CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	022037/Supplement 011
Priority or Standard	Standard
Submit Date(s)	04/22/2014
Labeling Due Date(s)	02/26/2015
PDUFA Goal Date	03/19/2015
Division / Office	DPP/ODE1
Reviewer Name(s)	Aeva Gaymon-Doomes, MD
Review Completion Date	02/24/2015
Established Name	Guanfacine Extended-Release
(Proposed) Trade Name	Intuniv®
Therapeutic Class	Selective α_2 Agonist
Applicant	Shire Development, Inc.
Formulation(s)	Extended-release Tablets
Dosing Regimen	1- 4 mg for children and 1-7mg for adolescents, Once Daily
Indication(s)	Monotherapy for maintenance treatment of Attention Deficit Hyperactivity Disorder
Intended Population(s)	Children (Ages 6-12 Years) and Adolescents (Ages 13-17 Years)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This sNDA, 022037/Supplement 011, is supported by Study SPD503-315.
The study was a Phase 3, Double-blind, Placebo-controlled, Multicenter, Randomized-withdrawal, Long-term Maintenance of Efficacy and Safety Study of Extended-release Guanfacine Hydrochloride in Children and Adolescents Aged 6-17 with Attention Deficit Hyperactivity Disorder (ADHD).

Based on the available data obtained from this study, in which both long-term maintenance of efficacy and safety have been demonstrated, we recommend an approval of this sNDA.

1.2 Risk Benefit Assessment

The long-term maintenance of efficacy and safety of once daily dosing with SPD503 in pediatric patients with a diagnosis of ADHD was demonstrated by the positive results from Study SPD503-315.

The safety evaluation demonstrated that the long term safety profile of once daily dosing of SPD503 in pediatric patients with ADHD was similar to what has been labeled.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This review did not identify any new major risks that would merit a Risk Evaluation and Mitigation Strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

No additional post-marketing studies are deemed necessary.

2 Introduction and Regulatory Background

2.1 Product Information

SPD503, an extended-release (ER) formulation of guanfacine, is a selective alpha-2A-adrenergic receptor agonist. It is commercially marketed in the United States (US) under the proprietary name Intuniv. It is currently available in 4 ER tablets: 1 mg, 2 mg, 3 mg and 4 mg designed for once daily in children and adolescents with ADHD.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following is a list of drugs approved under NDAs to treat ADHD:
Stimulants:

1. Adderall (mixed salts amphetamine) Tablets
2. Adderall XR (mixed salts amphetamine) Extended-Release Capsules
3. Concerta (methylphenidate hydrochloride) Extended-Release Tablets
4. Daytrana (methylphenidate) Transdermal System
5. Desoxyn (methamphetamine) Tablets
6. Dexedrine (dextroamphetamine sulfate) Capsules
7. Dexedrine (dextroamphetamine sulfate) Spansules
8. Dexedrine (dextroamphetamine sulfate) Tablets
9. Focalin (dexmethylphenidate HCl)
10. Focalin XR (dexmethylphenidate HCl)
11. Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
12. Metadate ER (methylphenidate hydrochloride) Extended-Release Tablets (ANDA)
13. Methylin (methylphenidate hydrochloride) Chewable Tablets
14. Methylin (methylphenidate hydrochloride) Oral Solution
15. Quillivant XR (methyphenidate HCl) Oral Solution
16. Ritalin (methylphenidate hydrochloride) Tablets
17. Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
18. Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
19. Vyvanse (Lisdexamfetamine Dimesylate: a pro-drug of amphetamine) Capsules

Non-stimulants:

1. Kapvay (clonidine) Extended-Release Tablets
2. Stratterra (atomoxetine HCl) Capsules
3. Intuniv (guanfacine) Extended-Release Tablets

2.3 Availability of Proposed Active Ingredient in the United States

Guanfacine is currently approved and marketed in the U.S. for the treatment of hypertension. Intuniv is an approved drug in the U.S. for the treatment of ADHD.

2.4 Important Safety Issues With Consideration to Related Drugs

There are two central α2 adrenergic receptor agonists that are approved by FDA for the treatment of ADHD, Kapvay (clonidine extended-release tablet) and Intuniv (guanfacine extended-release tablet).

The most common adverse events (AEs) reported with central α2 adrenergic receptor agonists are dry mouth and sedation. Other common AEs include orthostasis, hypotension, bradycardia, dizziness, fatigue, weakness, nausea, vomiting, constipation, sexual dysfunction, headache, withdrawal syndrome, nervousness, agitation, and weight gain. In overdose with central α2 adrenergic receptor agonists, patients may have a decreased level of consciousness, miosis, bradycardia, hypotension, respiratory depression, and hypotonia. CNS depression may range from drowsiness to coma. Respiratory depression, intermittent apnea, and bradycardia are relatively common in children.

