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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	22037
Supplement #:	S-10
Drug Name:	INTUNIV® (Guanfacine HCl) ER tablets
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Shire
Dates:	Submission date: 04/22/2014
	Assign date: 05/20/2014
	PDUFA V: 11/19/2014
Review Priority:	6 months priority
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Keywords:
NDA review, pediatric written request, mixed models, ANCOVA.

Reference ID: 3648993

Table of Contents

1 EXECUTIVE SUMMARY 5

2 INTRODUCTION 6

2.1 OVERVIEW 6
2.2 DATA SOURCES 6

3 STATISTICAL EVALUATION 7

3.1 DATA AND ANALYSIS QUALITY 7
3.2 EVALUATION OF EFFICACY 7
3.2.1 Study Design and Endpoints 7
3.2.2 Statistical Methodologies 9
3.2.3 Patient Disposition, Demographic and Baseline Characteristics 12
3.2.4 Sponsor's Efficacy Results and Conclusions 15
3.2.5 Reviewer's Results and Conclusions 19
3.3 EVALUATION OF SAFETY 22

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 23

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION 23
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 23
4.3 OTHER SPECIAL/SUBGROUP POPULATIONS 24

5 SUMMARY AND CONCLUSIONS 24

5.1 STATISTICAL ISSUES 24
5.2 COLLECTIVE EVIDENCE 24
5.3 CONCLUSIONS AND RECOMMENDATIONS 24

Reference ID: 3648993

LIST OF TABLES

Table 1. The key information about studies SPD503-312 and SPD503-316.....6
Table 2. Patients' disposition (Study SPD503-312).....12
Table 3. Demographic characteristics of the patients (SPD503-312).....12
Table 4. Patients' disposition (Study SPD503-316).....13
Table 5. Demographic characteristics of the patients (SPD503-316).....14
Table 6. Results of the primary efficacy endpoint analysis (MMRM) for study SPD503-312.....15
Table 7. Visit-wise results of the primary efficacy analysis for (FAS, SPD503-312).....17
Table 8. Results of the Pattern Mixture Model (FAS) using 1000 imputations for SPD503-312. 17
Table 9. Summary and analysis of the key secondary endpoint for Study SPD503-312 (FAS).....18
Table 10. Results of the primary efficacy endpoint analysis (LOCF ANCOVA) for study SPD503-316.....18
Table 11. Summary and analysis of the secondary endpoint for Study SPD503-316 (LOCF, FAS).....19
Table 12. Primary efficacy endpoint analysis results summarized by the reviewer (SPD503-312, FAS).....19
Table 13. Primary efficacy endpoint analysis results summarized by the reviewer (SPD503-316, FAS).....21
Table 14. Subgroup analysis for study SPD503-312.....23
Table 15. Subgroup analysis for study SPD503-316.....23

Reference ID: 3648993

LIST OF FIGURES

Figure 1. Schematic study design (SPD503-312). 8
Figure 2. Schematic study design (SPD503-316) 9
Figure 3. Number of Patients for each weight-adjusted dose of SPD503 at the endpoint (SPD503-312) 13
Figure 4. Number of Patients for each weight-adjusted dose of SPD503 at the endpoint (SPD503-316). 15
Figure 5. LS Means change from baseline in ADHD_RS-IV total score using MMRM (FAS, SPD503-312) 16
Figure 6. Mean ADHD-RS-IV total score by visit (FAS, LOCF) 19
Figure 7. Change from baseline in ADHD-RS-IV total score for patients grouped by drop-out-date (SPD503-312).20
Figure 8. Change from baseline in ADHD-RS-IV total score for patients grouped by drop-out-date (SPD503-316).22

Reference ID: 3648993

1 EXECUTIVE SUMMARY

Based on the statistical analysis results of the two studies (SPD530-312 and SPD503-316), the reviewer confirms sponsor's findings that INTUNIV® (Guanfacine hydrochloride) was statistically significantly superior to placebo in reducing symptoms of ADHD in children aged 6—12 and adolescents aged 13—17 years, as measured by the change from baseline in ADHD-RS-IV total scores. From the statistical perspective, the study SPD503-312 fulfills the Postmarketing Requirement 1538-2 and the Pediatric Written Request.

Reference ID: 3648993

2 INTRODUCTION

2.1 Overview

Guanfacine hydrochloride, hereafter referred to as SPD503 was approved in the US in September 2009 for the treatment of ADHD in children and adolescents aged 6-17 years old. The efficacy was supported based on two short-term, placebo-controlled, pivotal fixed-dose, efficacy studies. These studies enrolled both children (6-12 years) and adolescents (13-17 years) and utilized up to 4 mg/day of SPD503 administered once-daily. Subgroup analyses suggested a differential treatment effect between the children and the adolescent subgroups, particularly the inconclusive efficacy results in the adolescents subgroup. A possible contributing factor was the higher body weight in adolescents under the fixed-dose design. The Pediatric Written Request (PWR) was issued to address this concern in the treatment of adolescents.

This supplement includes two efficacy studies: SPD503-312 and SPD503-316. SPD503-312 was conducted in only adolescents to address the aforementioned concern and to fulfill the PWR. Study SPD503-316 was designed primarily to fulfill an EU regulatory requirement for a study with an active reference treatment and the sponsor had gained agreement on the current study designs including the length of the dose optimization and maintenance periods with the European Medicines Agency (EMA) before soliciting the FDA feedback. The study was included in the submission to provide additional information.

This review provides statistical evaluation of both studies SPD503-312 and SPD503-316. The key information is summarized in Table 1.

Table 1. The key information about studies SPD503-312 and SPD503-316.

Study name	Phase & Design	Treatment period	Follow-up Period	# of Subjects per Arm (randomized)	Study Population
SPD503-312	Phase 3	15 weeks	7(+2) days	SPD503: 157, Placebo: 157	Adolescents (13-17 years)
SPD503-316	Phase 3	10 weeks for children (6-12 years); 13 weeks for adolescents (13-17 years).	7-9 days	Placebo: 111, SPD503: 115, Strattera: 112	Children and adolescents (6-17 years)

Source: summarized by the reviewer.

The study SPD503-312 was conducted at 52 sites in the United States (US) only.

The study SDP503-316 was conducted at 58 sites, of which 11 sites were located in the US, 2 sites in Canada, and 45 sites in Europe (Austria, France, Germany, Ireland, Italy, Poland, Romania, Spain, Sweden, Ukraine, and United Kingdom).

2.2 Data Sources

The sponsor's submitted data and program listings are available in the following directory of the CDER' electronic document room (EDR): \\CDSESUB1\evsprod\NDA022037\0053

Reference ID: 3648993

On 07/02/2014 the sponsor provided the response to the information request regarding the blinded review of the sample size re-estimation during the interim analysis for Study SPD503-312 including the appropriate datasets and the SAS code. The submitted serial is available in the following directory of the CDER EDR: \\CDSESUB1\evsprod\NDA022037\0057\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data satisfying and acceptable for the review analysis. The reviewers were able to reproduce the primary analysis dataset from the raw data and trace how the primary endpoint was derived.

