration			Dose Maintenance			Dose Tapering		
Treatment Group	Day 1-7	Day 8-14	Day 15-21	Day 22-28	Day 29-35	Day 36-42	Day 43-49	Day 50-56	Day 57-63
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg
2mg	1mg	1mg	1mg	2mg	2mg	2mg	2mg	2mg	1mg
3mg	1mg	2mg	2mg	3mg	3mg	3mg	3mg	2mg	1mg
4mg	1mg	2mg	3mg	4mg	4mg	4mg	3mg	2mg	1mg

Source: Table 2 of Clinical Study 304 Report (pg. 36).

3.1.1.3 Efficacy Variables and Statistical Methods.

For both studies, the primary efficacy endpoint was the mean change from baseline to the end of the acute therapy phase in the ADHD-Rating Scale (ADHD-RS-IV) total score. ADHD-RS-IV is an 18-item rating scale for assessing severity of attention deficit/hyperactivity disorder in scores 0 to 3 for each item. Thus, the ADHD-RS-IV total score is the sum of all 18 items and ranges from 0 to 54. Higher scores indicate a greater degree of symptom severity. For Study 301, 2 mg/day, 3 mg/day and 4 mg/day groups vs. placebo group were to be conducted on the primary endpoint. For Study 304, the guanfacine 1 mg/day, 2 mg/day, 3 mg/day and 4 mg/day were compared with placebo group.

For each efficacy variable, the analysis included all Intent-to-treat patients. The Intent-to-treat (ITT) Population was defined as all subjects who were randomized to treatment and had the baseline and at least one post-randomization primary efficacy measurement during dose escalation.

The primary analysis for the primary and secondary efficacy endpoints was ANCOVA under LOCF data set. The model included the main effects of treatment and the corresponding baseline score (the covariate). Type III sum-of-squares for the least-squares means was used for the statistical comparison. The primary efficacy endpoint (mean change in ADHD-RS-IV score) had to show statistical significance in favor of guanfacine compared with placebo to establish efficacy.

For Study 301, Dunnett's adjustment for multiple pair-wise mean comparisons, which controlled the family-wise error rate at the predefined level, was employed to compare the ADHD-RS-IV change scores for the three active drug groups to placebo. For Dunnett's adjustment, the family-

wise Type I error rate for rejecting a null hypothesis was controlled at a 2-sided alpha level of 0.05. No other adjustment was made. For Study 304, hierarchical testing procedure for multiple pairwise comparisons (from high to low dose) controlled family-wise error rate at a significance level of 0.05. No other adjustment was made.

When computing total scores for ADHD-RS-IV with missing items the following procedure was used. If more than three items were missing, the ADHD-RS-IV total score was considered missing. Otherwise, missing items were replaced by the mean of the non-missing items. For Study 301, of 1744 ADHD-RS-IV assessments collected, twelve had one or two items missing and none had three items missing. For Study 304, of 1900 ADHD-RS-IV assessments collected, 13 had one or two items missing, and one had three or more items missing. If a subject randomized to the 4mg SPD503 group withdrew at Week 3, then efficacy and some safety data for this subject results from a 3mg dose. To provide further understanding of the efficacy and safety data collected, analyses based on the actual dose received have also been included.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics.

3.1.2.1 Patient Disposition.

Study 301

Study 301 was conducted in 48 study centers in the United States. In this study, a total of 345 patients were randomized and received study medication. During the course of study, 130 patients discontinued due to adverse events, lack of efficacy or administrative reasons. A total of 325 patients who had a post-baseline efficacy assessment constituted intent-to treat population.

Table 4. Study 301: Patient Distribution and Disposition by Randomized Dose (All Subjects)

	Placebo N=86	SPD503 2mg N=87	SPD503 3mg N=86	SPD503 4mg N=86	Total N=345
Study Subjects, n (%)					
Randomized	86 (100%)	87 (100%)	86 (100%)	86 (100%)	345 (100%)
Completed	53 (61.6%)	58 (66.7%)	55 (64.0%)	49 (57.0%)	215 (62.3%)
Early termination	33 (38.4%)	29 (33.3%)	31 (36.0%)	37 (43.0%)	130 (37.7%)
Intent-to-treat	78 (90.7%)	84 (96.6%)	82 (95.3%)	81 (94.2%)	325 (94.2%)
Per-protocol	61 (70.9%)	63 (72.4%)	62 (72.1%)	54 (62.8%)	240 (69.6%)
Reason for Early Termination, n (%)					
Adverse Event	1 (1.2%)	9 (10.3%)	13 (15.1%)	20 (23.3%)	43 (12.5%)
Protocol violation	1 (1.2%)	3 (3.4%)	0	0	4 (1.2%)
Subject choice	9 (10.5%)	2 (2.3%)	3 (3.5 %)	4 (4.7%)	18 (5.2%)
Lost to follow-up	3 (3.5%)	2 (2.3%)	4 (4.7%)	3 (3.5%)	12 (3.5%)
Lack of efficacy	15 (17.4%)	8 (9.2%)	6 (7.0%)	7 (8.1%)	36 (10.4%)
Other	4 (4.7%)	5 (5.7%)	5 (5.8%)	3 (3.5%)	17 (4.9%)

Source: Section 12.1 Table 1.2.1 of Study 301 Report (pg. 61)

Study 304

Study 304 was conducted at 51 centers in the United States. A total of 324 patients were randomly assigned to receive study medication: 258 were assigned to guanfacine (1mg, 2mg, 3mg and 4mg/day) and 66 were assigned to placebo. A total of 306 patients constituted intent-to treat population, 211 were able to complete the study.