With an overdose of central α2 adrenergic receptor agonists the frequency of CNS depression may be higher in children than in adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmia, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

08/03/2005: Based on FDA's preliminary view of the pivotal data, it was noted that the Pediatric Written Request might include one or more of the following studies:

- Adolescent ADHD study, since the preliminary pivotal data in this group is difficult to interpret.
- Combined use of Intuniv with stimulants, since alpha-2 agonists are often used with stimulants in ADHD treatment
- Placebo-controlled evening vs. morning dosing study (mono- or adjunctive -therapy), since guanfacine immediate-release is used mostly in the evening as an adjunctive therapy to stimulants during the day.
- A randomized withdrawal study to evaluate long-term efficacy

08/24/2006: Shire submitted an NDA (22037) for use of guanfacine ER for the treatment of ADHD in pediatric population based on results from 2 short-term placebo-controlled monotherapy studies (Studies 301 & 304).

09/02/2009 – Approval (NDA 22037): Guanfacine ER tablet (Intuniv) was approved as monotherapy in children and adolescents aged 6-17 years with the following post marketing requirements:

1. A long-term maintenance study of efficacy and safety of Intuniv as monotherapy in children and adolescents with ADHD
2. An efficacy and safety study of Intuniv in adolescents.
3. An efficacy and safety study of Intuniv as adjunctive treatment with oral psycho- stimulants
4. A cardiac toxicity study in rats
5. A reproductive toxicity assessment in juvenile rats

02/25/2011- Approval (NDA 22037/S-002): Intuniv was approved as adjunctive therapy to psychostimulants in children and adolescents aged 6-17 years.

02/20/2013: Approval (NDA 22037/S-08): the supplement NDA for changes of labeling to inform practitioners that Intuniv can be taken once daily, either in the morning or evening was proved.

11/19/2014: Approval (NDA 22037/S-10): Intuniv was approved for once daily dosing of up to 4mg per day in children ages 6-12 years, and up to 7mg per day in adolescents ages 13-17 years with a diagnosis of ADHD.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Adverse event safety data were audited for completeness and accuracy in a 5% sample (N=2) of submitted Case Report Forms (CRFs). The adverse events from the CRF for these subjects (Subject Identifier 103-0003 and Subject Identifier 801-0016) were compared to those in the narrative summary in the study body report and those listed in Adverse Event listings. No deficiencies or discrepancies were noted.

Two study sites were inspected. These sites had relatively higher enrollments. 20 subjects were enrolled in the study site of Dr. Michael McManus (Study SPD503-315), and 20 subjects were enrolled in the study site of Dr. Louise Thurman (Study SPD503-315). The clinical inspection summary was completed on October 22, 2014 by the Office of Scientific Investigations and no significant deficiencies were observed and a Form FDA 483 was not issued.

3.2 Compliance with Good Clinical Practices

Study SPD503-315 was conducted in accordance with International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) and local ethical and legal requirements, and with the Declaration of Helsinki, according to the sponsor.

3.3 Financial Disclosures

All clinical investigators except (b) (4) in Study SPD503-315 claimed nothing to disclose. The investigator who disclosed financial arrangements by the sponsor addressed the potential conflict of interest on the SPD503-315 study by claiming that he was not part of the protocol design; not be privy to the blinded status of subjects and he would not write up publications without peer review. Furthermore, this investigators site only entered (b) (4) subjects. A total of 316 subjects were randomized in Study SPD503-315. Since the number of subjects enrolled by this investigator was relatively small and since Study SPD503-315 used a randomized, double- blind design, it seems unlikely that these financial arrangements would have biased the overall efficacy results of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no CMC information provided in this submission.

4.2 Clinical Microbiology

No clinical microbiology study was submitted in this submission.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology study was submitted to this sNDA.

4.4 Clinical Pharmacology

No new PK/PD or drug-drug interaction study was submitted to this sNDA.

4.4.1 Mechanism of Action

SPD503 is a non-stimulant medication with a novel mechanism of action, (b) (4)

Approved pharmacotherapeutic agent approved for ADHD that is a selective α_{2A}-adrenergic agonist.

4.4.2 Pharmacodynamics

Guanfacine is a selective central alpha2A-adrenergic receptor agonist in that it has a 15-20 times higher affinity for this receptor subtype than for the alpha2B or alpha2C subtypes.

Guanfacine is a known antihypertensive agent. By stimulating central alpha2A-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

In a thorough QT study, the administration of two dose levels of immediate-release guanfacine (4 mg and 8 mg) produced concentrations approximately 2 to 4 times the concentrations observed with the maximum recommended dose of INTUNIV® of 0.12 mg/kg. Guanfacine was not shown to prolong the QTc interval to any clinically relevant extent.