Additional data regarding blinded review of the sample size during the interim analysis for study SPD503-312 were requested from the sponsor on 06/24/2014.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

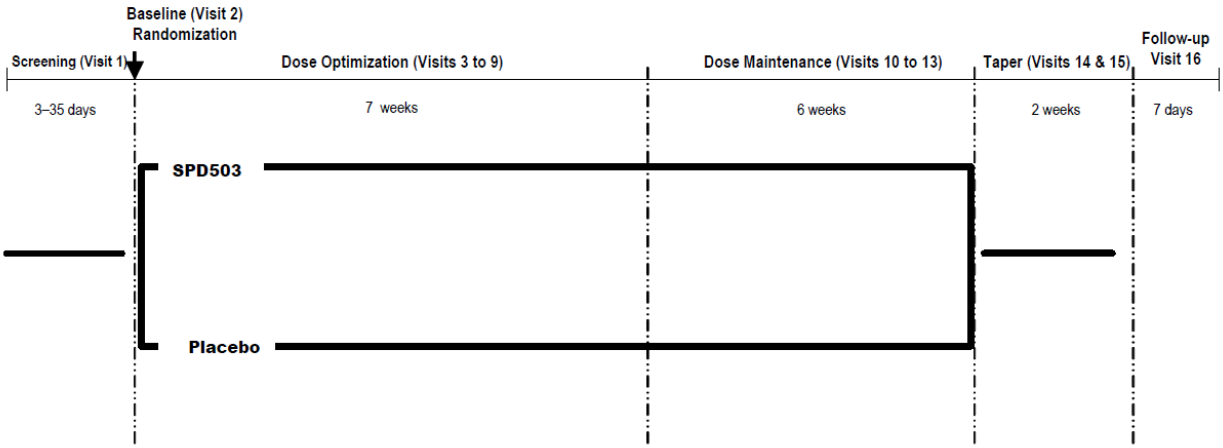
3.2.1.1 Study SPD503-312

The *primary objectiv*e of the study SPD503-312 was to assess the efficacy of once-daily dosing of optimized SPD503 compared to placebo in the treatment of adolescents aged 13—17 years diagnosed with ADHD as measured by the ADHD-RS-IV total score. The *key secondary objectives* were to assess efficacy based on the clinician's global impressions of ADHD severity as measured by the dichotomized CGI-S scale, and to evaluate efficacy on ADHD functional outcomes as measured by the WFIRS-P Learning and School Domain and WFIRS-P Family Domain.

Study SPD503-312 was a double-blind, randomized, placebo-controlled study conducted to assess the efficacy and safety of SPD503 in adolescents (aged 13-17 years) with ADHD. Patient randomization to treatment groups was stratified by weight group (34.0-41.4kg, 41.5-49.4kg, 49.5-58.4kg, and 58.5-91.0kg). The study was 15 weeks in duration consisting of a 7-week Dose-optimization Period (placebo or maximum of 7mg SPD503/day) and a 6-week Dose-maintenance Period, which was followed by a 2-week Dose-tapering Period. The schematic study design is presented in Figure 1.

Reference ID: 3648993

Figure 1. Schematic study design (SPD503-312).



Source: Fig.1 from the clinical study report for SPD503-312.

The *primary efficacy endpoint* was the change in the ADHD-RS-IV total score from the Baseline (Visit 2) to Week 13(Visit 13).

The CGI-S assessed at each visit from Visit 2 to Visit 13 was pre-specified as the *key secondary efficacy endpoint*. In the version 3.0 of the Statistical Analysis Plan, the sponsor also proposed to use the WFIRS-P Learning and School Domain and Family Domain results at Week 13/FOTA as an additional key secondary endpoint; however, it was not an acceptable key secondary endpoint.

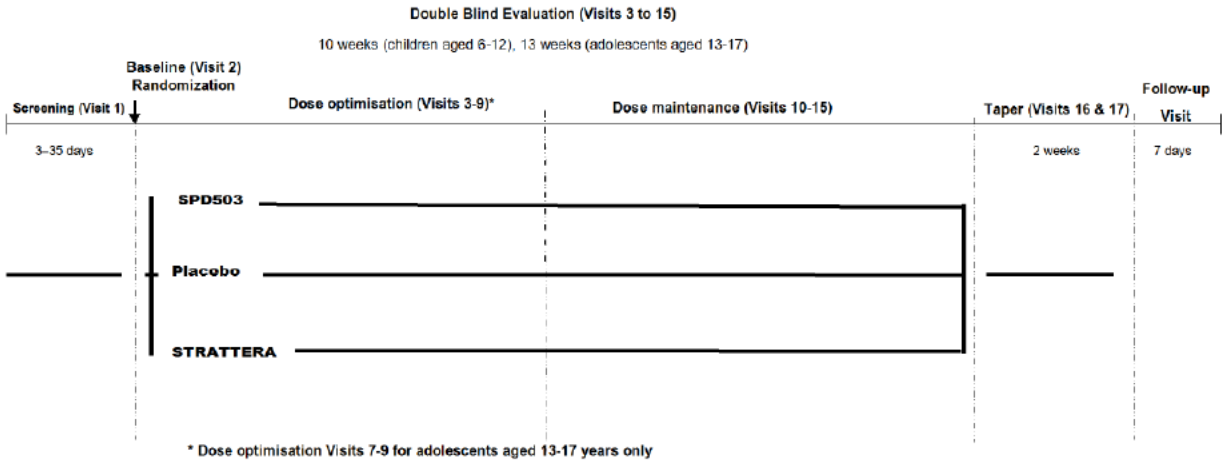
3.2.1.2 Study SPD503-316

The *primary objective* of the study SPD503-316 was to assess the efficacy of once-daily dosing of SPD503 (maximum of 4 or 7 mg SPD503/day for children and adolescents, respectively) as measured by the ADHD-RS-IV total score. The *key secondary objectives* were to assess efficacy based on the clinician's global impressions of ADHD improvement as measured by the dichotomized CGI-I scale, and to evaluate efficacy on ADHD functional outcomes as measured by the WFIRS-P Learning and School Domain and WFIRS-P Family Domain.

Study SPD503-316 was a Phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled study conducted to assess the efficacy and safety of SPD503 in male and female children and adolescents (aged 6-17 years) with ADHD, and included an active reference arm (STRATTERA®). Patient randomization to treatment groups was stratified by age group (6-12 years and 13-17 years) and country. The study was up to 10 weeks in duration for children and up to 13 weeks in duration for adolescents. This included a 4- or 7-week Dose-optimization Period for children and adolescents, respectively; a 6-week Dose-maintenance Period; and a 2-week Dose-tapering Period. The schematic study design is presented in Figure 2.

Reference ID: 3648993

Figure 2. Schematic study design (SPD503-316)



Source: Fig.1 from the clinical study report for SPD503-316.

The *primary efficacy endpoint* was the change from the Baseline Visit (Visit 2/Week 0) to Visit 15 for the ADHD-RS-IV total score (Week 10 for children aged 6-12 years and Week 13 for adolescents aged 13-17 years; or Early Termination) using LOCF.

The different durations of the periods for the primary efficacy comparison between these two age subgroups (10 vs. 13 weeks) resulted from the different durations of dose optimization period between children and adolescents (4 vs. 7 weeks). We acknowledged that the target doses are based on weight and that different target doses require variable durations of titration; however, in our Advice/Information Request Letter (03/11/2011) we asked the sponsor to discuss whether or not this might impact the efficacy analysis.

(b) (4)

. However, we would not accept these major changes at such a late stage of the trial, and would consider both CGI-I and WFIRS-P analyses to be exploratory as stated in the protocol.

3.2.2 Statistical Methodologies

3.2.2.1 Study SPD503-312

The *primary analysis* for the primary efficacy variable was a mixed effects linear model for repeated measures (MMRM) using unstructured covariance matrix with a random subject effect. The model contains one continuous covariate – baseline score, and three categorical covariates: treatment group (two levels), weight group (four levels), and visit (eleven levels). Interaction terms: treatment group-by-visit, and baseline value-by-visit.

Reference ID: 3648993

To explore the impact of dropouts on the primary efficacy analysis, a pattern mixture model was pre-specified to impute data for dropout subjects. Once the missing data have been imputed, the change from Baseline for the ADHD-RS-IV total score will be analyzed as a sensitivity analysis using the same method as the primary analysis.

