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 #:	22,037
Supplement #:	S-11
Drug Name:	INTUNIV® (Guanfacine HCl) ER tablets
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Shire
Dates:	Submission: 04/22/2014
	Labeling due: 02/26/2015
	PDUFA V goal: 03/19/2015
Review Priority:	Standard
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Keywords: Cochran-Mantel-Haenszel, logrank test, censored observations, subgroup analyses, sensitivity analyses, proportional hazards, Kaplan-Meier product limits.

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1 EXECUTIVE SUMMARY

Based on the statistical analysis results of the study SPD530-315 the reviewer confirms sponsor's findings that INTUNIV® (Guanfacine hydrochloride) was statistically significantly superior to placebo as a maintenance treatment in pediatric patients (6-17 years old) with attention deficit hyperactivity disorder, as measured by the time to treatment failure during the randomized withdrawal trial. From the statistical perspective, the study SPD503-312 fulfills the Postmarketing Requirement 1538-1.

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, however, 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. In order to address this concern, a Pediatric Written Request (PWR) was issued, and the sponsor conducted two short-term efficacy studies (SPD503-312 and SPD503-316) to fulfill the PWR under NDA 22037 (S-10).

The current supplement of NDA 22037 (S-011) includes one long-term maintenance study SPD503-315 which was intended to assess the long-term maintenance of efficacy using a placebo-controlled, randomized-withdrawal design to satisfy Postmarketing Requirement (PMR) 1538-1. The key information of the study is presented in Table 1.

Table 1. Key information about the study included in the analysis.

Study name	Phase & Design	Treatment Period	Follow-up Period	# of Subjects per arm (randomized)	Study Population
SPD503-315	Phase 3	26 weeks	1 week	SPD503: 157 Placebo: 159	Children and adolescents (6-17 years old)

Source: summarized by the reviewer.

(b) (4)

(b) (4)

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

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.

3.2 Evaluation of Efficacy

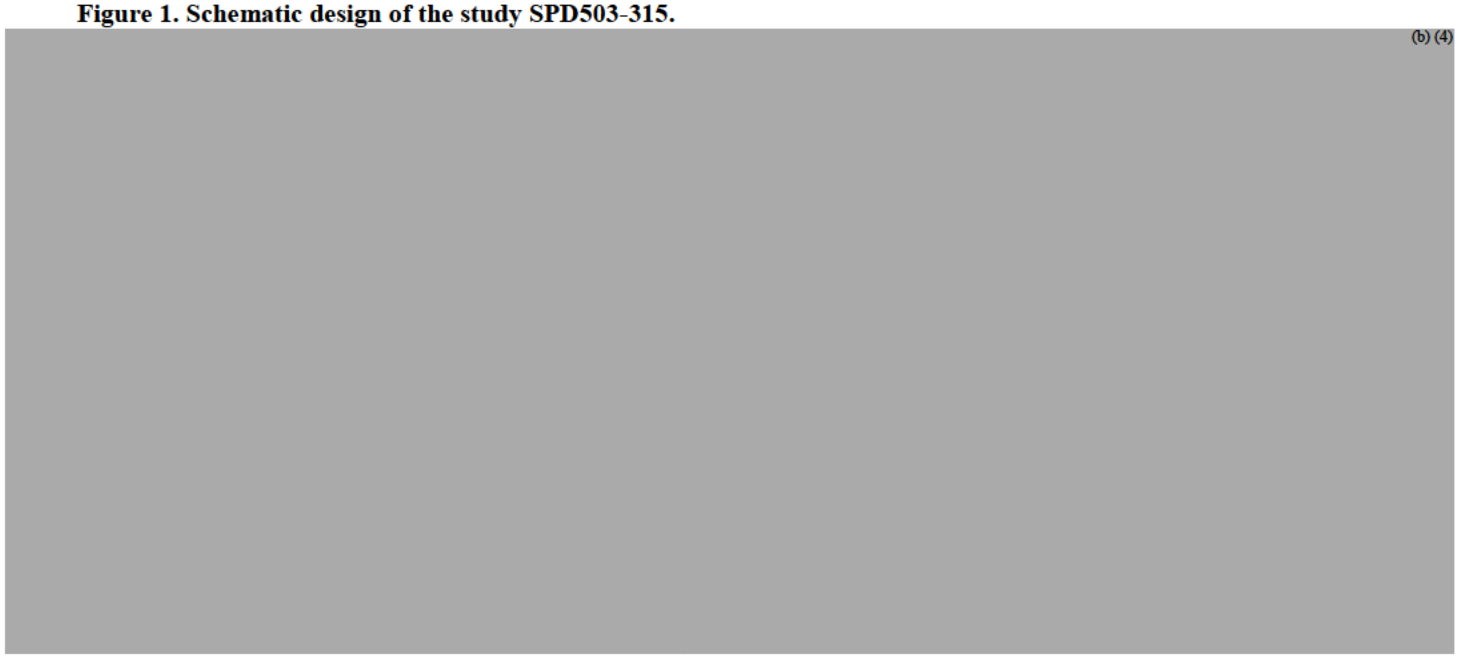
The *primary objective* of the study SPD503-315 was to evaluate the long-term efficacy of SPD503 as a maintenance treatment in children and adolescents (6-17 years old) with attention deficit hyperactivity disorder (ADHD) who respond to an initial open-label, short-term treatment with SPD503. The *key secondary objective* was to assess the time to treatment failure of SPD503 during the double-blind randomized-withdrawal phase.

3.2.1 Study Design and Endpoints

This was a phase 3, multicenter, international, double-blind, placebo-controlled, randomized-withdrawal, long-term maintenance study designed to assess the efficacy, safety, and tolerability of once-daily dosing with optimized SPD503 (Guanfacine Hydrochloride) in male and female children and adolescents aged 6-17 years with a diagnosis of ADHD.

The study started with a 7-week open-label optimization period to allow subjects to titrate to their optimal dose (1–7 mg), with 1 dose reduction permitted, if necessary. On completion of the open-label optimization period, all subjects entered a 6-week open-label maintenance period (at the optimal dose) and returned to the site for weekly or biweekly visits. Subjects who met the protocol-defined response criteria at both Visit 12/Week 12 and Visit 13/Week 13 were entered into a 26-week (6 months) double-blind randomized-withdrawal phase. At the Visit 13/Week 13 (Baseline) the eligible subjects were randomized using a 1:1 ratio to either continue on their optimized dose of SPD503 or switch to matching placebo, stratified within each country and age group (6-12 years and 13-17 years). Subjects who entered the double-blind phase were given a 2-week blinded taper during Weeks 14 and 15. The schematic study design is shown in Figure 1.

Figure 1. Schematic design of the study SPD503-315.



Source: The sponsor's SAP for SPD503-315 (pg. 8, Fig. 1)

The *primary efficacy endpoint* was treatment failure ('yes' or 'no') after the double-blind phase (Visit 23/Week 39). The *treatment failure* was set to 'yes' if a subject met the following criteria at two consecutive visits:

- a ≥ 50% increase in ADHD-RS-IV total score compared to their ADHD-RS-IV total score at the baseline visit), and
- a ≥ 2-point increase in CGI-S score relative to their CGI-S score at the baseline visit.