4.4.3 Pharmacokinetics

As listed in the label, exposure to guanfacine was higher in children (ages 6-12) compared to adolescents (ages 13-17) and adults. After oral administration of multiple doses of INTUNIV® 4 mg, the Cmax was 10 ng/mL compared to 7 ng/mL and the AUC was 162 ng h/mL compared to 116 ng h/mL in children (ages 6-12) and adolescents (ages 13-17), respectively. These differences are probably attributable to the lower body weight of children compared to adolescents and adults.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This submission includes 1 study: **Study SPD503-315**.

Study SPD503-315 was intended to satisfy post marketing requirement (PMR) 1538-1 (a deferred pediatric study under Pediatric Research Equity Act (PREA) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17). It was a Phase 3, double-blind, randomized-withdrawal, long-term maintenance, multicenter, placebo- controlled study.

The following table summarizes this study.

Table 1: Summary of the ADHD Studies in Children and Adolescents: SPD503-315

Study SPD503-315	
Number of Study Sites	26 sites in the US, 3 sites in Canada, and 38 sites in Europe
Study Dates	05/11/2010 – 06/03/2013
Study Design	Randomized-withdrawal, multicenter, long-term maintenance, double-blind, placebo-controlled study to evaluate the safety, efficacy and tolerability of once-daily dosing of SPD503 when given at doses up to 4mg (dosed once daily), in children aged 6-12 and given at doses up to 7mg (dosed daily), in adolescents aged 13-17 years with ADHD.
Study Drugs	SPD503 (guanfacine HCl ER)
Randomized/Treated	316/315
Gender/Mean Age (years)	Male (74.3%) female (25.7%)/mean age: 10.8 (6-17)
Endpoints Primary Key Secondary	 Proportion of patients relapse ≥ 50% increase (worsening) in ADHD-RS-IV total score and a ≥ 2 point increase in CGI-I as compared to the respective scores at the double-blind baseline visit (week 13), at two consecutive visits.

5.2 Review Strategy

I have reviewed the Clinical Study Report (CSR) of Study SPD503-315, clinical overview, proposed labeling, financial disclosure certification, audit certificate, patent certification, case report forms, dataset file, debarment certification and exclusivity request.

Dr. Andrejus Parfionovas is a statistical reviewer for the **efficacy analyses**. Please refer his review for detailed information in efficacy analyses and conclusion.

Dr. John Lee is the author of the **clinical inspection summary**; please refer to that review for detailed information concerning the clinical inspection report.

5.3 Discussion of Individual Studies/Clinical Trials

This submission relies solely on the data from one randomized-withdrawal long-term maintenance study, namely **study SPD503-315.**

Study SPD503-315 (referred to as study 315 in this review) assessed the long-term maintenance of efficacy and safety of once daily dosing, monotherapy of SPD503

compared to placebo in the treatment of ADHD in children aged 6-17 years. Please see the table 1 above of study 315 which is divided into the following two dosing phases (Open-label Phase and Double-blind Randomized-withdrawal Phase) and six periods.

1. Screening and Enrollment: 3-35 days
   Open-label Phase:
2. Optimization Period: 7 weeks
3. Open-label Maintenance Period: all subjects who completed the Dose-optimization Period entered the 6-week Dose-maintenance Period at their optimal SPD503 dose.
   Double-blind Randomized-withdrawal Phase:
4. Double-blind Maintenance Period: 26 weeks of treatment with optimized dose of SPD503 or matching placebo (randomized 1:1)
5. Double-blind Dose Tapering Period: 2 weeks
6. Follow-up: 1 week after the last dose of the investigational product

The study started with a 7-week Open-label Optimization Period to allow subjects to titrate to their optimal dose, with 1 dose reduction permitted, if necessary. During the Open-label Phase (Phase 1) all subjects initially received 1mg/day of SPD503, starting the morning after Visit 2/Week 0 (Open-label Baseline Visit). **The maximum dose was 4mg/day for children aged 6-12 years, and 4-7mg/day for adolescents aged 13-17 years depending on the subject's weight.**

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 Weeks 12 and 13 (Visits 12/Week 12 and 13/Week 13) entered into a 26-week (6-month), Double-blind Randomized-withdrawal Phase.

The response criteria were defined as a reduction of at least 30% from the Open-label Baseline Visit (Visit 2/Week 0) in the ADHD-RS-IV total score and a CGI-S score of 1 or 2 with tolerable side effects.

At the Double-blind Baseline Visit (Visit 13/Week 13), eligible subjects were randomized using a 1:1 ratio to either continue on their optimized dose of SPD503 or switch to matching placebo, which was maintained for 26 weeks. Allocation of treatment was balanced within each country and for age group (6-12 years versus 13-17 years).