As pre-specified in the SAP, the Full Analysis Set (FAS) was used to assess comparative efficacy information. The FAS was defined as all subjects who were randomized and had taken at least 1 dose of investigational product during the study.

To fulfill the PWR, an interim analysis was planned to re-assess the sample size based on a blinded estimation of the standard deviation (SD) of the primary efficacy measure. To be specific, if the interim observed pooled standard deviation is greater than the postulated at the design stage (10 points), the sample size (calculated based on t-distribution) will be increased to ensure a minimum 85% power; no sample size reduction will be considered regardless of the magnitude of the interim SD estimate. Based on the blinded interim look, the SD estimate was 12.5 points, i.e., larger than the postulated. However, the sponsor decided to use a smaller magnitude than the interim estimate to re-calculate the sample size. One of their reasons was that a blinded interim analysis will typically overestimate the variability. Another reason was that smaller SD's were observed from two historical studies. With many concerns taken together, the sponsor proposed to take an 8.1% reduction from the blinded SD estimate of 12.63 points, i.e., re-estimate the sample size based on the adjusted SD estimate of 11.6 points. This resulted in a sample size of 310 subjects (155 subjects in each arm).

We acknowledged that the blinded estimate of SD tends to be larger than the unblinded estimate if the treatment effect (after subtracting the placebo effect) is indeed present. However, based on non-model-based calculations, the difference between the blinded and the unblinded estimates of SD would be very subtle for this case. We pointed out that given an observed blinded SD, a larger assumed treatment effect tends to lead to a smaller unblinded SD. Also, the use of MMRM might tend to reduce the SD. We note that the amount of reduction in SDs differs largely between these two historical studies and thus it was uncertain whether this study would lead to a similar reduction. In addition, the explorations of these two historical trials were based on MMRM, which might tend to lead to a smaller SD than non-model based analyses.

In summary, we did not accept the sponsor's proposal because of many uncertainties such as those mentioned above. We mentioned that if the sponsor believes that the treatment effect from this ongoing study will far exceed the postulated, or if the actual SD will be smaller than the estimated one (12.6), it is at the sponsor's own risk to adjusting the sample size accordingly. We also noted that the sponsor may still fulfill the Written Request if efficacy is demonstrated in this study, i.e., the treatment effect in the final analysis is statistically significant, even if the sample size is not adequately increased from our perspective. However, we may not consider that the WR is fulfilled if the efficacy is not demonstrated and the sample size is not adequately increased.

For the *analysis of the key secondary efficacy endpoint* the CGI-S responses were dichotomized into 2 categories:

(1) "Improved", defined by CGI-S score of 1 or 2 (normal/borderline mentally ill),

Reference ID: 3648993

(2) “Not improved”, defined by CGI-S score > 2 (mild mentally ill or worse).

The dichotomized CGI-S responses will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by weight group to examine treatment group effects at the Endpoint visit.

The hierarchical testing procedure was pre-specified in the SAP as the multiplicity adjustment to control the overall Type I error rate at the pre-specified 0.05 (two-sided) alpha level for the primary and key secondary endpoints.

3.2.2.2 Study SPD503-316

The primary efficacy analysis was pre-specified to compare the change from baseline to Visit 15 between treatments (SPD503 and placebo) using LOCF ANCOVA model. The ANCOVA model will include terms for treatment group (the effect of interest), the corresponding baseline score (the covariate), and the blocking factors age group (6-12 years or 13-17 years) and country. Since there are some countries with few patients randomized, then countries will be pooled as following:

North America: USA and Canada
Eastern Europe: Poland and Romania
Western Europe: Italy, Austria, France, Sweden, Ireland and Great Britain

All other countries will remain as individual countries. This was determined prior to database lock and unblinding.

To assess the impact of missing data on the primary efficacy analysis, the sponsor pre-specified the following *sensitivity analyses*:

(1) Any subject who withdraws during the dose optimization phase will have their last score imputed for Visit 10 and the MMRM sensitivity analysis applied to all subjects for visits 10 – 15.
(2) An MMRM analysis will be performed on all observed data for all subjects collected at weeks 1 through 10. In this analysis subjects will have the opportunity to receive a maintenance dose for at least 3 weeks.
(3) An MMRM analysis will be performed on all observed data for all subjects collected for the last 10 weeks of the study, i.e. for children weeks 1-10 will be used and for adolescents weeks 4-13 will be used. In this analysis subjects will have the opportunity to receive a maintenance dose for at least 6 weeks. Any adolescent that withdraws prior to week 4 will have their last available value imputed for week 4.

It was specified in the SAP that the primary efficacy analysis will be performed over the Full Analysis Set (FAS), which was defined as all subjects who were randomized and had taken at least 1 dose of investigational product during the study.

There was no interim analysis planned for this study.

Reference ID: 3648993

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Disposition, Demographic and Baseline Characteristics for Study SPD503-312

Patients' disposition between the treatment arms during the trial is summarized in the Table 2. The FAS was defined as all subjects who were randomized and had taken at least 1 dose of investigational product during the study. Two subjects were randomized to placebo but did not receive the assigned treatment.

Table 2. Patients' disposition (Study SPD503-312)

	Placebo N (%)	**SPD503** N (%)	**Total** N (%)
Screened			401 (100.0)
Randomized	157 (100.0)	157 (100.0)	314 (100.0)
Full Analysis Set	155 (98.7)	157 (100.00)	312 (99.4)
Early Termination	55 (35.0)	52 (33.1)	107 (34.1)
due to			
Adverse Event	3 (1.9)	9 (5.7)	12 (3.8)
Protocol Violation	3 (1.9)	1 (0.6)	4 (1.3)
Subject's withdrawal	13 (8.3)	16 (10.2)	29 (9.2)
Lost to follow up	4 (2.5)	11 (7.0)	15 (4.8)
Lack of efficacy	25 (15.9)	9 (5.7)	34 (10.8)
Other	7 (4.5)	6 (3.8)	13 (4.1)

Source: Table 1.1.3, Clinical Study Report of the SPD503-312, Section 14.

The demographic and baseline characteristics are summarized in the Table 3.

Table 3. Demographic characteristics of the patients (SPD503-312)

	Placebo **N = 155**	**SPD503** **N = 157**	**Total** **N = 312**
Age *years*			
Mean (SD)	14.6 (1.44)	14.5 (1.35)	14.5 (1.39)
Min - Max	13—17	13—17	13—17
Gender *n (%)*			
Female	56 (36.1)	54 (34.4)	110 (35.3)
Male	99 (63.9)	103 (65.6)	202 (64.7)
Ethnicity *n (%)*			
Hispanic/Latino	26 (16.8)	40 (25.5)	66 (21.2)
Not Hispanic/Latino	129 (83.2)	117 (74.5)	246 (78.8)
Race *n (%)*			
White	114 (73.5)	113 (72.0)	227 (72.8)
Black or African American	29 (18.7)	24 (15.3)	53 (17.0)
Asian	3 (1.9)	2 (1.3)	5 (1.6)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (0.6)
Other	8 (5.2)	17 (10.8)	25 (8.0)
Height *cm*			
Mean (SD)	166.5 (9.82)	166.0 (9.62)	166.3 (9.71)
Min - Max	142—188	143—193	142—193
Weight *kg*			
Mean (SD)	60.54 (12.31)	61.05 (12.51)	60.80 (12.39)
Min – Max	34.6—90.8	34.6—91.0	34.6—91.0