Table 5. Study 304: Patient Distribution and Disposition by Randomized Dose (All Subjects)

	Placebo N=66	SPD503 1mg N=62	SPD503 2mg N=65	SPD503 3mg N=65	SPD503 4mg N=66	Total N=324
Study Subjects, n (%)						
Randomized	66 (100%)	62 (100%)	65 (100%)	65 (100%)	66 (100%)	324 (100%)
Completed	41 (62.1%)	45 (72.6%)	47 (72.3%)	38 (58.5%)	40 (60.6%)	211 (65.1%)
Early termination	25 (37.9%)	17 (27.4%)	18 (27.7%)	27 (41.5%)	26 (39.4%)	113 (34.9%)
Intent-to-treat	63 (95.5%)	57 (91.9%)	63 (96.9%)	60 (92.3%)	63 (95.5%)	306 (94.4%)
Per protocol	41 (62.1%)	45 (72.6%)	48 (73.8%)	37 (56.9%)	41 (62.1%)	212 (65.4%)
Safety	66 (100%)	61 (98.4%)	65 (100%)	65 (100%)	65 (98.5%)	322 (99.4%)
Reason for Early Termination, n (%)						
Adverse Event	5 (7.6%)	2 (3.2%)	2 (3.1%)	6 (9.2%)	9 (13.6%)	24 (7.4%)
Protocol violation	1 (1.5%)	1 (1.6%)	0	0	0	2 (0.6%)
Withdrew consent	5 (7.6%)	6 (9.7%)	8 (12.3%)	8 (12.3%)	4 (6.1%)	31 (9.6%)
Lost to follow-up	4 (6.1%)	4 (6.5%)	1 (1.5%)	5 (7.7%)	8 (12.1%)	22 (6.8%)
Other	10 (15.2%)	4 (6.5%)	7 (10.8%)	8 (12.3%)	5 (7.6%)	34 (10.5%)

Source: Section 12.1, Table 1.2.1 of Study 304 Report (pg. 70)

3.1.2.2 Patients Demographic and Baseline Characteristics

In both studies, treatment groups appeared to be comparable for age, gender, ethnic origin, weight and height. The following tables present patients demographic (and baseline) characteristics by treatment groups.

Study 301

Table 6. Study 301: Demographics and Baseline Characteristics (ITT population)

Characteristics	Placebo N=78	SPD503 2mg N=84	SPD503 3mg N=82	SPD503 4mg N=81	Total N=325
Age (years)					
Mean (SD)	10.6 (2.73)	10.6 (2.29)	10.8 (2.80)	10.1 (2.85)	10.5 (2.67)
Median	10.5	10.0	11.0	10.0	10.0
Min, Max	6, 17	6, 16	6, 17	6, 17	6, 17
Age category (years), n(%)					
6-18	22 (28.2%)	16 (19.0%)	20 (24.4%)	27 (33.3%)	85 (26.2%)
9-12	37 (47.4%)	51 (60.7%)	37 (45.1%)	39 (48.1%)	164 (50.5%)
13-17	19 (24.4%)	17 (20.2%)	25 (30.5%)	15 (18.5%)	76 (23.4%)
Gender, n (%)					
Male	58 (74.4%)	65 (77.4%)	66 (80.5%)	52 (64.2%)	241 (74.2%)
Female	20 (25.6%)	19 (22.6%)	16 (19.5%)	29 (35.8%)	84 (25.8%)
Ethnic origin, n (%)					
White	57 (73.1%)	57 (67.9%)	56 (68.3%)	58 (71.6%)	228 (70.2%)
Black	7 (9.0%)	17 (20.2%)	9 (11.0%)	10 (12.3%)	43 (13.2%)
Hispanic	7 (9.0%)	5 (6.0%)	13 (15.9%)	8 (9.9%)	33 (10.2%)
Asian or Pacific Islander	0	0	0	1 (1.2%)	1 (0.3%)
Native American	0	0	1 (1.2%)	0	1 (0.3%)
Other	7 (9.0%)	5 (6.0%)	3 (3.7%)	4 (4.9%)	19 (5.8%)
Weight (lb)					
Mean (SD)	93.8 (30.7)	99.4 (38.8)	98.2 (37.2)	93.6 (36.2)	96.3 (35.9)
Median	88.5	91.5	92.0	79.0	87.0
Min, Max	55, 175	55, 271	55, 197	54, 207	54, 271
Height (in)					
Mean (SD)	57.0 (6.68)	58.1 (6.13)	57.7 (7.15)	56.2 (6.10)	57.3 (6.54)
Median	56.3	57.0	57.0	55.0	56.0
Min, Max	46, 73	47, 73	44, 71	46, 71	44, 73
ADHD subtype, n (%)					
Inattentive	16 (20.5%)	28 (33.3%)	17 (20.7%)	23 (28.4%)	84 (25.8%)
Hyperactive-impulsive	0	3 (3.6%)	1 (1.2%)	2 (2.5%)	6 (1.8%)
Combined	62 (79.5%)	53 (63.1%)	64 (78.0%)	56 (69.1%)	235 (72.3%)
ADHD-RS-IV Total Score at Baseline					
Mean (SD)	38.14 (9.34)	36.10 (9.99)	36.77 (8.72)	38.40 (9.21)	37.33 (9.34)
Median	39.00	36.00	37.50	37.00	38.00
Min, Max	13, 54	11, 54	17, 54	15, 54	11, 54

Source: Section 12.1 Tables 1.3.2 and 2.1.1 of Study 301 Report (pg. 66 and 69)

Study 304

Table 7. Study 304: Demographics and Baseline Characteristics (ITT population)