Subjects who entered the Double-blind Randomized-withdrawal Phase were given a 2-week blinded taper during Weeks 14 and 15.

A subject who met the following treatment failure criteria at 2 consecutive visits during the Double-blind Randomized-withdrawal Phase was discontinued immediately from the study and was considered a treatment failure.

As stated previously, this review focuses on the Double-blind Randomized-withdrawal Phase data.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The clinical review for efficacy included review of one trial - Study SPD503-315. The sponsor submitted Study SPD503-315 to support the labeling changes conveying the safety and efficacy of long term maintenance treatment of ADHD using Intuniv.

6.1.1 Methods

Study SPD503-315 was conducted from 05/11/2010 to 06/03/2013 at 26 sites in the US, 3 sites in Canada, and 38 sites in Europe.

Overall Study Design
Study SPD503-315 was a phase 3, multicenter, randomized-withdrawal, double-blind, placebo-controlled, long-term maintenance study designed to assess the efficacy and safety of once daily dosing with SPD503 at doses up to 7mg per day as monotherapy compared with placebo in children aged 6-17 years with diagnosis of ADHD.

This study consisted of the following 6 periods.

Screening Period: 3-35 days

Open-label phase
Dose Optimization Period
All eligible patients underwent a 7-week double-blind Dose-Optimization Period to allow subjects to titrate to their optimal dose, with 1 dose reduction permitted if necessary. All subjects started at 1 mg/d and were titrated to an effective dose. The maximum dose was 4mg/day for children aged 6-12 years and 4-7mg/day for adolescents aged 13-17 years depending on the subject's weight.

Open-label Maintenance Period:
All subjects who completed the dose-optimization period entered the 6-week dose-maintenance period at their optimal SPD-503 dose. Dose change was not allowed (?).

Double-blind Randomized-withdrawal Phase
Double-blind Dose Maintenance Period
At the double blind randomized-withdrawal baseline visit (visit 13/week 13) eligible subjects were randomized **(1:1)** to either continue on their optimized dose of SPD503 or switch to matching placebo. The Dose Maintenance Period can be up to 26 weeks.

Dose Tapering Period: 2 weeks

Follow-up Period: one week after the last dose of investigational product (window of 7-9 days after last dose).

Figure 1: Study Design Schematic - Study SPD503-315

Source: Protocol SPD 503-315 page 8/ Fig 1

Selection of Study Population

Key Inclusion Criteria:

1. Male or female, aged 6-17 years at the time of consent/assent

2. Subject meets DSM-IV-TR criteria for a primary diagnosis of ADHD, combined sub-type or hyperactive/impulsive sub-type, based on a detailed psychiatric evaluation using the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version (K-SADS-PL)

3. ADHD-RS-IV Total score of ≥32 at the Baseline Visit

4. CGI-S score ≥4 at Baseline at the Baseline Visit

5. Subject has normal or clinically insignificant screening (Visit 1) ECG findings

6. Subject has a supine and standing BP measurement within the 95th percentile for age, gender, and height.

7. All female subjects had to have a negative β-hCG at the Screening Visit (Visit 1) and a negative urine pregnancy test at the Baseline Visit (Visit 2) and agree to abstain from sexual activity or comply with any applicable contraceptive requirements of the protocol

Key Exclusion Criteria:

1. Subject has a current, controlled (requiring a prohibited medication or behavioral modification program) or uncontrolled, comorbid psychiatric diagnosis (except Oppositional Defiant Disorder), but including all anxiety disorders (except simple phobias), all major depressive disorders (dysthymia allowed unless medication required), and any severe comorbid Axis II disorders or severe Axis I disorders such as Post Traumatic Stress Disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder, or other symptomatic manifestations that, in the opinion of the Investigator, contraindicate SPD503 treatment or confound efficacy or safety assessments

2. Subject has any condition or illness including clinically significant abnormal screening (Visit 1) laboratory values which, in the opinion of the Investigator, represents an inappropriate risk to the subject and/or could confound the interpretation of the study

3. Subject has a known history or presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (e.g., clinically significant heart block), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia

4. Subject with orthostatic hypotension or a known history of controlled or uncontrolled hypertension

5. Subject had clinically significant ECG findings as judged by the investigator with consideration of the central ECG interpretation

6. used any prohibited medication or other medications, including herbal supplements that that affect blood pressure, heart rate, have central nervous system effects, or affect cognitive performance, such as sedating antihistamines and decongestant

sympathomimetics (inhaled bronchodilators were permitted) or a history of chronic use of sedating medications (i.e., antihistamines) at the Baseline Visit

7. Subject has a history of alcohol or other substance abuse or dependence, as defined by DSM-IV (with the exceptions of nicotine) within the last 6 months.