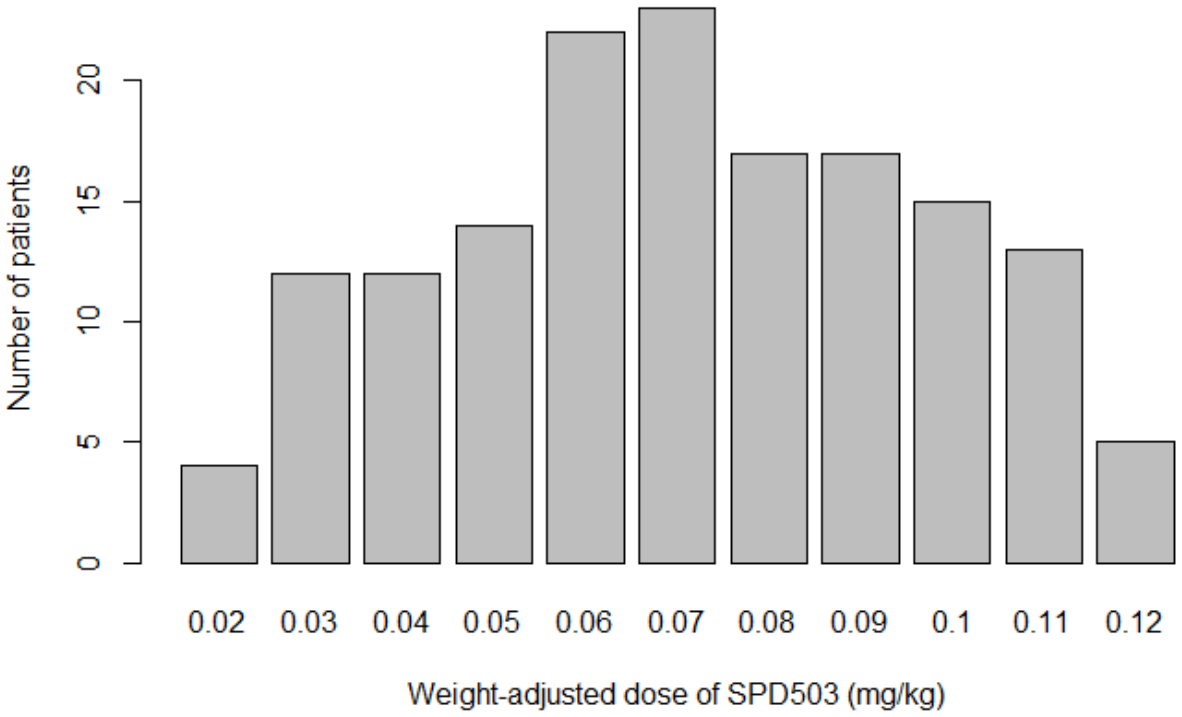
Reference ID: 3648993

Body Mass Index *kg/m²*			
Mean (SD)	21.69 (3.24)	22.00 (3.34)	21.85 (3.29)
Min – Max	14.7—34.1	15.2—31.1	14.7—34.1

Source: Section 14, Table 1.2.1 and Appendix 16.2, Listing 4.2 of the SPD503-312 Clinical Study Report.

Figure 3 summarizes the numbers of patients receiving different doses of the SPD503 at the Endpoint visit. There appears to be no tendency towards extremely high or low drug doses among the patients. The summary for the placebo patients is not presented, because there were no dose-related data for them.

Figure 3. Number of Patients for each weight-adjusted dose of SPD503 at the endpoint (SPD503-312)



Source: Computed by the reviewer.

3.2.3.2 Disposition, Demographic and Baseline Characteristics for Study SPD503-316

Patients' disposition between the treatment arms during the trial is summarized in the Table 4.

Table 4. Patients' disposition (Study SPD503-316)

	Placebo N (%)	**SPD503** N (%)	**Strattera** N (%)	**Total** N (%)
Screened				404
Randomized	111 (100.0)	115 (100.0)	112 (100.0)	338 (100.0)
Full Analysis Set	111 (100.0)	114 (99.1)	112 (100.0)	337 (99.7)
Early Termination due to	19 (17.1)	24 (20.9)	23 (20.5)	66 (19.5)

Reference ID: 3648993

Adverse Event	1 (0.9)	9 (7.8)	5 (4.5)	15 (4.4)
Protocol Violation	0	0	0	0
Subject's withdrawal	4 (3.6)	4 (3.5)	9 (8.0)	17 (5.0)
Lost to follow up	0	6 (5.2)	3 (2.7)	9 (2.7)
Lack of efficacy	14 (12.6)	5 (4.3)	5 (4.5)	24 (7.1)
Other	0	0	1 (0.9)	1 (0.3)

Source: Table 1.1.3 and Table 1.1.5, Clinical Study Report of the SPD503-316, Section 14.

The demographic and baseline characteristics were summarized in the Table 5.

Table 5. Demographic characteristics of the patients (SPD503-316)

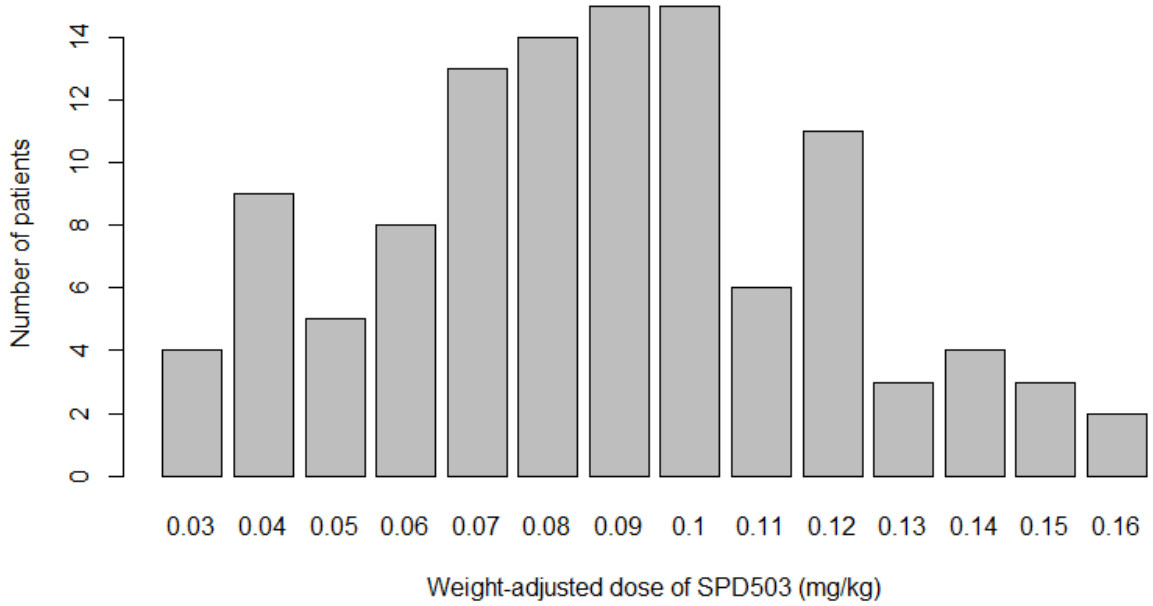
	Placebo N = 111	**SPD503 N = 114**	**Strattera N = 112**	**Total N = 337**
Age *years*				
Mean (SD)	11.0 (2.76)	10.9 (2.77)	10.5 (2.81)	10.8 (2.78)
Min - Max	6—17	6—17	6—16	6—17
Gender *n (%)*				
Female	25 (22.5)	38 (33.3)	25 (22.3)	88 (26.1)
Male	86 (77.5)	76 (66.7)	87 (77.7)	249 (73.9)
Ethnicity *n (%)*				
Hispanic/Latino	6 (5.4)	6 (5.3)	3 (2.7)	15 (4.5)
Not Hispanic/Latino	103 (92.7)	106 (93.0)	107 (95.5)	316 (93.8)
Not reported	2 (1.8)	2 (1.8)	2 (1.8)	6 (1.8)
Race *n (%)*				
White	104 (93.7)	105 (92.1)	101 (90.2)	310 (92.0)
Black or African American	3 (2.7)	5 (4.4)	7 (6.3)	15 (4.5)
American Indian or Alaska Native	0	1 (0.9)	0	1 (0.3)
Other	2 (1.8)	1 (0.9)	2 (1.8)	5 (1.5)
Not reported	2 (1.8)	2 (1.8)	2 (1.8)	6 (1.8)
Height *cm*				
Mean (SD)	146.4 (15.03)	147.2 (15.74)	144.3 (17.40)	146.0 (16.08)
Min - Max	117—188	116—187	114—184	114—188
Weight *kg*				
Mean (SD)	41.37 (13.31)	41.93 (14.29)	40.57 (15.31)	41.30 (14.30)
Min - Max	25.0—78.0	25.0—77.7	25.0—87.0	25.0—87.0
Body Mass Index *kg/m^2*				
Mean (SD)	18.78 (2.76)	18.79 (3.02)	18.74 (2.95)	18.77 (2.91)
Min - Max	14.3—26.7	13.5—27.6	14.0—27.4	13.5—27.6