Characteristics	Placebo N=63	SPD503 1mg N=57	SPD503 2mg N=63	SPD503 3mg N=60	SPD 503 4mg N=63	Total N=306
Age (years)						
Mean (SD)	10.7 (2.92)	9.2 (2.17)	10.7 (2.76)	11.1 (2.76)	10.6 (2.55)	10.5 (2.71)
Median	11.0	9.0	10.0	10.5	10.0	10.0
Min, Max	6, 17	6, 13	6, 17	6, 17	6, 16	6, 17
Age category (years), n (%)						
6-12	45 (71.4%)	50 (87.7 %)	46 (73.0%)	41 (68.3%)	48 (76.2 %)	230 (75.2%)
13-17	18 (28.6%)	7 (12.3%)	17 (27.0%)	19 (31.7%)	15 (23.8%)	76 (24.8%)
Gender, n (%)						
Male	44 (69.8%)	37 (64.9%)	44 (69.8%)	44 (73.3%)	51 (81.0%)	220 (71.9%)
Female	19 (30.2%)	20 (35.1%)	19 (30.2%)	16 (26.7%)	12 (19.0%)	86 (28.1%)
Ethnic origin, n (%)						
White	38 (60.3%)	39 (68.4%)	40 (63.5%)	43 (71.7%)	43 (68.3%)	203 (66.3%)
Black	14 (22.2%)	10 (17.5%)	13 (20.6%)	6 (10.0%)	10 (15.9%)	53 (17.3%)
Hispanic	7 (11.1%)	3 (5.3%)	5 (7.9%)	6 (10.0%)	6 (9.5%)	27 (8.8%)
Asian or Pacific Islander	1 (1.6%)	3 (5.3%)	2 (3.2%)	0	3 (4.8%)	9 (2.9%)
Native American	0	0	0	0	1 (1.6%)	1 (0.3%)
Other	3 (4.8%)	2 (3.5%)	3 (4.8%)	5 (8.3%)	0	13 (4.2%)
Weight						
Mean (SD)	98.37 (37.90)	76.61 (16.62)	99.25 (31.79)	101.10 (38.15)	101.51 (37.72)	95.68 (34.69)
Median	90.0	74.0	98.0	85.5	88.0	85.0
Min, Max	55.0, 237.0	55.0, 109.0	55.0, 183.0	57.0, 220.0	55.0, 185.0	55.0, 237.0
Weight category (lb)						
<75	21 (33.3%)	29 (50.9%)	19 (30.2%)	18 (30.0%)	20 (31.7%)	107 (35.0%)
75<= x < 110	18 (28.6%)	28 (49.1%)	20 (31.7%)	21 (35.0%)	19 (30.2%)	106 (34.6%)
>= 110	24 (38.1%)	0	24 (38.1%)	21 (35.0%)	24 (38.1%)	93 (30.4%)
Height (in)						
Mean (SD)	57.56 (6.38)	54.10 (4.60)	57.76 (6.20)	57.99 (6.08)	57.69 (6.07)	57.07 (6.05)
Median	57.5	52.5	58.9	57.5	57.8	57.0
Min, Max	40.7, 71.0	47.4, 63.7	47.0, 71.3	48.0, 72.0	47.5, 68.3	40.7, 72.0
ADHD Subtype, n (%)						
Inattentive	22 (34.9%)	12 (21.1%)	14 (22.2%)	15 (25.0%)	18 (28.6%)	81 (26.5%)
Hyperactive/Impulsive	3 (4.8%)	1 (1.8 %)	1 (1.6 %)	1 (1.7%)	0	6 (2.0%)
Combined	38 (60.3%)	44 (77.2%)	48 (76.2%)	44 (73.3%)	45 (71.4%)	219 (71.6%)
ADHD Total Score at Baseline						
Mean (SD)	39.3 (8.85)	41.7 (7.81)	39.9 (8.74)	39.1 (9.22)	40.6 (8.57)	40.09 (8.65)
Median	40.0	42.0	40.0	40.5	41.0	41.00
Min, Max	24, 54	24, 54	21, 54	18, 52	25, 54	18, 54

Source: Section 12.1 Tables 1.3.3 and 2.1.1 of Study 304 Report (pg. 79 and 84)

3.1.3 Efficacy results for studies 301, 304

3.1.3.1 Primary Analysis on the Primary Efficacy Endpoint

This reviewer confirmed the sponsor's analysis results for primary endpoint ADHD-RS-IV. Treatment group differences were evaluated using the ANCOVA model with treatment term and baseline covariate by LOCF method. Table 8 and Table 9 list sponsor's primary efficacy results of the two studies. The findings indicate that all of the guanfacine treatment arms (2mg/day, 3mg/day and 4mg/day for study 301, and 1mg/day, 2mg/day, 3mg/day and 4mg/day for study 304) were statistically significantly superior to placebo in reducing ADHD rating scale IV (ADHD-RS-IV) total score of the patients with attention deficit/hyperactivity disorder (ADHD).

Study 301

Table 8. Study 301: ADHD-RS-IV Total Score at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	N=325	78	84	82	81
Baseline	Mean (SD)	38.14 (9.34)	36.10 (9.99)	36.77 (8.72)	38.40 (9.21)
Endpoint	Mean (SD)	29.28 (14.94)	20.69 (13.45)	20.98 (13.87)	19.43 (11.91)
Change from Baseline	Mean (SD)	-8.86 (12.90)	-15.40 (12.82)	-15.79 (13.00)	-18.96 (13.71)
Placebo-adjusted difference	LS mean	NA	-7.42	-7.52	-9.99
	95% CI	NA	(-12.07, -2.77)	(-12.19, -2.85)	(-14.67,-5.32)
	P-Value (Dunnett)	NA	0.0006	0.0005	<0.0001

Source: Section 12.1, Table 2.1.1 of Study 301 Report (pg. 73)

Study 304

Table 9. Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	N=306	63	57	63	60	63
Baseline	Mean (SD)	39.25 (8.85)	41.70 (7.81)	39.92 (8.74)	39.07 (9.22)	40.60 (8.57)
Endpoint	Mean(SD)	27.1 (15.02)	21.30 (12.78)	21.9 (14.08)	19.7 (12.46)	19.7 (11.01)
Change fr. Baseline	Mean (SD)	-12.2 (12.96)	-20.4 (14.00)	-18.0 (14.88)	-19.4 (14.62)	-20.9 (11.89)
Placebo-adjusted difference	LS mean	NA	-6.75	-5.41	-7.31	-7.88
	95% CI	NA	(-11.3, -2.2)	(-9.9, -0.9)	(-11.8, -2.8)	(-12.3, -3.4)
	P-Value	NA	0.0041	0.0176	0.0016	0.0006

Source: Section 12.1, Table 2.1.1 of Study 304 Report (pg.87)

This reviewer also performed treatment comparisons at each visit time as an exploratory analysis for both studies. The purpose of the comparisons was to explore whether effects were consistent across the visits. The results are summarized in Table 10 and Table 11. It is to be noted that interpretation of these two tables should incorporate dosing regimens in Table 2 and Table 3.

Study 301

Table 10. Study 301: LS Mean Change in ADHD-RS-IV Total Score by Visit (ITT Population)

Visit (week)	Placebo Mean (SE)	SPD503 2mg Mean (SE); p-value vs. placebo	SPD503 3mg Mean (SE); p-value vs. placebo	SPD503 4mg Mean (SE); p-value vs. placebo
1 (week 1)	-5.97 (1.11)	-7.74 (1.07); 0.253	-7.31 (1.08); 0.388	-8.22 (1.09); 0.148
2 (week 2)	-8.12 (1.19)	-12.54 (1.15); 0.008	-11.20 (1.16); 0.065	-12.66 (1.17); 0.007
3 (week 3)	-8.34 (1.31)	-13.66 (1.26); 0.004	-14.59 (1.27); <0.001	-15.58 (1.28); <0.001
4 (week 4)	-8.43 (1.35)	-15.03 (1.30); <0.001	-15.05 (1.32); <0.001	-18.44 (1.33); <0.001
5 (week 5)	-8.83 (1.43)	-15.74 (1.38); <0.001	-16.03 (1.39); <0.001	-18.74 (1.40); <0.001