Subjects who met these criteria were regarded as treatment failures regardless of whether they were withdrawn. All subjects who discontinued the study for any reason were also regarded as treatment failures for the primary analysis.

An alternative definition of treatment failure – the *sensitivity definition* was also defined by the sponsor in order to perform a sensitivity analysis. For this alternative definition, the subject will be considered a treatment failure if any of the following are met:

1. Treatment failure criteria met at 2 consecutive visits, or
2. Reason for discontinuation is "Treatment failure criteria met", or
3. Treatment failure criteria met at 1 visit, and discontinued due to "Lack of efficacy" at that visit or subject had no further visit, or
4. Treatment failure criteria met at 1 visit and then discontinued due to "Lack of efficacy" at the next visit without further efficacy assessments.

The *key secondary endpoint* was the time to treatment failure (days) measured during the double blind randomized withdrawal phase (from Visit 13/Week 13 to Visit 23/Week 39/ET).

In the advice/information request letter sent to the sponsor by email communication on 03/11/2011 regarding the protocol SPD503-315 (IND 63,551) FDA had commented that (b) (4)

3.2.2 Statistical Methodologies

In the Statistical Analysis Plan (SAP) the sponsor pre-specified that the primary efficacy endpoint (treatment failure rates) will be analyzed using a *Cochran-Mantel-Haenszel (CMH) test* stratified by age group (6-12 and 13-17 years) and country. The null hypothesis stating that there is no difference in treatment failure rates between SPD503 and placebo will be tested at the 0.05 significance level with the 2-sided alternative of a non-zero difference between groups.

The key secondary endpoint (time to treatment failure) for all randomized subjects will be analysed using a *logrank test* stratified by age group and country. The null hypothesis states that there is no difference in time to treatment failure (days) between SPD503 and placebo. The Kaplan-Meier estimates of treatment failure rates will be presented for each treatment group, and median and upper and lower quartiles for the time to treatment failure and associated 95% confidence intervals will also be presented for each treatment group.

To control the overall Type I Error, pre-specified at a 2-sided 0.05 significance level, the primary and key secondary endpoints will be tested using a hierarchical testing structure. The primary efficacy variable will be assessed first at the 0.05 significance level. Only if that is significant the key secondary endpoint will be tested at the 0.05 level for confirmatory purposes. If the null hypothesis for the primary analysis is not rejected in favor of the corresponding alternative hypothesis at the 0.05 level, the key secondary efficacy test will be reported as non-significant for confirmatory purposes.

According to the SAP the primary efficacy analysis should be conducted over the randomized Full Analysis Set (FAS) using the data from the double-blind randomized-withdrawal phase (visits between 13 and 23), regardless of whether investigational product was stopped prior to the visit. The primary analysis will also be repeated as a *sensitivity analysis* using an alternative definition of treatment failure – the *sensitivity definition*.

In the IND 63,551 SN 139/SDN 391 (10/05/2012) the sponsor reported an incidence of GCP noncompliance during the 09/28/2012 site monitoring visit to site 801 (b) (4) The sponsor took appropriate actions to discontinue subjects and to close the study at site 801. On 29th November 2012 the decision was made by the sponsor to exclude the subjects enrolled at site 801 from the Full Analysis Sets. The Enrolled Subjects and the Safety Populations include

subjects enrolled at site 801. No statistical review of the aforementioned serial (SN 139/SDN 391) was performed, and no comments were conveyed to the sponsor at that time. To investigate the exclusion of data from site 801, (b) (4)

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients' disposition between the treated arms is presented in Table 2. The randomized FAS contains subjects who took at least 1 dose of investigational product during the randomized-withdrawal phase. The sponsor excluded the site 801 (14 randomized subjects) from the randomized FAS.

Table 2. Patients' disposition between the treatment arms.

	SPD503 N (%)	Placebo N (%)	Total N (%)
All Randomized	157 (100.0)	159 (100.0)	316 (100)
Randomized Safety Population	157 (100.0)	158 (99.4)	315 (99.7)
Randomized FAS	150 (95.5)	151 (95.0)	301 (95.3)
Early Termination (Safety Population)	81 (51.6)	106 (66.7)	187 (59.2)
due to			
Adverse Event	3 (1.9)	2 (1.3)	5 (1.6)
Protocol Violation	1 (0.6)	0	1 (0.3)
Subject's withdrawal	10 (6.4)	8 (5.0)	18 (5.7)
Lost to follow up	3 (1.9)	2 (1.3)	5 (1.6)
Lack of efficacy	13 (8.3)	20 (12.6)	33 (10.4)
Treatment failure criteria met	47 (29.9)	71 (44.7)	118 (37.3)
Other	4 (2.5)	3 (1.9)	7 (2.2)

Source: Table 1.1.5, Clinical Study Report of the SPD503-315, Amendment 1 (pg. 195).

The disposition of the early termination reasons among the patients from the randomized FAS is presented in Table 3.

Table 3. Disposition of the patients' reasons for early termination by treatment arm (Randomized FAS with site 801 excluded).

	SPD503 N (%)	Placebo N (%)	Total N (%)
Randomized FAS	150	151	301
Early Termination (Randomized FAS)	74	98	172
due to			
Adverse Event	3	1	4
Protocol Violation	1	0	1
Subject's withdrawal	10	8	18
Lost to follow up	3	1	4
Lack of efficacy	12	19	31
Treatment failure criteria met	44	68	112
Other	1	1	2

Source: computed by the reviewer.

The demographic and baseline characteristics are summarized in the Table 4.

Table 4. Demographic characteristics of the patients (Randomized FAS with site 801 excluded).

	SPD503 N = 150	Placebo N = 151	Total N = 301
Age *years*			
Mean (SD)	10.6 (2.64)	11.0 (2.68)	10.8 (2.66)
Min – Max	6 – 17	6 – 17	6 – 17
Age Group			
6 – 12 years	113 (75.3)	113 (74.8)	226 (75.1)
13 – 17 years	37 (24.7)	38 (25.2)	75 (24.9)
Gender *n (%)*			
Female	37 (24.7)	40 (26.5)	77 (25.6)
Male	113 (75.3)	111(73.5)	224 (74.4)
Ethnicity *n (%)*			
Hispanic/Latino	18 (12.0)	26 (17.2)	44 (14.6)
Not Hispanic/Latino	128 (85.3)	121 (80.1)	249 (82.7)
Missing / not specified	4 (2.7)	4 (2.6)	8 (2.7)
Race *n (%)*			
Asian	3 (2.0)	2 (1.3)	5 (1.7)
American Indian / Alaska Native	0	1 (0.7)	1 (0.3)
Black / African American	22 (14.7)	24 (15.9)	46 (15.3)
Native Hawaiian / Pacific Islander	0	1 (0.7)	1 (0.3)
White	113 (75.3)	118 (78.1)	231 (76.7)
Other	8 (5.3)	1 (0.7)	9 (3.0)
Missing / not specified	4 (2.7)	4 (2.6)	8 (2.7)
Height *cm*			
Mean (SD)	146.55 (16.11)	148.98 (15.77)	147.77 (15.96)
Min – Max	119.0 – 189.5	119.0 – 186.0	119.0 – 189.5
Weight *kg*			
Mean (SD)	41.39 (14.25)	43.47 (14.52)	42.43 (14.40)
Min – Max	25.0 – 90.5	25.0 – 90.0	25.0 – 90.5
Body Mass Index *kg/m^2*			
Mean (SD)	18.70 (2.84)	19.03 (3.07)	18.87 (2.96)
Min – Max	14.0 – 29.7	12.4 – 30.1	12.4 – 30.1

Source: Table 1.2.2.2, Clinical Study Report of the SPD503-315, Amendment 1 (pg. 276)

The SAP pre-specified that at least 40% of randomized subjects will come from European sites as requested by the EMA Pediatric Committee (PDCO) as part of their agreement to the Sponsor's Pediatric Investigational Plan (PIP). The remaining 60% were to come from North America (Canada and the United States) with at least 25% being adolescents aged 13-17 years, and at least 25% being females. The randomized FAS is consistent with the prespesified proportion. Most of the studied patients were males (74.4%), white (76.7%), and within the 6-12 years age range (75.1%). No remarkably unbalanced distributions of the patients were found between the SDP503 treatment and the placebo arms.