Source: Section 14, Table 1.2.1 and Appendix 16.2, Listing 4.2 of the SPD503-316 Clinical Study Report.

Figure 4 summarizes the number of patients receiving different doses of the SPD503 at the Endpoint visit. There appears to be no tendency towards extremely high or low drug doses among the patients. The summary for the placebo patients is not presented, because there were no dose-related data for them.

Reference ID: 3648993

Figure 4. Number of Patients for each weight-adjusted dose of SPD503 at the endpoint (SPD503-316).



Source: Computed by the reviewer.

3.2.4 Sponsor's Efficacy Results and Conclusions

3.2.4.1 Sponsor's Results and Conclusions for Study SPD503-312

The sponsor found statistically significantly difference (p-value < 0.001) between SPD503 and placebo in reducing the ADHD symptoms in adolescent patients (13 to 17 years of age) as measured by the change from the baseline in ADHD-RS-IV total score (primary efficacy endpoint). The results of the sponsor's primary efficacy analysis are presented in the Table 6.

Table 6. Results of the primary efficacy endpoint analysis (MMRM) for study SPD503-312.

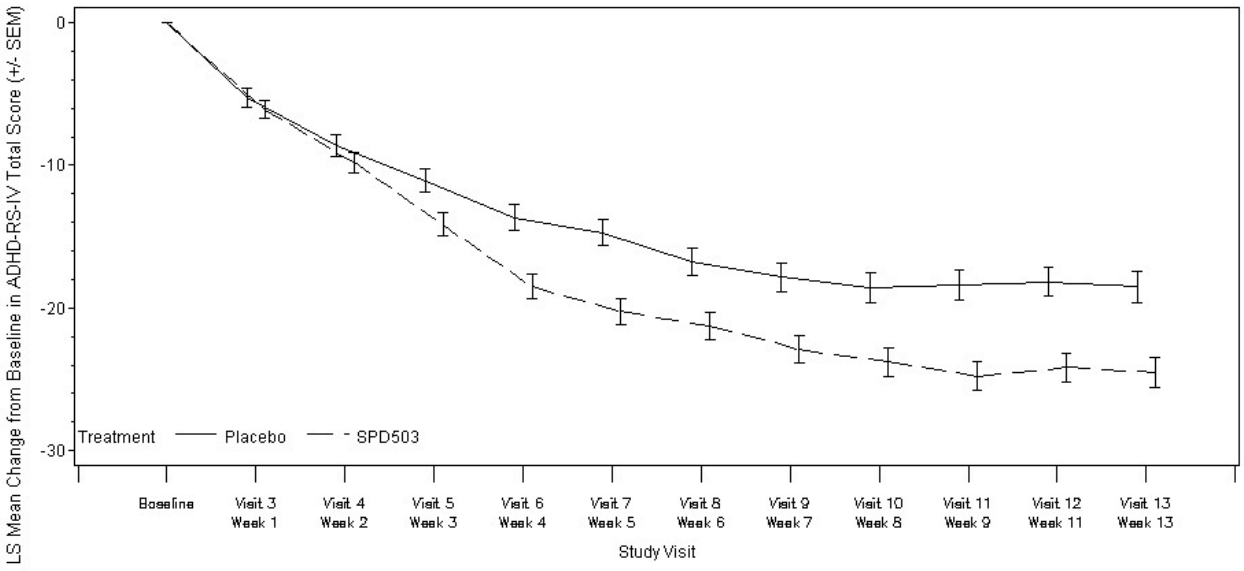
ADHD-RS-IV Total Score	**Placebo**	**SPD503**
Baseline		
N	155	157
Mean (SD)	40.0 (6.11)	39.9 (5.57)
Visit 13		
N	106	109
Mean (SD)	20.3 (13.35)	14.1 (9.38)
Change from Baseline		
Mean (SD)	-19.5 (12.63)	-25.7 (10.09)
Comparison to Placebo		
LS mean	-18.527	-24.552
Difference in LS means		-6.026
95% CI		(-8.865, -3.187)
Effect size		0.52
p-value		<0.001

Source: Table 11 of the SPD503-312 Clinical Study Report, Section 9.2.

Reference ID: 3648993

The least-square mean change from the baseline in ADHD-RS-IV total score by visit is summarized in Figure 5. The error bars on the graph extend ±1 standard error around the LS means. The difference between the SPD503 and the placebo arms appears to emerge during the course of the study and stayed through the end of the study.

Figure 5. LS Means change from baseline in ADHD_RS-IV total score using MMRM (FAS, SPD503-312)



Source: Figure 2 of the SPD503-312 Clinical Study Report, pg. 84.

The visit-wise MMRM results of the primary MMRM analysis are presented in Table 7.

Results from the pattern mixture model used as the sensitivity analysis on the change from baseline in ADHD-RS-IV total score are presented in Table 8. The results were consistent with that from the primary analysis.

Reference ID: 3648993

Table 7. Visit-wise results of the primary efficacy analysis for (FAS, SPD503-312).

Comparison	Visit	LS Mean (SE)[1] SPD503	LS Mean (SE)[1] Placebo	Difference in LS Mean SPD503 - Placebo (95% CI)[1]	Effect Size (95% CI)[1]	P-Value[1]
SPD503 vs Placebo	Visit 3 (Week 1)	-6.103 (0.6362)	-5.255 (0.6347)	-0.848 (-2.352, 0.656)	0.13 (-0.10, 0.35)	0.268
	Visit 4 (Week 2)	-9.808 (0.7573)	-8.627 (0.7562)	-1.181 (-3.070, 0.707)	0.14 (-0.08, 0.37)	0.219
	Visit 5 (Week 3)	-14.167 (0.8195)	-11.077 (0.8237)	-3.090 (-5.179, -1.001)	0.34 (0.11, 0.56)	0.004
	Visit 6 (Week 4)	-18.503 (0.8901)	-13.662 (0.8944)	-4.841 (-7.144, -2.538)	0.48 (0.25, 0.71)	<0.001
	Visit 7 (Week 5)	-20.258 (0.8987)	-14.737 (0.9054)	-5.521 (-7.853, -3.189)	0.54 (0.30, 0.78)	<0.001
	Visit 8 (Week 6)	-21.260 (0.9304)	-16.763 (0.9428)	-4.496 (-6.931, -2.061)	0.43 (0.19, 0.67)	<0.001
	Visit 9 (Week 7)	-22.911 (0.9516)	-17.856 (0.9681)	-5.055 (-7.559, -2.551)	0.47 (0.23, 0.72)	<0.001
	Visit 10 (Week 8)	-23.807 (0.9981)	-18.589 (1.0164)	-5.217 (-7.862, -2.573)	0.46 (0.21, 0.72)	<0.001
	Visit 11 (Week 9)	-24.789 (1.0148)	-18.408 (1.0378)	-6.380 (-9.081, -3.680)	0.56 (0.31, 0.82)	<0.001
	Visit 12 (Week 11)	-24.180 (0.9981)	-18.179 (1.0212)	-6.000 (-8.651, -3.350)	0.55 (0.28, 0.81)	<0.001
	Visit 13 (Week 13)	-24.552 (1.0625)	-18.527 (1.0841)	-6.026 (-8.865, -3.187)	0.52 (0.24, 0.79)	<0.001

[1] LS Mean, standard error (SE), effect size and P-Value is based on repeated measures analysis for the change from Baseline scores at Visits 3 to 13, with an unstructured covariance structure, random subject effect, treatment (2 levels), time (11 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including Baseline and baseline-by-time as covariates. A negative difference in LS Mean (SPD503 - placebo) indicates a positive effect of the active treatment over the placebo.