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study 304

Table 11. Study 304: LS Mean Change in ADHD-RS-IV Total Score by Visit (ITT Population)

Visit (week)	Placebo Mean (SE)	SPD503 1mg Mean (SE); p-value vs. placebo	SPD503 2 mg Mean (SE); p-value vs. placebo	SPD503 3 mg Mean (SE); p-value vs. placebo	SPD503 4 mg Mean (SE); p-value vs. placebo
1 (week1)	-5.82 (1.11)	-10.90 (1.18); 0.002	-6.67 (1.12); 0.589	-7.93 (1.13); 0.183	-9.18 (1.11); 0.033
2 (week 2)	-9.57 (1.35)	-12.86 (1.42); 0.095	-13.42 (1.36); 0.046	-15.33 (1.38); 0.003	-13.14 (1.35); 0.063
3 (week 3)	-9.38 (1.45)	-15.93 (1.53); 0.002	-13.82 (1.45); 0.031	-16.98 (1.49); <0.001	-16.63 (1.45); <0.001
4 (week 4)	-10.33 (1.51)	-18.09 (1.59); <0.001	-14.73 (1.51); 0.040	-19.39 (1.55); <0.001	-19.98 (1.51); <0.001
5 (week 5)	-12.27 (1.54)	-18.84 (1.62); 0.004	-15.52 (1.54); 0.136	-19.96 (1.58); <0.001	-19.57 (1.54); <0.001
6 (week 6)	-12.72 (1.60)	-19.43 (1.69); 0.004	-17.99 (1.60); 0.021	-19.91 (1.64); 0.002	-20.56 (1.60); <0.001

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

3.1.3.2 Sensitivity Analysis on the Primary Endpoint

Table 12 and Table 13 show results from the repeated measures analysis of the ADHD-RS-IV Total Score for Studies 301 and 304. The model includes patient random effect, fixed effects treatment and visit with the treatment by visit interaction term, and baseline score as a covariate. In both studies, the results were consistent with those from primary analysis (ANCOVA) by visit. Again, dosing regimens (Table 2 and Table 3) should be incorporated in interpretation of these results.

Study 301

Table 12. Study 301: Repeated measures analysis on ADHD-RS-IV Total Score

Visit (week)	Study Treatment	Number of patients	LS Change Mean (SE)	p-value when compared with Placebo
1 (1)	Placebo	78	-5.85 (1.11)	
1 (1)	SPD503 2 mg	84	-7.79 (1.07)	0.2128
1 (1)	SPD503 3 mg	82	-7.30 (1.08)	0.3518
1 (1)	SPD503 4 mg	81	-8.08 (1.09)	0.1532
2 (2)	Placebo	74	-8.37 (1.20)	
2 (2)	SPD503 2 mg	81	-12.68 (1.15)	0.0101
2 (2)	SPD503 3 mg	76	-11.36 (1.18)	0.0772
2 (2)	SPD503 4 mg	79	-12.73 (1.17)	0.0098
3 (3)	Placebo	74	-8.70 (1.32)	
3 (3)	SPD503 2 mg	74	-13.85 (1.30)	0.0058
3 (3)	SPD503 3 mg	72	-15.25 (1.32)	0.0005
3 (3)	SPD503 4 mg	68	-16.40 (1.34)	<.0001
4 (4)	Placebo	65	-9.17 (1.39)	
4 (4)	SPD503 2 mg	68	-15.61 (1.36)	0.0011
4 (4)	SPD503 3 mg	62	-16.29 (1.40)	0.0004
4 (4)	SPD503 4 mg	60	-20.46 (1.42)	<.0001
5 (5)	Placebo	62	-9.87 (1.48)	
5 (5)	SPD503 2 mg	64	-16.92 (1.44)	0.0007
5 (5)	SPD503 3 mg	62	-17.53 (1.47)	0.0003
5 (5)	SPD503 4 mg	53	-20.93 (1.52)	<.0001

Source: Reviewer's results

Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study 304

Table 13. Study 304: Repeated Measures Analysis on ADHD-RS-IV Total Score

Visit (week)	Study Treatment	Number of patients	LS Change Mean (SE)	p-value when compared with Placebo
1 (1)	Placebo	63	-5.94 (1.11)	
1 (1)	SPD503 1 mg	56	-10.76 (1.18)	0.0032
1 (1)	SPD503 2 mg	61	-6.56 (1.12)	0.6935
1 (1)	SPD503 3 mg	60	-8.06 (1.14)	0.1820
1 (1)	SPD503 4 mg	62	-9.30 (1.12)	0.0341
2 (2)	Placebo	60	-9.74 (1.38)	
2 (2)	SPD503 1 mg	55	-13.03 (1.44)	0.1006
2 (2)	SPD503 2 mg	58	-13.84 (1.39)	0.0371
2 (2)	SPD503 3 mg	57	-15.43 (1.41)	0.0042
2 (2)	SPD503 4 mg	62	-13.29 (1.36)	0.0679
3 (3)	Placebo	59	-9.53 (1.50)	
3 (3)	SPD503 1 mg	53	-16.49 (1.58)	0.0016
3 (3)	SPD503 2 mg	55	-14.37 (1.52)	0.0244
3 (3)	SPD503 3 mg	51	-17.51 (1.57)	0.0003
3 (3)	SPD503 4 mg	58	-16.85 (1.50)	0.0006
4 (4)	Placebo	52	-10.65 (1.59)	
4 (4)	SPD503 1 mg	51	-18.76 (1.64)	0.0005
4 (4)	SPD503 2 mg	54	-15.58 (1.58)	0.0288
4 (4)	SPD503 3 mg	47	-20.76 (1.66)	<.0001
4 (4)	SPD503 4 mg	53	-20.81 (1.57)	<.0001
5 (5)	Placebo	48	-13.43 (1.63)	
5 (5)	SPD503 1 mg	49	-19.51 (1.66)	0.0096
5 (5)	SPD503 2 mg	48	-17.02 (1.63)	0.1203
5 (5)	SPD503 3 mg	44	-21.62 (1.70)	0.0006
5 (5)	SPD503 4 mg	47	-20.21 (1.62)	0.0035
6 (6)	Placebo	44	-14.16 (1.73)	
6 (6)	SPD503 1 mg	48	-20.35 (1.74)	0.0123
6 (6)	SPD503 2 mg	47	-20.15 (1.71)	0.0145
6 (6)	SPD503 3 mg	39	-21.46 (1.81)	0.0039
6 (6)	SPD503 4 mg	43	-21.82 (1.73)	0.0019

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

3.1.3.3 Analysis by Actual Dose on the Primary Endpoint.

To provide further understanding of the efficacy data, this sponsor has included analyses based on the actual dose and weight-adjusted actual dose received at Endpoint. The actual dose is the maximal dose achieved during Titration and Maintenance Phases. That is, if a subject

randomized to the 4mg SPD503 group withdrew at Week 3, then efficacy data for this subject results from an actual dose of 3mg. Weight-adjusted actual dose is defined as the actual dose received at each visit divided by the weight at Baseline. Table 14 and Table 17 give the information about how many patients from each randomized dose group received actual doses of 1mg, 2mg, 3mg and 4mg/day respectively.