3.2.4 Sponsor's Results and Conclusions

The sponsor found a statistically significant difference (p-value = 0.006) between the SPD503 and placebo in reducing the treatment failure rate. The results of the sponsor's efficacy analysis (CMH test) are presented in the Table 5.

Table 5. Sponsor's results of the CMH test using primary treatment failure definition (Randomized FAS with site 801 excluded).

Treatment failure:	SPD503 N = 150	Placebo N = 151
Yes *n (%)*	74 (49.3)	98 (64.9)
No *n (%)*	76 (50.7)	53 (35.1)
Difference in treatment failures *(%)*	-15.6	
95% confidence interval	(-26.6, -4.5)	
p-value from CMH-test	0.006	

Source: Table 12, Clinical Study Report of the SPD503-315 (page 88).

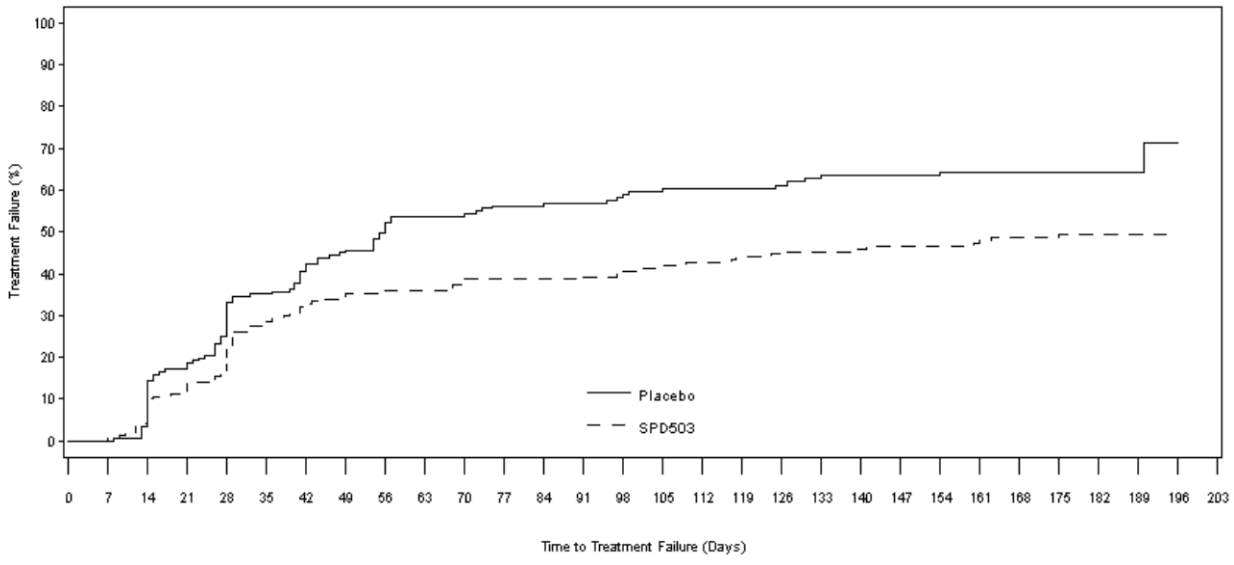
Following the hierarchical testing structure, after the primary efficacy endpoint was found statistically significant at the 0.05 significance level, the sponsor has tested the time to treatment failure using the logrank test at a 0.05 significance level. The result was statistically significant (p-value = 0.003) as presented in Table 6. The Kaplan-Meier estimates of the treatment failure rate (percent) over the time (days) are shown in Figure 2.

Table 6. Sponsor's results of the log-rank test using primary treatment failure definition (Randomized FAS with site 801 excluded).

	SPD503 N = 150	Placebo N = 151
Total number of treatment failures	74	98
Number of censored	76	53
Median time to treatment failure (days)	56.0	218.0
p-value from logrank test	0.003	

Source: Table 13, Clinical Study Report of the SPD503-315 (page 89).

Figure 2. Kaplan-Meier estimates of the proportions of patients with treatment failures (Randomized FAS with site 801 excluded, *n*=301).



Source: Figure 3.1.3.4 , Clinical Study Report of the SPD503-315 (pg. 4423).

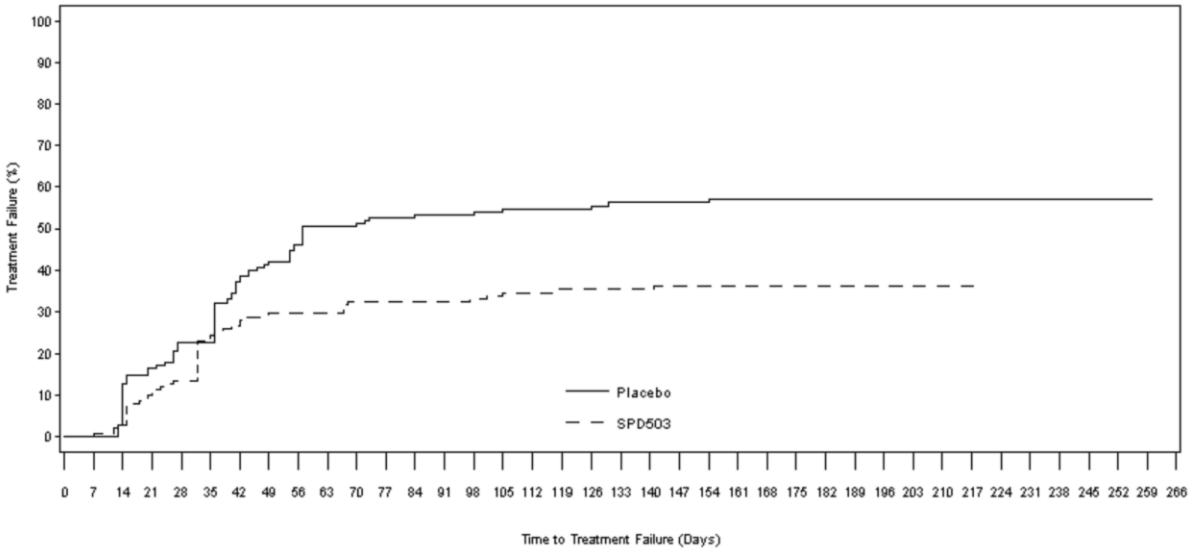
The results using the pre-specified sensitivity definition of the treatment failure were consistent with those using the primary definition (see Table 7 and Figure 3). Using this definition, not all patients who had early discontinuation were considered as having an event.