Source: Table 3.1.1.3 of the SPD503-312 Clinical Study Report (pg. 252).

Table 8. Results of the Pattern Mixture Model (FAS) using 1000 imputations for SPD503-312.

Comparison	Visit	LS Mean (SE)[1] SPD503	LS Mean (SE)[1] Placebo	Difference in LS Mean SPD503 - Placebo (95% CI)[1]	Effect Size (95% CI)[1]	P-Value[1]
SPD503 vs Placebo	Visit 3 (Week 1)	-6.083 (0.6389)	-5.234 (0.6374)	-0.848 (-2.346, 0.650)	0.13 (-0.10, 0.35)	0.267
	Visit 4 (Week 2)	-9.782 (0.7594)	-8.606 (0.7583)	-1.176 (-3.057, 0.705)	0.14 (-0.08, 0.36)	0.221
	Visit 5 (Week 3)	-14.107 (0.8191)	-11.049 (0.8223)	-3.058 (-5.128, -0.988)	0.33 (0.10, 0.55)	0.004
	Visit 6 (Week 4)	-18.363 (0.8971)	-13.631 (0.8998)	-4.731 (-7.036, -2.426)	0.46 (0.23, 0.68)	<0.001
	Visit 7 (Week 5)	-20.039 (0.9041)	-14.668 (0.9081)	-5.372 (-7.698, -3.045)	0.51 (0.29, 0.74)	<0.001
	Visit 8 (Week 6)	-21.089 (0.9404)	-16.691 (0.9558)	-4.397 (-6.841, -1.954)	0.40 (0.18, 0.63)	<0.001
	Visit 9 (Week 7)	-22.675 (0.9685)	-17.775 (0.9897)	-4.900 (-7.433, -2.368)	0.43 (0.21, 0.66)	<0.001
	Visit 10 (Week 8)	-23.539 (1.0255)	-18.416 (1.0488)	-5.123 (-7.823, -2.423)	0.42 (0.20, 0.65)	<0.001
	Visit 11 (Week 9)	-24.272 (1.0524)	-18.172 (1.0890)	-6.100 (-8.890, -3.310)	0.49 (0.26, 0.71)	<0.001
	Visit 12 (Week 11)	-23.661 (1.0307)	-18.058 (1.0550)	-5.603 (-8.304, -2.902)	0.46 (0.24, 0.69)	<0.001
	Visit 13 (Week 13)	-24.069 (1.0945)	-18.293 (1.1134)	-5.776 (-8.659, -2.892)	0.45 (0.22, 0.67)	<0.001

[1] LS Mean, standard error (SE), effect size and P-Value is based on repeated measures analysis for the change from Baseline scores at Visits 3 to 13, with an unstructured covariance structure, random subject effect, treatment (2 levels), time (11 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including Baseline and baseline-by-time as covariates. A negative difference in LS Mean (SPD503 - placebo) indicates a positive effect of the active treatment over the placebo.

Source: Table 3.1.1.4 of the SPD503-312 Clinical Study Report (pg. 252).

Reference ID: 3648993

The sponsor has also performed analysis of the *key secondary endpoint* (the dichotomized CGI-S score). The result was statistically significant as presented in the Table 9.

Table 9. Summary and analysis of the key secondary endpoint for Study SPD503-312 (FAS).

	Placebo (N = 155)	**SPD503 (N = 157)**
Number of patients:		
Last valid assessment obtained after the baseline	155	154
Normal/borderline mentally ill (CGI-S ≤ 2)	56 (36.1 %)	78 (50.6)
Mildly ill or worse (CGI-S > 2)	99 (63.9 %)	76 (49.4 %)
p-value of the CMH test stratified by weight	0.010	

Source: Table 13 of the SPD503-312 Clinical Study Report, pg. 88.

3.2.4.2 Results and Conclusions for Study SPD503-316

The sponsor found statistically significantly difference (p-value < 0.001) between SPD5003 and placebo in reducing the symptoms of ADHD in pediatric patients (6 to 17 years of age). The results of the primary efficacy analysis are presented in the Table 10.

Table 10. Results of the primary efficacy endpoint analysis (LOCF ANCOVA) for study SPD503-316

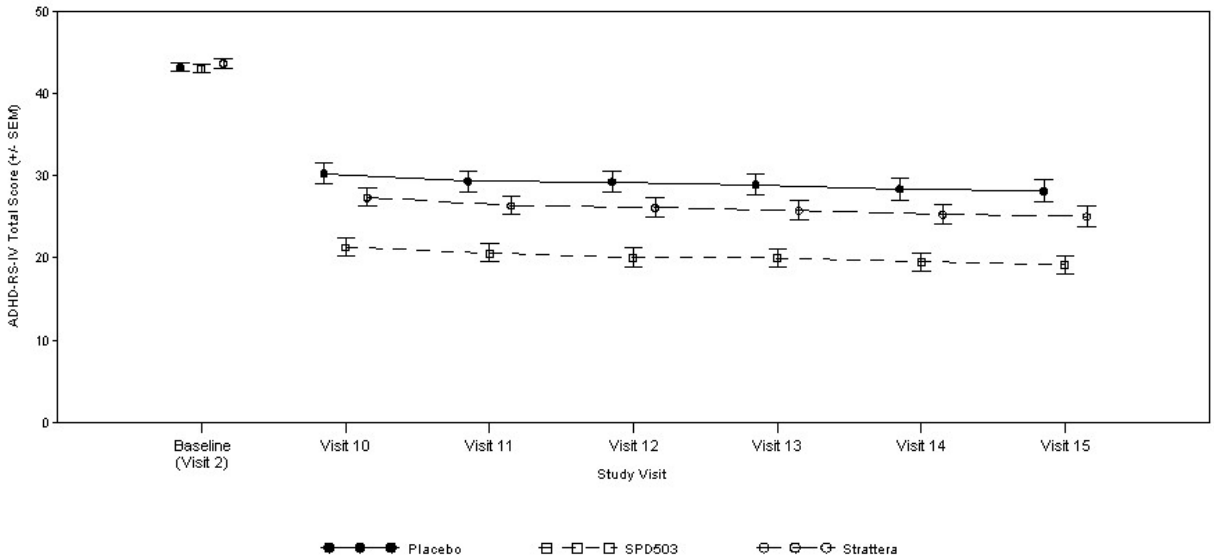
ADHD-RS-IV Total Score	**Placebo**	**SPD503**	**Strattera**
Baseline			
N	111	114	112
Mean (SD)	43.2 (5.60)	43.1 (5.47)	43.7 (5.86)
Visit 15			
N	111	112	112
Mean (SD)	43.2 (5.60)	19.2 (11.85)	25.0 (12.97)
Change from Baseline			
Mean (SD)	-15.0 (13.07)	-23.9 (12.41)	-18.6 (11.91)
Comparison to Placebo			
LS mean	-15.0	-23.9	-18.8
Difference in LS means		-8.9	-3.8
95% CI		(-11.9, -5.8)	(-6.8, -0.7)
Effect size		0.76	0.32
p-value *(not adjusted for multiplicity)*		<0.001	0.017

Source: Table 15 of the SPD503-316 Clinical Study Report, Section 9.2.