The results of actual dose analysis support the primary analysis. For study 301, the placebo-adjusted LS mean endpoint changes from Baseline were numerically sound for the 2mg, 3mg, and 4mg guanfacine actual doses. For study 304, all guanfacine actual doses (1mg, 2mg, 3mg and 4mg) were numerically superior to placebo. Numerically, for both studies all weight-adjusted guanfacine doses demonstrated efficacy compared to placebo. The results of analysis by actual dose and by weight-adjusted actual dose presented below are sponsor's findings. The reviewer's results were similar.

Study 301

Table 14. Study 301: Patient Distribution by Randomized and Actual Doses

Actual Dose (highest dose actually received)	Randomized Dose			
	Placebo N=78	SPD503 2mg N=84	SPD503 3mg N=82	SPD503 4mg N=81
Placebo N=78	78	0	0	0
SPD503 1mg N=12	0	3	6	3
SPD503 2mg N=95	0	81	4	10
SPD503 3mg N=81	0	0	72	9
SPD503 4mg N=59	0	0	0	59

Source: Reviewer's results

Table 15. Study 301: ADHD-RS-IV Total Score by Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Endpoint	N patients	78	12	95	81	59
	Mean(SD)	29.28 (14.94)	25.50 (13.59)	22.01 (13.83)	19.81 (13.00)	17.46 (11.32)
Change from Baseline	Mean (SD)	-8.86 (12.90)	-9.50 (12.85)	-14.52 (12.31)	-16.32 (12.92)	-22.20 (13.59)
Placebo-adjusted difference	LS mean	NA	-1.91	-6.31	-8.28	-12.73
	95% CI	NA	(-11.38, 7.55)	(-10.98, -1.65)	(-13.12, -3.43)	(-17.99, -7.46)
	P-Value (Dunnett)	NA	0.9699	0.0035	0.0001	<0.0001

Source: Section 12.1 Table 2.13.5 of Clinical Study 301 Report (pg. 74)

Table 16. Study 301: ADHD-RS-IV Total Score by Weight-adjusted Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 0.01-0.04 mg/kg	SPD503 0.05-0.08 mg/kg	SPD503 0.09-0.12 mg/kg	SPD503 0.13-0.17 mg/kg
Endpoint	N patients	78	62	112	51	22
	Mean(SD)	29.28 (14.94)	22.15 (13.68)	22.65 (13.82)	15.47 (9.94)	15.14 (9.51)
Change from Baseline	Mean (SD)	-8.86 (12.90)	-11.48 (12.19)	-15.12 (13.32)	-21.71 (10.39)	-27.86 (11.63)
Placebo-adjusted difference	LS mean	NA	-4.30	-6.40	-13.21	-17.20
	95% CI	NA	(-9.43, 0.82)	(-10.78, -2.01)	(-18.57, -7.85)	(-24.43, -9.96)
	P-Value (Dunnett)	NA	0.1308	0.0014	<0.0001	<0.0001

Source: Section 12.1 Table 2.13.1 of Clinical Study 301 Report (pg. 75)

Study 304

Table 17. Study 304: Patient Distribution by Randomized and Actual Dose

Actual Dose (highest dose actually received)	Randomized Dose				
	Placebo N=63	SPD503 1mg N=57	SPD503 2mg N=63	SPD503 3mg N=60	SPD503 4mg N=63
Placebo N=63	63	0	0	0	0
SPD503 1mg N=68	0	57	8	2	1
SPD503 2mg N=69	0	0	55	11	3
SPD503 3mg N=52	0	0	0	47	5
SPD503 4mg N=54	0	0	0	0	54

Source: Reviewer's results

Table 18. Study 304: ADHD-RS-IV Total Score by Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Endpoint	N patients	63	68	69	52	54
	Mean(SD)	27.1 (15.02)	23.5 (13.14)	21.2 (13.67)	17.9 (12.08)	19.1 (10.25)
Change from Baseline	Mean (SD)	-12.2 (12.96)	-17.8 (14.34)	-18.8 (14.58)	-21.7 (14.22)	-21.1 (11.66)
Placebo-adjusted difference	LS mean	NA	-4.38	-6.18	-9.29	-8.33
	95% CI	NA	(-8.7, 0.0)	(-10.5, -1.8)	(-13.9, -4.6)	(-12.9, -3.7)
	P-Value	NA	0.0485	0.0053	0.0001	0.0004

Source: Section 12.1 Table 2.1.1.1 of Clinical Study 304 Report (pg. 88)

Table 19. Study 304: ADHD-RS-IV Total Score by Weight-adjusted Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 0.01-0.04 mg/kg	SPD503 0.05-0.08 mg/kg	SPD503 0.09-0.12 mg/kg	SPD503 0.13-0.16 mg/kg
Endpoint	N patients	63	112	84	33	14
	Mean(SD)	27.1 (15.02)	22.1 (13.17)	19.7 (12.44)	19.8 (11.55)	16.8 (10.47)
Change from Baseline	Mean (SD)	-12.2 (12.96)	-17.6 (14.05)	-20.0 (13.82)	-23.5 (13.35)	-24.8 (11.05)
Placebo-adjusted difference	LS mean	NA	-5.13	-7.56	-8.98	-11.24
	95% CI	NA	(-9.0, -1.2)	(-11.7, -3.4)	(-14.4, -3.6)	(-18.6, -3.9)
	P-Value (Dunnett)	NA	0.0104	0.0004	<0.0012	<0.0028

Source: Section 12.1 Table 2.1.4.1 of Clinical Study 304 Report (pg. 89)

3.1.3.4 Primary Analysis on Subscale Scores of the Primary Endpoint

The eighteen ADHD-RS-IV items were grouped into two subscales: hyperactivity/impulsivity (even numbered items) and inattentiveness (odd numbered items). Tables below present a summary and analysis of ADHD-RS-IV inattentiveness and hyperactivity/impulsivity subscales by randomized dose for ITT Population. The analysis was performed by the reviewer. The results confirmed sponsor's results. For both studies, all guanfacine treatment arms were numerically superior to placebo.