Table 7. Sponsor's results of the CMH test using the sensitivity definition of the treatment failure (Randomized FAS with site 801 excluded, *n*=301)

	SPD503 N = 150	**Placebo** N = 151
Treatment failure:		
Yes *n (%)*	53 (35.3)	83 (55.0)
No *n (%)*	97 (64.7)	68 (45.0)
Difference in treatment failures *(%)*	-19.6	
95% confidence interval	(-30.7, -8.6)	
p-value from CMH-test	<.001	

Source: Table 3.1.2.1, Clinical Study Report of the SPD503-315 (page 431).

Figure 3. Kaplan-Meier estimates of the proportions of patients with treatment failures using sensitivity definition (Randomized FAS with site 801 excluded, *n*=301)



Source: Figure 3.1.3.2, Clinical Study Report of the SPD503-315 (pg. 4421).

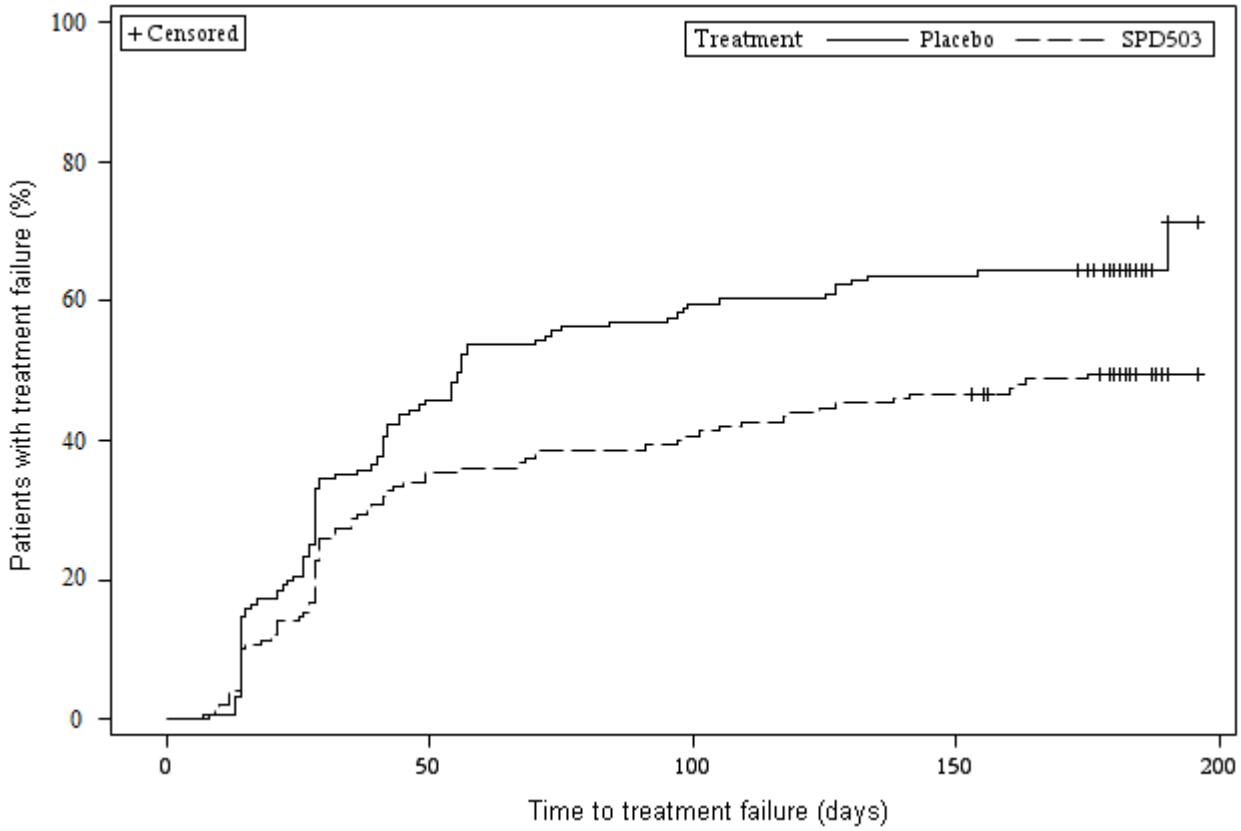
3.2.5 Reviewer's Results and Conclusions

The statistical reviewer confirmed the sponsor's analysis results as summarized in the preceding section. (b) (4)

(b) (4)

The reviewer's Kaplan-Meier cumulative probability of the treatment failure for SPD503 and placebo patients of the randomized FAS is presented in Figure 4. The plot shows the proportion of the patients (in each treatment arm) who had experienced a treatment failure by a given day after the randomization and also indicates the censored patients, which are not shown on the sponsor's plot (Figure 2). The examination of the Figure 2 and Figure 4 suggests that the curves corresponding to the SPD503 and placebo arms appear to be distinct during the 26 weeks double-blind withdrawal period starting in the early stage of the double-blind period.

Figure 4. Kaplan-Meier estimates of the treatment failure rates (Randomized FAS with site 801 excluded, *n*=301).



Source: computed by the reviewer.

The reviewer also performed the exploratory analysis of the Maximum Likelihood Estimate (MLE) of the hazard ratio (SPD503 vs. Placebo), stratified by age-group and country. The results of the analysis are presented in Table 8. The estimated hazard ratio and its 95% confidence interval imply that the patients in the SPD503 treatment arm were experiencing treatment failure at a lower rate than the patients in the placebo arm.

Table 8. Analysis of the MLE of the Hazard Ratio (Randomized FAS with site 801 excluded, *n*=301).

DF	Log-hazard ratio	Standard Error	Chi-Square	p-value	Hazard Ratio (SPD503 / Placebo)	95% Confidence Interval
1	-0.44848	0.15621	8.2423	0.0041	0.639	(0.470, 0.867)

Source: computed by the reviewer.

Regarding the subjects removal, our position is that all randomized patients, whether GCP-violation identified or not, should be included in the primary analysis set. Patients from GCP-violated sites should be excluded from the per-protocol analysis set instead of the primary analysis set. The reviewer repeated the efficacy analyses over the randomized *safety population* (randomized FAS including the 14 randomized subjects from site 801). The results are consistent with the sponsor's findings (see Table 10 and Figure 5). The estimated hazard ratio is in Table 9.