8. Subject is significantly overweight which is defined as a BMI >95th percentile for this study.

9. Body weight of <34 kg or >91 kg at the Screening Visit

10. Subject has a known or suspected allergy, hypersensitivity, or clinically significant intolerance to guanfacine hydrochloride or any components found in SPD503

11. Clinically important abnormality on urine drug and alcohol screen (UDS) (excluding the subject's current ADHD stimulant, if applicable)

12. Subject is female and is pregnant or currently lactating

13. Subject failed screening or was previously enrolled in this study

14. Subject, who is currently considered a suicide risk, has previously made a suicide attempt or has a prior history of, or is currently demonstrating suicidal ideation.

15. History of failure to respond to an adequate trial (consisting of an appropriate dose and adequate duration of therapy) of a α2-agonist for the treatment of ADHD.

16. Subject has a history of seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years) or a history of a tic disorder (including Tourette's)

The Primary and Secondary Efficacy Endpoints

The *primary efficacy endpoint* was the *proportion* of treatment failures at the end of the Double-blind Randomized-withdrawal Phase. The 'treatment failure criteria' was defined as a ≥50% increase (worsening) in ADHD-RS-IV total score and a ≥2-point increase in CGI-S score compared to the respective scores at the Double-blind Baseline Visit (Visit13/Week 13). If a subject met these criteria at any single visit during the Double-blind Randomized-withdrawal Phase and was unwilling to remain in the study because of worsening symptoms, *or the subject did not return for another visit*, that subject was also considered a *treatment failure*.

ADHD-RS-IV is a commonly used psychiatric rating scale and is well validated in ADHD clinical trials. It consists of 18 items. Each item is scored from 0 (no symptoms) to 3

(severe symptoms) with total scores ranging from 0 - 54. The 18 items may be grouped into two sub- scales: hyperactivity/impulsivity (even number items 2-18) and inattentiveness (odd number items 1-17). ADHD-RS-IV has been accepted by DPP as a valid primary efficacy measure in ADHD clinical trials.

The CGI Scale is a standardized global assessment tool. Its goal is to allow the clinician to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI Scale is widely used in clinical psychopharmacology trials as an outcome measure. The measure had been accepted by DPP as a reasonable secondary endpoint for many psychiatric clinical trials.

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).

Statistical Methods

The **Enrolled Population** included all subjects who were dispensed study medication at the Enrollment visit (Visit 2/Week 0; Open-label Baseline Visit).

The **Randomized Analysis Set (FAS)** included all subjects who took at least one randomized dose of study medication during the Double-blind Randomized-withdrawal Phase of this trial. The efficacy assessment used this data set.

The **Randomized Safety Population** included all subjects who were randomized and who took at least *one randomized dose* of study medication during the Double-blind Randomized-withdrawal Phase of this trial. The safety assessment used this population dataset.

In this trial, 316 subjects were randomized. 1 did not receive at least 1 randomized dose of investigational product. Therefore, FAS included 315 subjects.

The primary efficacy measurement (treatment failure rates) was 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 was analyzed 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.

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 (Netherlands). 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.

There were a total of (b) (4) subjects out of 316 subjects at site 801 or 4.4% of the total number of subjects in the randomized withdrawal population.

6.1.2 Demographics

Demographics
Demographic characteristics for the Safety Population are presented in the following table.

There were no clinically significant differences between the treatment groups for demographic characteristics. The majority of subjects was male (74.4%), and white (75.3%). The male predominance was consistent with the prevalence of ADHD (2 times more common in male than in female) and the white predominance was consistent with the ethnic profile in most areas where the study was conducted.

The mean age of subjects was 10.8 years (range 6-17 years). The BMI was comparable among all treatment groups.

Table 2: Demographic Characteristics (Safety Population of Study 315) 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)

Baseline Disease Characteristics

The two treatment groups were similar with respect to baseline disease characteristics. Most subjects (84.1%) in the Randomized Safety Population had the combined subtype of ADHD at baseline. The baseline disease characteristics, which were demonstrated in ADHD subtypes, time since diagnosis, Baseline ADHD-RS-IV total score and Baseline CGI severity rating and current psychiatric comorbidity, were comparable among all treatment groups.

The mean time since diagnosis of ADHD was 5.9 years and the mean ADHD-RS-IV total score at baseline was 43.5. All subjects were at least moderately ill as defined by the CGI-S score at baseline. Overall, 27.0% of subjects had a current diagnosis of Oppositional Defiant Disorder at baseline and approximately half (63.1%) exhibited significant oppositional symptoms. They were summarized in the following table.