Study 301

Table 20. Study 301: ADHD-RS-IV Inattentiveness Subscale Scores at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	325	78	84	82	81
Baseline	Mean (SD)	20.86 (4.93)	20.76 (4.85)	20.84 (4.21)	21.67 (4.18)
Endpoint	Mean (SD)	15.96 (8.04)	12.45 (7.35)	12.13 (7.06)	12.05 (7.19)
Change from Baseline	Mean (SD)	-4.90 (7.95)	-8.31 (7.28)	-8.71 (7.27)	-9.62 (7.64)
Placebo-adjusted difference	LS mean	NA	-3.47	-3.82	-4.28
	95% CI	NA	(-5.67, -1.26)	(-6.04,-1.60)	(-6.51,-2.05)
	P-Value	NA	0.0022	0.0008	0.0002

Source: Reviewer's results
Corresponds to Table 22 of Clinical Study 301 Report (pg. 85)
Note: the reported p-values and CIs are nominal and are not adjusted for multiplicity.

Table 21. Study 301: ADHD-RS-IV Hyperactivity/Impulsivity Subscale Scores at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	325	78	84	82	81
Baseline	Mean (SD)	17.28 (6.61)	15.33 (7.00)	15.93 (6.53)	16.73 (6.65)
Endpoint	Mean (SD)	13.00 (8.41)	8.48 (7.26)	8.84 (7.56)	7.16 (5.86)
Change from Baseline	Mean (SD)	-4.28 (6.32)	-6.86 (6.47)	-7.09 (6.96)	-9.57 (7.24)
Placebo-adjusted difference	LS mean	NA	-3.38	-3.36	-5.51
	95% CI	NA	(-5.30, -1.46)	(-5.29, -1.43)	(-7.44,-3.58)
	P-Value	NA	0.0006	0.0007	<0.0001

Source: Reviewer's results
Corresponds to Table 22 of Clinical Study 301 Report (pg. 85)
Note: the reported p-values CIs are nominal and are not adjusted for multiplicity.

Study 304

Table 22 Study 304: ADHD-RS-IV Inattentiveness Subscale score at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	306	63	57	63	60	63
Baseline	Mean(SD)	22.16 (4.17)	22.09 (3.79)	22.48 (4.19)	22.63 (3.56)	22.54 (3.74)
Endpoint	Mean(SD)	15.78 (7.86)	11.60 (6.68)	12.98 (7.74)	12.57 (7.86)	11.98 (6.35)
Change fr. Baseline	Mean (SD)	-6.38 (7.08)	-10.49 (7.02)	-9.49 (8.36)	-10.07 (7.77)	-10.56 (6.42)
Placebo-adjusted difference	LS mean	NA	-4.15	-2.95	-3.44	-3.98
	95% CI	NA	(-6.70, -1.59)	(-5.44, -0.46)	(-5.96, -0.92)	(-6.47,-1.49)
	P-Value	NA	0.002	0.020	0.008	0.002

Source: Reviewer's results
Corresponds to Table 19 of Clinical Study 304 Report (pg. 93)
Note: the reported p-values and CIs are nominal and are not adjusted for multiplicity.

Table 23 Study 304: ADHD-RS-IV Hyperactivity/Impulsivity Subscale Score at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	306	63	57	63	60	63
Baseline	Mean(SD)	17.10 (6.71)	19.61 (5.01)	17.44 (6.86)	16.43 (7.08)	18.06 (6.58)
Endpoint	Mean(SD)	11.25 (8.34)	9.70 (6.87)	9.02 (8.03)	7.17 (5.72)	7.16 (5.86)
Change fr. Baseline	Mean (SD)	-5.84 (7.08)	-9.91 (7.67)	-8.43 (7.83)	-9.32 (8.05)	-10.32 (6.72)
Placebo-adjusted difference	LS mean	NA	-2.64	-2.39	-3.85	-3.93
	95% CI	NA	(-5.00, -0.28)	(-4.67, -0.11)	(-6.16, -1.54)	(-6.21, -1.64)
	P-Value	NA	0.028	0.040	0.001	0.001

Source: Reviewer's results
Corresponds to Table 21 of Clinical Study 304 Report (pg. 95)
Note: the reported p-values and CIs are nominal and are not adjusted for multiplicity.

3.1.3.5 Exploratory Secondary Efficacy measures

The sponsor reported the following analyses results:

Study 301

The main exploratory secondary efficacy measures were Conners' Parent & Teacher Rating Scales-Revised (CPRS-R & CTRS-R), Clinical Global Impression of Improvement (CGI-I) Scale, Parent's Global Assessment (PGA) and the Child Health Questionnaire (CHQ-PF50 and CHQ-CF87).

The secondary efficacy variables CPRS-R, CTRS-R, CHQ-PF50 and CHQ-CF87 were analyzed

using the same ANCOVA model as was used for the primary efficacy variable. For the CGI-I and PGA, the nonparametric Cochran-Mantel-Haenszel (CMH) test was used to examine treatment.

According to the sponsor's results, all guanfacine treatment arms demonstrated numerical superiority to Placebo in all secondary efficacy variables except SPD503 2mg dose in CHQ-CF87 Family Activity and Bodily Pain Scales.

Study 304

The main exploratory secondary efficacy measures were Conners' Parent Rating Scale-Revised (CPRS-R), Clinical Global Impression of Improvement (CGI-I) Scale, Parent's Global Assessment (PGA) and the Child Health Questionnaire-Parent Form (CHQ-PF50).

The secondary efficacy variables CPRS-R and CHQ-PF50 were analyzed using the same ANCOVA model as was used for the primary efficacy variable. For the CGI-I and PGA, the nonparametric Cochran-Mantel-Haenszel (CMH) test was used to examine treatment.

Based on the sponsor's findings, all SPD503 treatment arms demonstrated numerical superiority to Placebo in all secondary efficacy variables except CHQ-PF50 Physical Category.