Table 9. Analysis of the MLE of the Hazard Ratio (safety population including site 801, *n*=315)

DF	Log-hazard Ratio	Standard Error	Chi-Square	p-value	Hazard Ratio (SPD503 / Placebo)	95% Confidence Interval
1	-0.43168	0.14988	8.2957	0.0040	0.649	(0.484, 0.871)

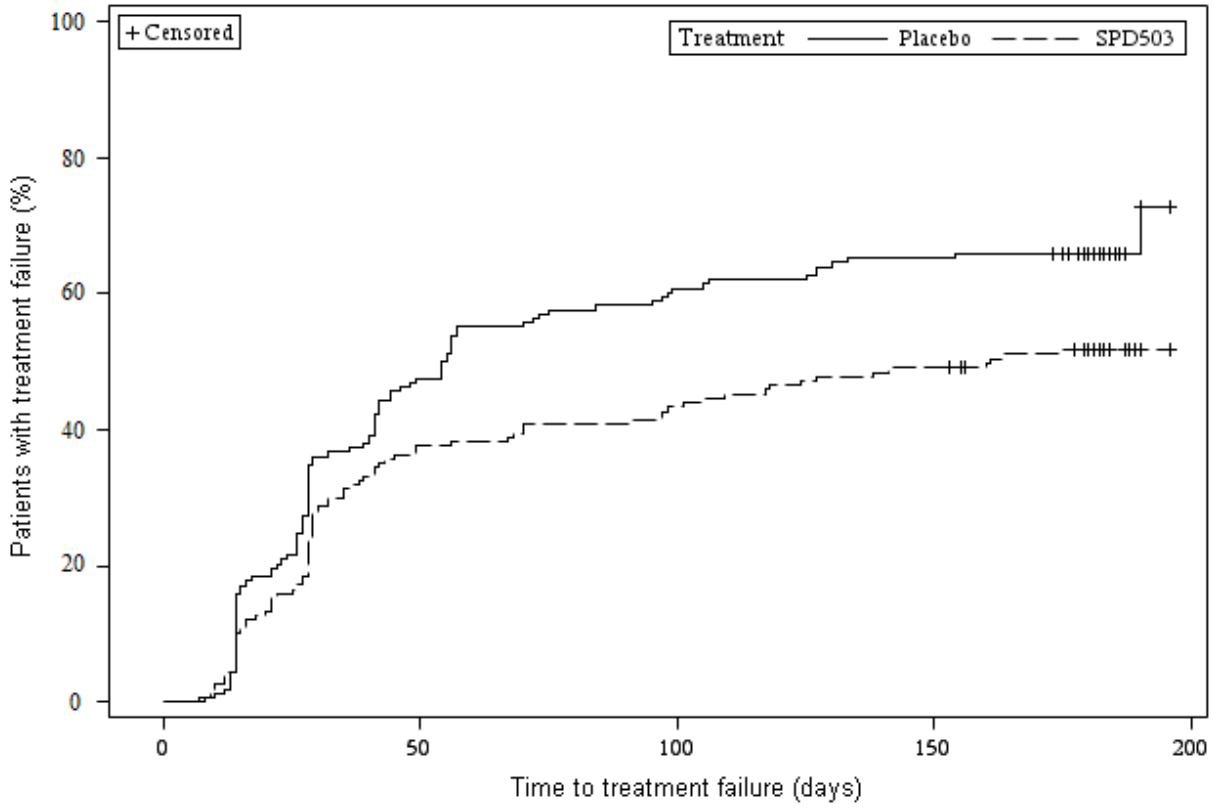
Source: computed by the reviewer.

Table 10. Summary of the treatment failure rates (safety population including site 801, *n*=315)

Treatment failure:	SPD503 N = 157	Placebo N = 158	Total N = 315
Yes *n (%)*	81 (51.6)	105 (66.5)	186 (59.0)
No *n (%)*	76 (48.4)	53 (33.5)	129 (41.0)

Source: Computed by the reviewer.

Figure 5. Kaplan Meier estimates of the treatment failure rates (safety population including site 801, *n*=315)



Source: computed by the reviewer.

Regarding the *sensitivity analyses*, the sponsor's provided results only over the FAS (with site 801 excluded; *n* = 301), see Table 7 and Figure 3. The reviewer verified the sponsor's results, and also

repeated these analyses over the randomized safety population (n = 315). The results of the logrank test and the hazard ratio analysis using the *sensitivity definition* of the treatment failure (i.e., subjects meeting the treatment failure criteria at 2 consecutive visits or at 1 visit and subject discontinued due to "lack of efficacy", and censor the other) over the randomized safety population are consistent with the primary endpoint definition (see Table 11,Table 12 and Figure 6).

Table 11. Analysis of the MLE of the Hazard Ratio using sensitivity definition (safety population including site 801, *n*=315)

DF	Log-hazard Ratio	Standard Error	Chi-Square	p-value	Hazard Ratio (SPD503 / Placebo)	95% Confidence Interval
1	-0.57396	0.17190	11.1485	0.0008	0.563	(0.402, 0.789)

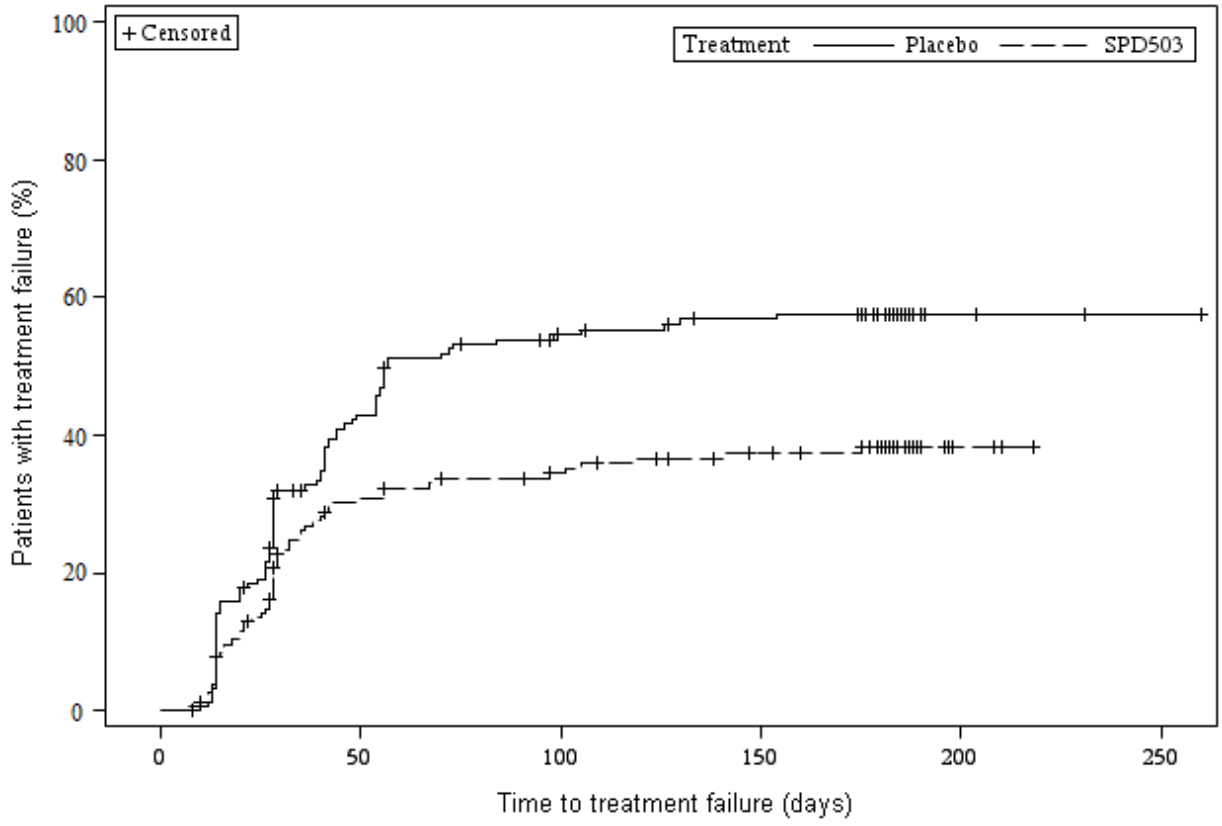
Source: computed by the reviewer.