Table 3: Baseline Disease Characteristics (Safety Population of Study SPD503-315)

	Placebo (N = 158)	SPD503 (N = 157)	Total (N = 315)
ADHD subtype, n (%)			
Predominately inattentive	18 (11.4)	20 (12.7)	38 (12.1)
Predominately hyperactive-impulsive	8 (5.1)	4 (2.5)	12 (3.8)
Combined subtype	132 (83.5)	133 (84.7)	265 (84.1)
Time since ADHD diagnosis (yrs)			
Mean (SD)	2.8 (2.97)	2.5 (2.75)	2.6 (2.86)
Median	2.0	1.5	2.0
Min, Max	0, 14	0, 11	0, 14

ADHD=attention-deficit/hyperactivity disorder; CPRS-R:L=Connors' Parent Rating Scale-Revised: Long Form
CGI-S=Clinical Global Impressions–Severity; ODD=oppositional defiant disorder;
SD=standard deviation
Source: Study Body Report page 83/4553

6.1.3 Subject Disposition

A total of 528 subjects were enrolled at 67 sites in the US, Canada, and Europe. The most frequently given reason for not entering the Double-blind Randomized-withdrawal Phase was "lack of efficacy" (10.6%), followed by "response criteria not met" (8.7%), and AEs (8.0%). The disposition and reasons for not entering the Double-blind Randomized-withdrawal Phase were similar between the 2 age groups (6-12 years and 13-17 years). There were 316 subjects (59.8%) who entered the Double-blind Randomized-withdrawal Phase.

A total of 316 subjects were randomized; 127 completed to the end of the Taper Period, 121 completed the study, and 315 were included in the full analysis set.

The completion rate at visit 23 (completed randomized withdrawal phase before taper) was 48.4% and 33.3% for SPD503 and placebo, respectively.

Table 4 summarizes the disposition of all randomized subjects and subjects who terminated the study in randomized withdrawal phase.

Table 4: Disposition of All Randomized Subjects in Study SPD503-315

	Statistic	Placebo (N=159)	SPD503 (N=157)	Total (N=316)
Subjects Who Were				
Randomised	n (%)	159 (100.0)	157 (100.0)	316 (100.0)
Randomised Safety Population[1]	n (%)	158 (99.4)	157 (100.0)	315 (99.7)
Randomised Full Analysis Set[2]	n (%)	151 (95.0)	150 (95.5)	301 (95.3)
Completed Randomised-withdrawal Phase through Visit 23	n (%)	53 (33.3)	76 (48.4)	129 (40.8)
Completed Randomised-withdrawal Phase through Visit 24 (Includes Taper Period)	n (%)	53 (33.3)	74 (47.1)	127 (40.2)
Completed Randomised-withdrawal Phase through Visit 25 (includes Follow-up)	n (%)	49 (30.8)	72 (45.9)	121 (38.3)
Early Terminated in Randomised-withdrawal Phase	n (%)	106 (66.7)	81 (51.6)	187 (59.2)
Subjects Who Terminated Study in Randomised-withdrawal Phase Due to				
Adverse Event	n (%)	2 (1.3)	3 (1.9)	5 (1.6)
Protocol Violation	n (%)	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawal by subject	n (%)	8 (5.0)	10 (6.4)	18 (5.7)
Lost to follow-up	n (%)	2 (1.3)	3 (1.9)	5 (1.6)
Lack of efficacy	n (%)	20 (12.6)	13 (8.3)	33 (10.4)
Treatment failure criteria met	n (%)	71 (44.7)	47 (29.9)	118 (37.3)
Other	n (%)	3 (1.9)	4 (2.5)	7 (2.2)

[1] Randomised Safety Population is defined as all subjects who received 1 dose of investigational product during the randomised-withdrawal phase.
[2] Randomised Full Analysis Set is defined as all subjects who received 1 dose of investigational product during the randomised-withdrawal phase, but excludes subjects from Site 801.
Percentages are based on the number of randomised subjects in each treatment group.

Source Study Report Body 195/4553

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Concomitant Medication Use

Listings of concomitant medications (Safety Population) in the submission (Section 14, Table 1.3.9) were reviewed. The prohibited medications that were used and might have confounded the evaluation of efficacy included: guanfacine hydrochloride (1 in placebo and 1 in SPD503), hydrocortisone (4 in placebo and 1 in SPD503), lisdexamfetamine mesilate (1 in placebo and 3 in SPD503), methylphenidate hydrochloride (1 in SPD503), morphine (1 in SPD503), morphine hydrochloride (1 in placebo) and prednisolone (1 in placebo).

This reviewer concluded that it was unlikely that the concomitant medication during this trial had affected the overall final efficacy outcome.

Protocol Deviations

1 subject was discontinued from the study for protocol violations: one subject in the SPD503 group was withdrawn due to failure to meet eligibility criteria.

The Summary of protocol violations is shown in the following table 5 below.