The mean ADHD-RS-IV total score by treatment group using LOCF is presented in Figure 6. Visit 10 is the first visit after the dose optimization. Error bars extend ±1 standard error around the mean values. The difference between the SPD503 and the placebo arms appears to be consistently evident starting with Visit 10.

Reference ID: 3648993

Figure 6. Mean ADHD-RS-IV total score by visit (FAS, LOCF)



Source: Figure 2 from the SPD503-316 Clinical Study Report, pg. 88.

The sponsor has also performed analysis of the *secondary efficacy endpoint* dichotomized CGI-I score ('very much improved' or 'much improved' versus all other categories) at visit 15 (Week 10/13) using CMH test stratified by weight group to examine treatment group effects. The summary and the results of the test are presented in the Table 11.

Table 11. Summary and analysis of the secondary endpoint for Study SPD503-316 (LOCF, FAS).

Number of patients:	Placebo (N = 111)	SPD503 (N=114)	Strattera (N = 112)
CGI-I improved or very much improved	49 (44.1%)	76 (67.9%)	63 (56.3%)
No improvement (all other CGI-I)	62 (55.9%)	36 (32.1%)	49 (43.8%)
p-value of the CMH test (compared to placebo) stratified by weight and age group and not adjusted for multiplicity		<.001	0.024

Source: Table 16 of the Clinical Study Report, pg. 90.

3.2.5 Reviewer's Results and Conclusions

3.2.5.1 Reviewer's Results and Conclusions for Study SPD503-312

The reviewer confirms the sponsor's analysis results for the primary efficacy endpoint (Table 12).

Table 12. Primary efficacy endpoint analysis results summarized by the reviewer (SPD503-312, FAS)

Difference	Visit #	N	Estimate	SE	DF	t-value	p-value	95% Confidence Interval	
SPD503 – Placebo	**13**	309	**-6.03**	1.44	262	-4.18	**<.0001**	-8.86	-3.19

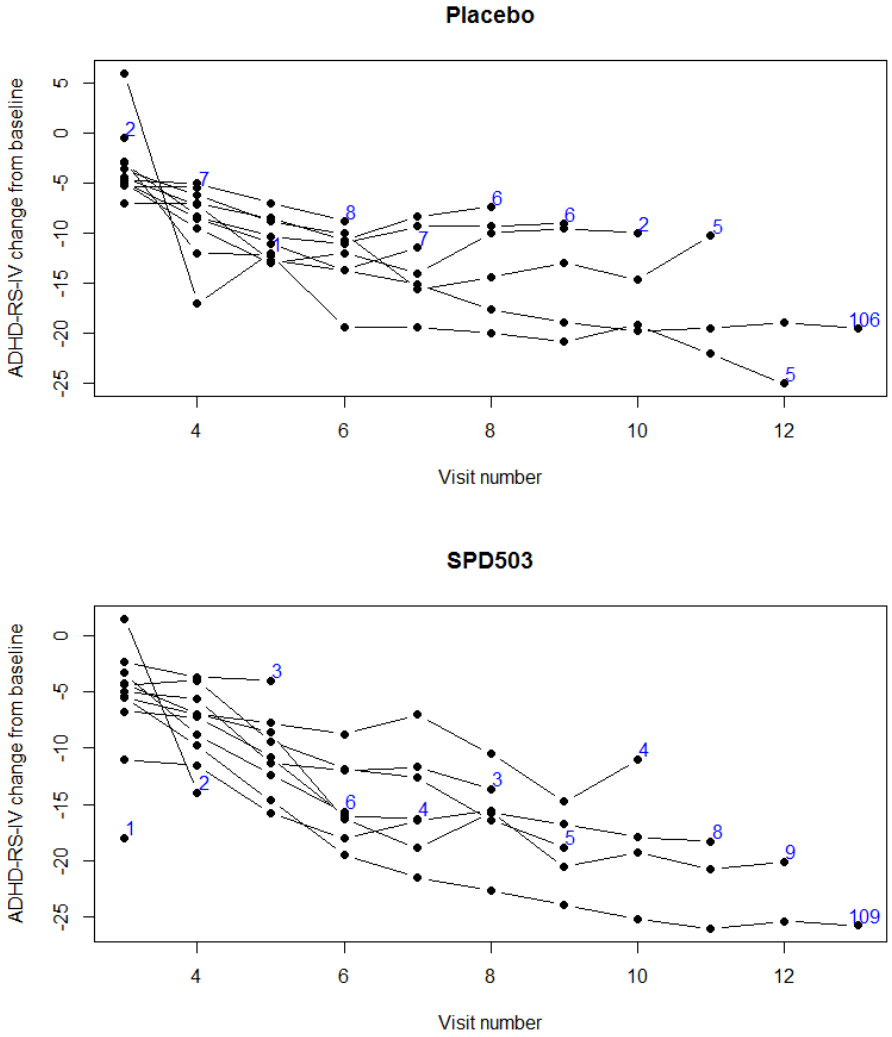
Source: computed by the reviewer.

Reference ID: 3648993

The FAS was defined as all subjects who were randomized and had taken at least 1 dose of investigational product during the study; however, not all of them had post-baseline assessments. There were three patients (subject IDs: 004-0006, 034-0001 and 037-0004) in the FAS who had no records of the post baseline visit. Thus, only 309 observations can be used for the primary efficacy analysis. Even when included in the analysis, the SAS automatically deletes the observations without any post-baseline data.

The reviewer explored the potential impact of the dropouts on the efficacy results by comparing the average change from the baseline in the primary efficacy endpoint between the treatment arm and placebo for each drop-out date (see Figure 7).

Figure 7. Change from baseline in ADHD-RS-IV total score for patients grouped by drop-out-date (SPD503-312).



Source: Computed by the reviewer.

The two graphs (one for each treatment arm) show the average change from baseline in the ADHD-RS-IV total score) computed for the patients, after they were grouped according to the

Reference ID: 3648993

date of their drop-out. Each curve is labeled with the number of patients in the group. The visual analysis of the data did not appear to indicate an obvious deviation from missing at random (MAR) assumption.

3.2.5.2 Reviewer's Results and Conclusions for Study SPD503-316

The reviewer confirms the sponsor's analysis results for the primary efficacy endpoint (Table 13).