Table 12. Summary of the treatment failure rates using sensitivity definition (safety population including site 801, *n*=315)

Treatment failure:	SPD503 N = 157	Placebo N = 158	Total N = 315
Yes *n (%)*	57 (36.3)	87 (55.1)	144 (45.7)
No *n (%)*	100 (63.7)	71 (44.9)	171 (54.3)

Source: Computed by the reviewer.

Figure 6. Kaplan-Meier estimates of the treatment failure rates using sensitivity definition (safety population including site 801, *n*=315)



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.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The reviewer performed exploratory analysis of the treatment failure rates for the following subgroups: gender, age category (children vs. adolescents), race/ethnicity, and geographical region using randomized *safety population*. The results are summarized in the Table 13.

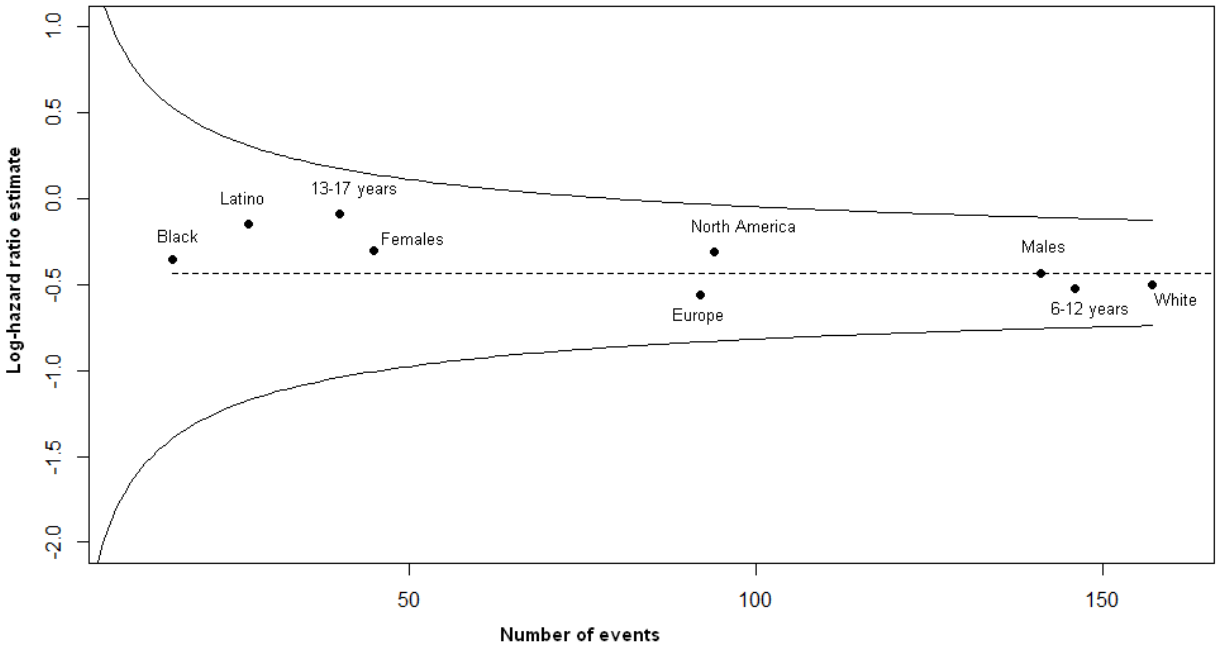
Table 13. Primary efficacy endpoint analyses (CMH test) by subgroup (safety population*, *n*=315)

	N	Treatment failure		SPD503-Placebo difference (%)
		SPD503	Placebo	
Gender				
Female	81	18 (46.2%)	27 (64.3%)	-18.1
Male	234	63 (53.4%)	78 (67.2%)	-13.8
Age Group				
6—12 years	235	62 (53.0%)	84 (71.2%)	-18.2
13—17 years	80	19 (47.5%)	21 (52.5%)	-5.0
Race/Ethnicity				
Asian	5	1 (33.3%)	1 (50.0%)	-16.7
Black/African American	46	7 (31.8%)	9 (37.5%)	-5.7
Hispanic / Latino	44	11 (61.1%)	16 (61.5%)	-0.4
White	244	67 (55.8%)	90 (72.6%)	-16.8
Geographic Region				
North America	172	43 (50.0%)	51 (59.3%)	-9.3
Europe	143	38 (53.5%)	54 (75.0%)	-21.5

* The subgroup analyses using randomized FAS (i.e., site 801 excluded) are presented in the Appendix Table 17.
Source: computed by the reviewer.

The time to treatment failure was also analyzed for each subgroup using Cox-proportional hazard analysis. The estimated hazard ratio and the 95% confidence intervals are presented in Table 14. The visual representation of the log-hazard ratios for the different subgroups with respect to the number of relapses are presented in a funnel plot on Figure 7. The funnel plot suggests that the subgroups with larger number of events result in estimates closer to the estimate of the entire population. The plot does not show clear outliers, and no visible systematic bias.

Figure 7. Funnel plot for the subgroups' log-hazard ratios to the number of events (safety population*)



*The funnel plot for subgroups over the randomized FAS (i.e., site 801 excluded) is presented in the Appendix Figure 9. Source: computed by the reviewer.

Table 14. Cox-proportional hazard analyses of the time to treatment failure by subgroup (safety population*, *n*=315)

	N	Treatment Failure		Hazard Ratio (SPD503/Placebo)	95% CI
		SPD503	Placebo		
Gender					
Female	81	18 (46.2%)	27 (64.3%)	0.738	(0.393, 1.388)
Male	234	63 (53.4%)	78 (67.2%)	0.648	(0.462, 0.909)
Age Group					
6—12 years	235	62 (53.0%)	84 (71.2%)	0.593	(0.426, 0.825)
13—17 years	80	19 (47.5%)	21 (52.5%)	0.919	(0.487, 1.733)
Race/Ethnicity					
Asian	5	1 (33.3%)	1 (50.0%)	-	-
Black/ African American	46	7 (31.8%)	9 (37.5%)	0.704	(0.261, 1.898)
Hispanic / Latino	44	11 (61.1%)	16 (61.5%)	0.861	(0.378, 1.965)
White	244	67 (55.8%)	90 (72.6%)	0.606	(0.438, 0.837)
Geographic Region					
North America	172	43 (50.0%)	51 (59.3%)	0.735	(0.488, 1.105)
Europe	143	38 (53.5%)	54 (75.0%)	0.570	(0.373, 0.871)

* The subgroup analyses using randomized FAS (i.e., site 801 excluded) are presented in the Appendix Table 18. Source: computed by the reviewer.

The results of the exploratory subgroup analyses suggest numerically consistent trend across the subgroups except for the age groups, where the effect seems to be mainly driven by 6—12 years old children, which accounted approximately 75% of the study population. The reviewer explored the distribution of the weight adjusted dose received by the patients randomized to the SPD503 arm during the randomized withdrawal phase, which is presented in Table 15. The summary of the SPD503 doses received by the each age group is presented in Table 16.