A decision was made by the sponsor to exclude the subjects enrolled at Site 801 from the study populations due to the identification of a serious breach of Good Clinical Practice.

These protocol deviations, other than those at site 801 which is excluded, would probably not have biased efficacy in favor of the drug because they were excluded due to protocol violations at the site, and totaled (b) (4) subjects out of 316 subjects or (b) (4) % of the total number of subjects in the randomized withdrawal population.

Table 5: Summary of Protocol Deviations

(Safety Population of Study SPD503-315)

	Placebo (N=158) n (%)	SPD503 (N=157) n (%)	Total (N=315) n (%)
Any violation or significant deviation	69 (43.7)	65 (41.8)	134(42.5)
Failed to meet inclusion/exclusion criteria	30 (19.0)	15 (9.6)	45 (14.3)
Took prohibited medication	26 (16.5)	29 (18.5)	55 (17.5)
Insufficient washout	1 (0.6)	0 (0.0)	1 (0.3)
Became pregnant	0	0 (0.0)	0 (0.0)
Overdosed, abused or misused investigational product	28 (17.7)	28 (17.8)	56 (17.8)
Received incorrect investigational product	0 (0.0)	2 (1.3)	2 (0.6)
Treatment compliance	0	0 (0.0)	0 (0.0)
Other	3 (1.9)	9 (5.7)	12 (3.8)

Source: Study Report Body page 372/4553

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was the *percentage* of treatment failures during the double-blind randomized-withdrawal period. "Treatment failure" was defined as a ≥50% increase (worsening) in ADHD-RS-IV total score and a ≥2-point increase in CGI-S score compared to the respective scores at the Double-blind Baseline Visit. The criteria were met at 2 consecutive visits, or subject discontinued for any reason.

SPD503 was effective compared with placebo with regard to cumulative treatment failures, with 49.3% of subjects in the SPD503 group categorized as treatment failures compared with 64.9% of subjects in the placebo group at visit 23/week 39.

The **effect size** is the difference in percentage of relapse between two treatment groups (-15.6). The results were statistically significant in favor of SPD503 (p=0.006) (see

Table 6: Summary and Analysis of Cumulative Treatment Failure Rates during the Double-blind Randomized-withdrawal Phase (Visit 23/Week 39) below).

Table 6: Summary and Analysis of Cumulative Treatment Failure Rates during the Double-blind Randomized-withdrawal Phase (Visit 23/Week 39)

Treatment Failure	Statistic	Placebo (N=151)	SPD503 (N=150)	Difference in Treatment Failures from Placebo	95% CI for Difference	p-value [a]
No	n (%)	53 (35.1)	76 (50.7)			
Yes	n (%)	98 (64.9)	74 (49.3)	-15.6	-26.6, -4.5	0.006
95% CI for % of treatment failures		57.3, 72.5	41.3, 57.3			

Note: Percentages are based on the number of subjects in each treatment group. Data exclude subjects at Site 801.
Treatment failure criteria (defined as ≥50% increase in ADHD-RS-IV total score and ≥2 point increase in CGI-S compared with respective scores at Double-blind Baseline Visit (Visit 13/Week 13) met at 2 consecutive visits, or subject discontinued for any reason. The overall treatment failure rates are the cumulative treatment failure rates at Visit 23/Week 39.
[a] p-value is based on Cochran-Mantel-Haenszel statistic comparing the treatment groups with age group and country as stratification factors.
ADHD-RS-IV=Attention-deficit/Hyperactive Disorder Rating Scale-IV; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval

Source: Table 12, Study Report Body

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.

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint is *time to treatment failure*. The difference in time to treatment failure was statistically significant in favor of SPD503 (p=0.003). The median time to treatment failure was 218 days (95% CI: 118.0, not calculable) for the SPD503 group and 56.0 days (95% CI: 44.0, 97.0) for the placebo group (see Table 7).