Table 13. Primary efficacy endpoint analysis results summarized by the reviewer (SPD503-316, FAS)

Difference	Visit #	N	Estimate	SE	DF	t-value	p-value	95% Confidence Interval	
SPD503 – Placebo	**15**	335	**-8.88**	1.56	325	-5.70	**<.0001**	-11.94	-5.81

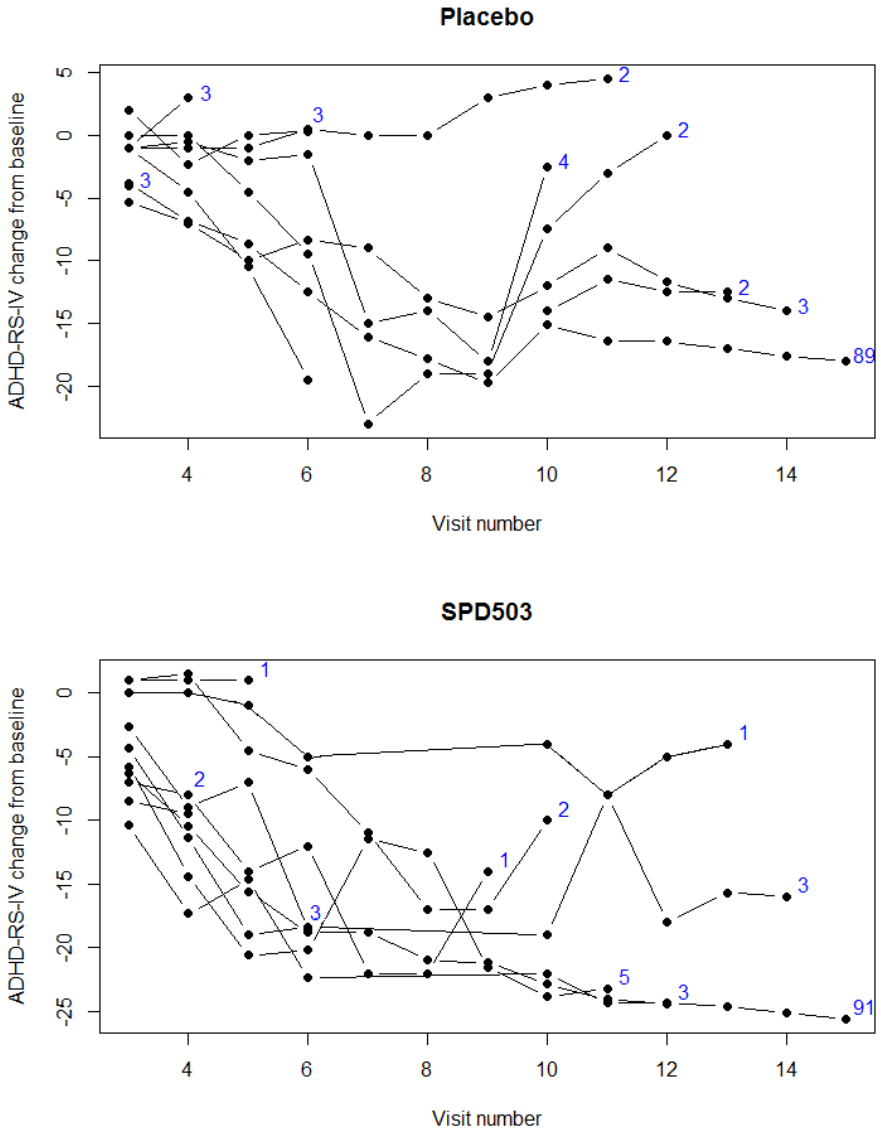
Source: computed by the reviewer.

The FAS was defined as all subjects who were randomized and had taken at least 1 dose of investigational product during the study; however, not all of them had post-baseline assessments. There were two patients (subject IDs: 351-0002 and 807-0006) in the FAS who had no records of the post baseline visit. Thus, only 335 observations can be used for the primary efficacy analysis. Even when included in the analysis, the SAS automatically deletes the observations without any post-baseline data.

The reviewer explored the potential impact of the dropouts on the efficacy results by comparing the average change from the baseline in the primary efficacy endpoint between the treatment arm and placebo for each drop-out date (see Figure 8). The two graphs (one for each treatment arm) show the average change from baseline in the ADHD-RS-IV total score) computed for the patients, after they were grouped according to the date of their drop-out. Each curve is labeled with the number of patients in the group. The visual analysis of the data did not appear to indicate an obvious deviation from missing at random (MAR) assumption.

Reference ID: 3648993

Figure 8. Change from baseline in ADHD-RS-IV total score for patients grouped by drop-out-date (SPD503-316)



Source: Computed by the reviewer.

3.3 Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

Reference ID: 3648993

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1.1 Reviewer's Results and Conclusions for Study SPD503-312

This section contains the reviewer's results of the exploratory subgroup analysis for patients according to their gender, race, and ethnicity (see Table 14). No age subgroup analysis was performed, since all the patients were adolescents (13-17 years old). No subgroup analysis by region/country was performed, since all the study centers were located in the US.

Table 14. Subgroup analysis for study SPD503-312.

	N	SPD503 - Placebo LS means difference (SE)	Unadjusted 95% confidence interval
Gender			
Female	110	-7.72 (2.36)	(-12.41, -3.03)
Male	199	-4.76 (1.82)	(-8.36, -1.16)
Race/Ethinicity			
White	226	-6.52 (1.77)	(-10.00, -3.03)
Black or African American	51	-3.57 (3.52)	(-10.71, 3.57)
Hispanic or Latino	66	-8.27 (2.91)	(-14.11, 2.43)

Source: computed by the reviewer.

Based on this reviewer's analysis, there does not appear to be substantial heterogeneity in treatment efficacy among the subgroups.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

4.2.1.1 Reviewer's Results and Conclusions for Study SPD503-316

This section contains the reviewer's results of the exploratory subgroup analysis for patients according to their gender, age group, race, ethnicity and geographic region (see Table 15).

Table 15. Subgroup analysis for study SPD503-316.

	N	SPD503 - Placebo LS means difference (SE)	Unadjusted 95% confidence interval
Gender			
Female	88	-7.40 (2.63)	(-12.64, -2.16)
Male	247	-8.29 (1.93)	(-12.10, -4.49)
Age group			
6—12 years old	240	-10.49 (1.87)	(-14.18, -6.80)
13—17 years old	95	-4.74 (2.77)	(-10.24, 0.76)
Race/Ethinicity			
White	309	-9.05 (1.62)	(-12.24, -5.85)
Black or African American	14	1.56 (13.62)	(-29.25, 32.36)
Hispanic or Latino	15	-4.79 (8.16)	(-23.61, 14.03)

Reference ID: 3648993

Geographic Region			
Europe	261	-9.13 (1.75)	(-12.57, -5.69)
Canada or USA	74	-8.01 (3.30)	(-14.59, -1.44)

Source: computed by the reviewer.

Based on this reviewer's analysis, there does not appear to be substantial heterogeneity in treatment efficacy among the subgroups. Although the observed treatment effect in the adolescents subgroup (13—17 years old) was almost twice smaller than that in the children subgroup (6—12 years old), results from both age subgroups still suggest the efficacy of SPD503 compared to placebo in both children and adolescents populations. The only subgroup that had opposite sign for numeric estimate for the efficacy effect was the Black/African American subgroup of patients, which is inconsistent with the rest of the subgroups. The reason for that could possibly be attributed to the relatively large variance in quite a small subgroup (14 observations).

4.3 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study SPD503-312 was conducted to fulfill the PWR. To ensure sufficient statistical power, an interim analysis was conducted to re-calculate the sample size based on a blinded estimate of the standard deviation (SD) of the primary efficacy measure. The SD estimate at the interim look was 12.5 points, relatively larger than the postulated 10 points at the design stage, but the sponsor decided to use 11.6 points to re-calculate the sample size. This led to a smaller increase in sample size than had 12.5 points been used. Despite this, efficacy was demonstrated in this trial. Otherwise, this trial alone would not be sufficient to address the efficacy concern raised in the PWR.

5.2 Collective Evidence

The results of the statistical analyses of both studies (SPD503-312 and SPD503-316) appear to be consistent. The exploratory subgroup analyses did not reveal noticeable heterogeneity with respect to the primary efficacy measure (change from baseline in ADHD-RS-IV total score).

5.3 Conclusions and Recommendations

The reviewer confirmed the sponsor's analysis results that INTUNIV® (Guanfacine HCl) was statistically significantly superior to placebo (p-value < 0.001 for both studies) in reducing the symptoms of ADHD in pediatric patients 6 to 17 years of age. From the statistical perspective, there is no evidence against fulfilling the PMR and PWR.

Reference ID: 3648993

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/s/

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