Table 15. Summary of the weight adjusted dose categories by age group (Safety population*, SPD503 arm)

Age Group	Weight Adjusted Dose Category (mg/kg)				Total
	0.01 – 0.04	0.05 – 0.08	0.09 – 0.12	0.13 – 0.16	
6—12 years	8	40	51	18	117
13—17 years	5	20	15	0	40
Total	13	60	66	18	157

* The summary of the weight adjusted dose categories in the FAS (i.e., site 801 excluded) is presented in the Appendix Table 19. Source: computed by the reviewer.

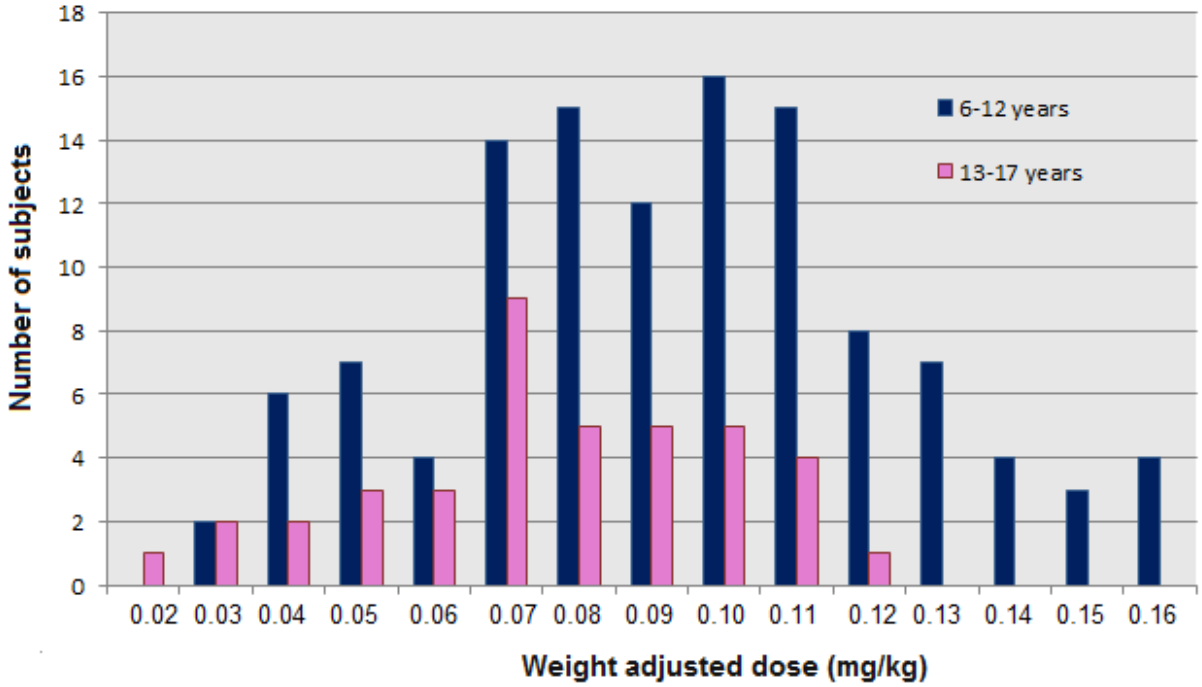
Table 16. Summary of the SPD503 dose received by each age group (Safety population*, SPD503 arm)

Age Group	Dose of the SPD503 received during the randomized withdrawal phase							Total
	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg	
6—12 years	6	17	42	52	0	0	0	117
13—17 years	0	2	10	10	13	4	1	40
Total	6	19	52	62	13	4	1	157

* The summary of the SPD503 dose by weight category in the FAS (i.e., site 801 excluded) is presented in the Appendix Table 20. Source: computed by the reviewer.

The distributions of the weight adjusted doses assigned to the patients in the two age groups are shown graphically in Figure 8.

Figure 8. Distribution of the weight adjusted dose of SPD503 for children and adolescents (safety population*, SPD503 arm)



* The summary of the SPD503 dose by weight category in the FAS (i.e., site 801 excluded) is presented in the Appendix Figure 10. Source: computed by the reviewer.

The sponsor claims that the doses of SPD503 chosen for this study were designed to allow all subjects (children aged 6-12 years and adolescents aged 13-17 years) the opportunity to receive mg/kg doses within the efficacious range identified in the short-term pivotal studies described

above (0.05mg/kg to 0.12 mg/kg). The Table 15 and Figure 8, however, show that the weight-adjusted doses for the adolescent subjects (13-17 years) were overall slightly lower than for the children subjects. This may potentially explain the smaller treatment effect observed in the adolescent subgroup.

4.2 Other Special/Subgroup Populations

No other subgroup analyses were explored.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The observed treatment effect in the adolescents' subgroup was relatively small, which might be due to the generally lower weight-adjusted doses received by these patients.

It is not preferable to [redacted] (b) (4) . The comparison of time-to treatment-failure seems to be able to provide more information.

All randomized patients should be included in the primary efficacy analysis set regardless of their identified GCP-violations.

5.2 Collective Evidence

There was only one study reviewed in this submission. Based on the statistical analysis results of the study SPD530-315, the reviewer confirms sponsor's findings that INTUNIV® (Guanfacine hydrochloride) was statistically significantly superior to placebo as a maintenance treatment in children and adolescents (6-17 years old) with attention deficit hyperactivity disorder, as measured by the time to treatment failure during the randomized withdrawal trial.

5.3 Conclusions and Recommendations

The statistical results of the study provide adequate evidence that INTUNIV® (1 – 7 mg) prolongs the time to treatment failure as compared with placebo in pediatric patients with ADHD. From the statistical perspective, the study SPD503-312 fulfills the Postmarketing Requirement 1538-1.

APPENDIX (SUBGROUP ANALYSES OF THE SAFETY POPULATION)

Table 17. Primary efficacy endpoint analyses (CMH test) by subgroup (Randomized FAS with site 801 excluded, *n*=301)

	N	Treatment failure		SPD503-Placebo difference (%)
		SPD503	Placebo	
Gender				
Female	77	16 (43.2%)	25 (62.5%)	-19.3
Male	224	58 (51.3%)	73 (65.8%)	-14.5
Age Group				
6—12 years	226	58 (51.3%)	79 (69.9%)	-18.6
13—17 years	75	16 (43.2%)	19 (50.0%)	-6.8
Race/Ethnicity				
Asian	5	1 (33.3%)	1 (50.0%)	-16.7
Black/African American	46	7 (31.8%)	9 (37.5%)	-5.7
Hispanic / Latino	44	11 (61.1%)	16 (61.5%)	-0.4
White	231	60 (53.1%)	84 (71.2%)	-18.1
Geographic Region				
North America	172	43 (50.0%)	51 (59.3%)	-9.3
Europe	129	31 (48.4%)	47 (72.3%)	-23.9