Reviewer's comment: These were the sponsor's exploratory analyses and the results are considered exploratory only.

3.1.3.6 Results and Conclusions

For studies 301 and 304, this reviewer confirmed the sponsor's analysis results for the primary endpoint. In these studies, the primary efficacy measure, ADHD-RS-IV total score demonstrated efficacy of each dose group of guanfacine.

3.2 Evaluation of Safety

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Tables below present reviewer's efficacy results from exploratory subgroup analyses by age, gender and race. The results coincide with the sponsor' results. For both studies, this reviewer noticed that patients in the age group 13-17 did not seem to show numerical difference between

the placebo group and almost all guanfacine dose groups in change from baseline to endpoint in ADHD-RS-IV total score.

Study 301

Table 24 Study 301: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Age Subgroups (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Age 6-8 years					
No patients	85	22	16	20	27
Baseline	Mean (SD)	40.41 (8.94)	37.88 (10.94)	37.00 (8.45)	41.96 (7.52)
Endpoint	Mean(SD)	36.09 (10.06)	21.88 (13.48)	19.15 (13.83)	15.63 (9.78)
Change fr. Baseline	Mean (SD)	-4.32 (9.60)	-16.00 (13.17)	-17.85 (14.41)	-26.33 (11.74)
Placebo-adjusted difference	LS mean	NA	-13.17 (3.67)	-15.53 (3.47)	-21.10 (3.20)
	95% CI	NA	(-20.48, -5.86)	(-22.44, -8.63)	(-27.48, -14.73)
	P-Value	NA	0.0006	<0.0001	<0.0001
Age 9-12					
No patients	164	37	51	37	39
Baseline	Mean (SD)	37.43 (10.38)	36.82 (9.98)	38.24 (8.57)	36.97 (9.90)
Endpoint	Mean(SD)	27.92 (15.75)	20.35 (14.54)	21.32 (14.85)	21.72 (12.79)
Change fr. Baseline	Mean (SD)	-9.51 (12.71)	-16.47 (12.85)	-16.92 (13.32)	-15.26 (12.32)
Placebo adjusted difference	LS mean	NA	-7.11 (2.72)	-7.20 (2.93)	-5.86 (2.89)
	95% CI	NA	(-12.49, -1.74)	(-12.98, -1.41)	(-11.57, -0.15)
	P-Value	NA	0.010	0.015	0.044
Age 13-17 years					
No patients	76	19	17	25	15
Baseline	Mean (SD)	36.89 (7.45)	32.24 (8.63)	34.40 (8.98)	35.67 (8.70)
Endpoint	Mean(SD)	22.79 (16.27)	21.47 (11.92)	21.92 (12.77)	19.13 (12.42)
Change fr. Baseline	Mean (SD)	-14.11 (16.00)	-10.76 (11.49)	-12.48 (11.09)	-16.53 (16.40)
Placebo adjusted difference	LS mean	NA	0.86 (4.42)	0.30 (3.98)	-3.08 (4.50)
	95% CI	NA	(-7.94, 9.67)	(-7.63, 8.23)	(-12.04, 5.87)
	P-Value	NA	0.846	0.940	0.495

Source: Reviewer's results
Corresponds to Section 12.1 Tables 2.2.2, 2.2.3, and 2.2.4 of Clinical Study 301 Report (pg. 86)
Note: the reported p-values and 95% CIs are nominal and are not adjusted for multiplicity.

Table 25 Study 301: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Gender Subgroups (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Males					
No patients	241	58	65	66	52
Baseline	Mean (SD)	38.90 (8.81)	36.48 (9.73)	36.55 (8.80)	37.94 (9.46)
Endpoint	Mean(SD)	31.64 (13.41)	21.23 (13.62)	20.91 (14.10)	21.17 (12.23)
Change fr. Baseline	Mean (SD)	-7.26 (12.35)	-15.25 (12.61)	-15.64 (13.16)	-16.77 (13.97)
Placebo-adjusted difference	LS mean	NA	-9.04 (2.25)	-9.40 (2.24)	-9.93 (2.37)
	95% CI	NA	(-13.47, -4.61)	(-13.82, -4.99)	(-14.59, -5.26)
	P-Value	NA	<0.0001	<0.0001	<0.0001
Females					
No patients	84	20	19	16	29
Baseline	Mean (SD)	35.95 (10.69)	34.79 (11.02)	37.69 (8.61)	39.21 (8.86)
Endpoint	Mean(SD)	21.25 (17.54)	19.63 (14.32)	21.25 (13.31)	15.69 (10.80)
Change fr. Baseline	Mean (SD)	-14.70 (14.18)	-15.16 (13.37)	-16.44 (12.71)	-23.52 (12.54)
Placebo adjusted difference	LS mean	NA	-0.92 (4.06)	-1.05 (4.25)	-7.53 (3.71)
	95% CI	NA	(-9.00, 7.16)	(-9.52, 7.42)	(-14.91, -0.14)
	P-Value	NA	0.822	0.806	0.046

Source: Reviewer's results

Note: the reported p-values and 95% CIs are nominal and are not adjusted for multiplicity.

Table 26 Study 301: ADHD-RS-IV Total Score by Randomized Dose and Race Subgroups (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Caucasians					
No patients	228	57	57	56	58
Baseline	Mean (SD)	37.46 (8.96)	37.19 (10.01)	37.18 (8.90)	38.17 (9.69)
Endpoint	Mean(SD)	28.12 (15.25)	21.84 (14.41)	23.18 (13.98)	17.45 (11.74)
Change fr. Baseline	Mean (SD)	-9.33 (13.23)	-15.35 (12.50)	-14.00 (12.50)	-20.72 (14.24)
Placebo-adjusted difference	LS mean	NA	-6.12 (2.37)	-4.77 (2.38)	-11.12 (2.36)
	95% CI	NA	(-10.79, -1.44)	(-9.47, -0.08)	(-15.77, -6.46)
	P-Value	NA	0.011	0.046	<0.0001
Others					
No patients	97	21	27	26	23
Baseline	Mean (SD)	40.00 (10.30)	33.78 (9.74)	35.88 (8.43)	38.96 (8.06)
Endpoint	Mean(SD)	31.29 (15.03)	18.81 (12.11)	16.23 (12.62)	23.65 (11.62)
Change fr. Baseline	Mean (SD)	-8.71 (13.31)	-14.96 (13.36)	-19.65 (13.45)	-15.30 (11.99)
Placebo adjusted difference	LS mean	NA	-9.60 (3.64)	-13.15 (3.61)	-7.15 (3.68)
	95% CI	NA	(-16.83, -2.36)	(-20.33, -5.98)	(-14.45, 0.15)
	P-Value	NA	0.010	0.001	0.055