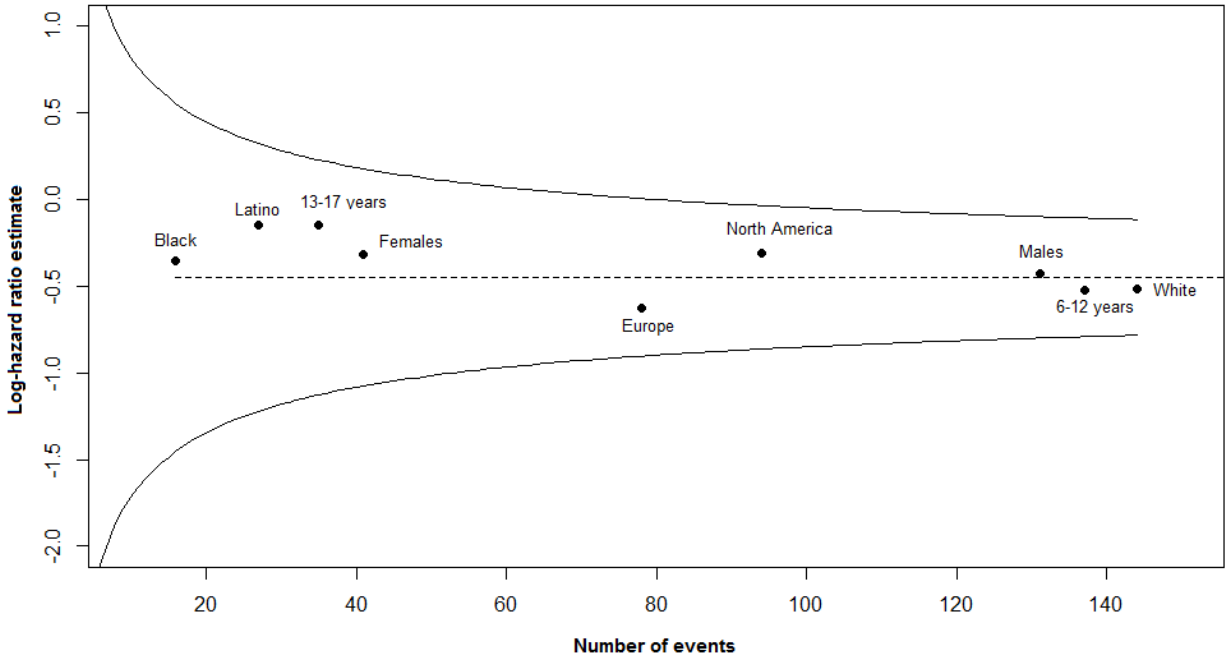
Source: computed by the reviewer.

Table 18. Cox-proportional hazard analyses of the time to treatment failure by subgroup (Randomized FAS with site 801 excluded, *n*=301)

	N	Treatment failure		Hazard Ratio (SPD503/Placebo)	95% CI
		SPD503	Placebo		
Gender					
Female	77	16 (43.2%)	25 (62.5%)	0.728	(0.374, 1.417)
Male	224	58 (51.3%)	73 (65.8%)	0.653	(0.460, 0.928)
Age Group					
6—12 years	226	58 (51.3%)	79 (69.9%)	0.593	(0.421, 0.835)
13—17 years	75	16 (43.2%)	19 (50.0%)	0.864	(0.437, 1.709)
Race/Ethnicity					
Asian	5	1 (33.3%)	1 (50.0%)	-	-
Black/ African American	46	7 (31.8%)	9 (37.5%)	0.704	(0.261, 1.898)
Hispanic / Latino	44	11 (61.1%)	16 (61.5%)	0.861	(0.378, 1.965)
White	231	60 (53.1%)	84 (71.2%)	0.598	(0.426, 0.840)
Geographic Region					
North America	172	43 (50.0%)	51 (59.3%)	0.735	(0.488, 1.105)
Europe	129	31 (48.4%)	47 (72.3%)	0.534	(0.335, 0.851)

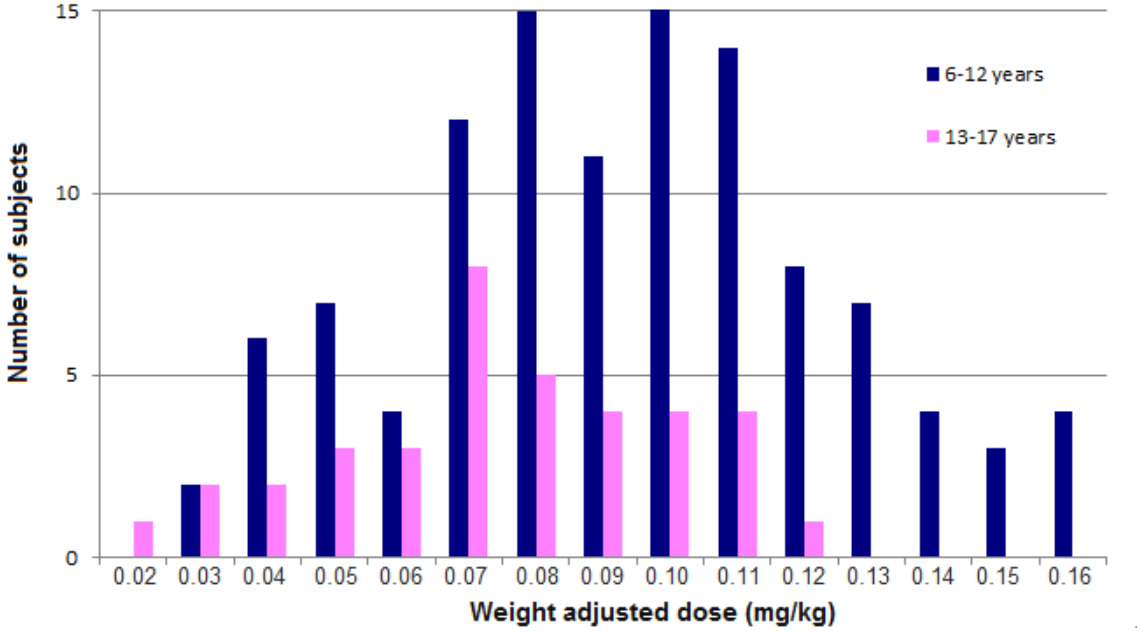
Source: computed by the reviewer.

Figure 9. Funnel plot for the subgroups' log-hazard ratios to the number of events (Randomized FAS with site 801 excluded, *n*=301)



Source: computed by the reviewer.

Figure 10. Distribution of the weight-adjusted dose of SPD503 for children and adolescents (Randomized FAS with site 801 excluded, SPD503 arm)



Source: computed by the reviewer.

Table 19. Summary of the weight-adjusted dose categories by age group (Randomized FAS with site 801 excluded, SPD503 arm)

Age Group	Weight Adjusted Dose Category (mg/kg)				Total
	0.01 – 0.04	0.05 – 0.08	0.09 – 0.12	0.13 – 0.16	
6—12 years	8	38	49	18	113
13—17 years	5	19	13	0	37
Total	13	57	62	18	150

Source: computed by the reviewer.

Table 20. Summary of the SPD503 dose received by each weight group (Randomized FAS with site 801 excluded, SPD503 arm)

	Dose of the SPD503 received during the randomized withdrawal phase							
Age Group	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg	Total
6—12 years	6	16	40	51	0	0	0	113
13—17 years	0	2	10	9	11	4	1	37
Total	6	18	50	60	11	4	1	150

Source: computed by the reviewer.

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/s/

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02/11/2015

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