Source: Reviewer's results

Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

Study 304

Table 27 Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Age Subgroups (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Age 6-12 years						
No patients	230	45	50	46	41	48
Baseline	Mean (SD)	41.33 (8.85)	42.16 (7.78)	40.57 (9.02)	41.59 (8.27)	41.50 (8.27)
Endpoint	Mean(SD)	29.82(14.86)	21.12 (12.87)	24.26 (14.57)	19.68 (13.22)	19.17 (10.35)
Change fr. Baseline	Mean (SD)	-11.51 (13.71)	-21.04 (14.45)	-16.30 (14.78)	-21.90 (13.97)	-22.33 (11.59)
Placebo-adjusted difference	LS mean	NA	-9.04	-5.25	-10.24	-10.72
	95% CI	NA	(-14.23,-3.85)	(-10.55,0.05)	(-15.69,-4.79)	(-15.96, -5.48)
	P-Value	NA	0.0007	0.052	0.0003	<0.0001
Age 13-17 years						
No patients	76	18	7	17	19	15
Baseline	Mean (SD)	34.06 (6.53)	38.43 (7.76)	38.18 (7.92)	33.63 (8.99)	37.73 (9.16)
Endpoint	Mean(SD)	20.06 (13.29)	22.57 (13.05)	16.00 (10.40)	19.95 (10.93)	21.53 (13.15)
Change fr. Baseline	Mean (SD)	-14.00 (10.95)	-15.86 (9.89)	-22.18 (14.32)	-13.68 (15.02)	-16.20 (12.01)
Placebo-adjusted difference	LS mean	NA	1.10	-5.39	0.03	0.29
	95% CI	NA	(-9.54, 11.74)	(-13.51, 2.73)	(-7.75, 7.81)	(-8.07, 8.65)
	P-Value	NA	0.837	0.190	0.994	0.946

Source: Reviewer's results
Corresponds to Section 12.1, Table 2.1.3 of Clinical Study 304 Report (pg. 92)
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

Table 28 Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Gender Subgroups (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Males						
No patients	220	44	37	44	44	51
Baseline	Mean (SD)	40.68 (8.41)	40.27 (8.14)	40.45 (8.33)	38.43 (9.23)	40.86 (8.35)
Endpoint	Mean(SD)	27.18 (15.24)	22.11 (12.73)	22.00 (14.52)	20.02 (13.06)	19.47 (11.03)
Change fr. Baseline	Mean (SD)	-13.50 (13.39)	-18.16 (13.90)	-18.45 (14.02)	-18.41 (14.88)	-21.39 (12.27)
Placebo-adjusted difference	LS mean	NA	-4.89	-5.08	-6.17	-7.79
	95% CI	NA	(-10.54, 0.75)	(-10.48, 0.31)	(-11.58, -0.75)	(-12.99, -2.58)
	P-Value	NA	0.089	0.065	0.026	0.003
Females						
No patients	86	19	20	19	16	12
Baseline	Mean (SD)	35.95 (9.17)	44.35 (6.53)	38.68 (9.76)	40.81 (9.24)	39.50 (9.77)
Endpoint	Mean(SD)	26.68 (14.83)	19.80 (13.08)	22.11 (13.05)	19.06 (10.94)	20.83 (11.34)
Change fr. Baseline	Mean (SD)	-9.26 (11.65)	-24.55 (13.57)	-16.58 (16.75)	-21.75 (14.34)	-18.67 (10.31)
Placebo-adjusted difference	LS mean	NA	-9.92	-5.57	-9.38	-7.14
	95% CI	NA	(-18.36, -1.49)	(-13.73, 2.59)	(-18.00, -0.75)	(-16.43, 2.16)
	P-Value	NA	0.022	0.178	0.033	0.131

Source: Reviewer's results
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

Table 29 Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Race Subgroups (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Caucasians						
No patients	203	38	39	40	43	43
Baseline	Mean (SD)	39.03 (9.00)	40.05 (7.81)	40.90 (8.39)	38.02 (9.01)	41.09 (8.75)
Endpoint	Mean(SD)	26.68 (15.90)	22.54 (11.41)	22.35 (14.49)	19.51 (12.85)	20.63 (11.34)
Change fr. Baseline	Mean (SD)	-12.34 (13.78)	-17.51 (12.64)	-18.55 (14.96)	-18.51 (14.63)	-20.47 (11.53)
Placebo-adjusted difference	LS mean	NA	-4.60	-5.17	-6.72	-6.98
	95% CI	NA	(-10.33, 1.12)	(-10.87, 0.53)	(-12.32, -1.13)	(-12.58, -1.38)
	P-Value	NA	0.114	0.075	0.019	0.015
Others						
No patients	103	25	18	23	17	20
Baseline	Mean (SD)	39.60 (8.78)	45.28 (6.68)	38.22 (9.27)	41.71 (9.47)	39.55 (8.29)
Endpoint	Mean(SD)	27.56 (13.81)	18.61 (15.36)	21.48 (13.37)	20.41 (11.72)	17.80 (10.28)
Change fr. Baseline	Mean (SD)	-12.04 (11.84)	-26.67 (15.12)	-16.74 (14.72)	-21.29 (15.12)	-21.75 (12.89)
Placebo-adjusted difference	LS mean	NA	-10.96	-5.59	-7.89	-9.74
	95% CI	NA	(-18.97, -2.95)	(-12.92, 1.74)	(-15.88, 0.10)	(-17.34, -2.14)
	P-Value	NA	0.008	0.133	0.053	0.013

Source: Reviewer's results
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both studies have demonstrated that guanfacine in the dose range of 2mg, 3mg and 4mg was effective in the treatment of attention deficit/hyperactivity disorder in the overall intent-to-treat population. Study 304 has also demonstrated that guanfacine in dose 1 mg/day was effective in the overall intent-to-treat population. However, for both studies patients in the age group 13-17 did not show numerical difference between the placebo group and almost all guanfacine dose groups (refer to Section 4.1).

5.2 Conclusions and Recommendations

Guanfacine in doses 1 mg/day, 2 mg/day, 3 mg/day and 4 mg/day demonstrated statistically significant treatment effect in the pre-specified primary efficacy endpoint.

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