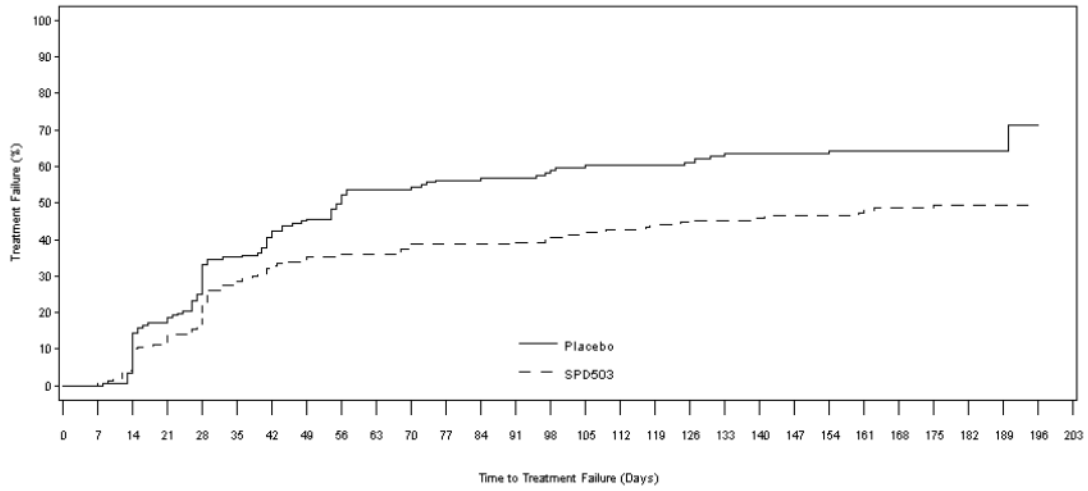
Table 7: Life Table Analysis of Treatment Failure- Primary Definition (Randomized FAS)

	Placebo (N=151)	SPD503 (N=150)
Total number of treatment failures	98	74
Number censored	53	76
Median time to treatment failure (days)	56.0	218.0
95% confidence interval	44.0, 97.0	118.0, NC
Lower quartile for time to treatment failure (days)	28.0	29.0
95% confidence interval	24.0, 29.0	28.0, 42.0
Upper quartile for time to treatment failure (days)	231.0	NC
95% confidence interval	231.0, NC	218.0, NC
p-value from logrank test	0.003	

Note: The p-value is from a logrank test stratified by age group and country. The primary definition of treatment failure is ≥50% increase in ADHD-RS-IV total score and ≥2 point increase in CGI-S compared with respective scores at the Double-blind Baseline Visit (Visit 13/Week 13) at 2 consecutive visits or subjects who discontinued for any reason. Subjects 101-0002 and 119-0004 had an extended time to treatment failure (discontinued at 218 and 231 days, respectively).
ADHD-RS-IV=Attention-deficit/Hyperactive Disorder Rating Scale-IV; CGI-S=Clinical Global Impressions-Severity; FAS=full analysis set; NC=non-calculable.

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).

6.1.7 Subpopulations

Please refer to the statistical review for a fuller discussion of subgroups. A large percentage of the study were male, therefore the study was insufficiently powered to see a difference between males and females. In addition, a significant majority of patients were Caucasian compared to any other racial subgroup, and no conclusions can be made from the data collected regarding efficacy response by race.

The statistical 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 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. Our statistician also found that the overall weight adjusted doses for adolescents were lower.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

At the time of this study, the efficacy of doses of SPD503 higher than 4mg had not been studied in a placebo-controlled clinical study; however, the safety and tolerability of doses up to 9mg/day had been evaluated in adolescents with ADHD in Study SPD503-113.

The selection of the doses for adolescents (up to 7mg/day) was made after evaluation of available literature describing doses used in clinical studies with IR guanfacine for the treatment of pediatric ADHD as well as the opinions of physician experts experienced in the use of IR guanfacine in the treatment of adolescent ADHD. In addition, prescribing data documenting the average number of milligrams of IR guanfacine used for ADHD was considered along with safety and pharmacokinetic data from the Shire adolescent study (SPD503-113) using doses of up to 9mg/day.

SPD503-315 is an optimal dosed (1- 4 mg/d for children and 1-7 mg/d for adolescents) study with a randomized withdrawal design. This kind of study cannot provide dose response information.

The summary of optimal dose during the Double-blind Randomized-withdrawal Phase is listed below. The mean (SD) optimal SPD503 dose during the Double-blind Randomized-withdrawal Phase was 3.5 (1.06) mg. The mean (SD) weight-adjusted optimal dose was 0.089 mg/kg, with most (80.3%) subjects optimized at either 0.05-0.08 mg/kg (60/157) or 0.09-0.12 mg/kg (66/157).

Table 8: Summary of Optimal Dose of SPD503 in Randomized-withdrawal Phase

	Placebo (N=158)	SPD503 (N=157)
Optimal dose, mg [a]		
n	158	157
Mean (SD)	3.5 (1.12)	3.5 (1.06)
Median	3.5	4.0
Min, max	1, 7	1, 7
Subjects receiving, n (%)		
1mg	6 (3.8)	6 (3.8)
2mg	15 (9.5)	19 (12.1)
3mg	58 (36.7)	52 (33.1)
4mg	58 (36.7)	62 (39.5)
5mg	12 (7.6)	13 (8.3)
6mg	7 (4.4)	4 (2.5)
7mg	2 (1.3)	1 (0.6)
Weight-adjusted optimal dose, mg/kg [b]		
Mean (SD)	0.086 (0.0287)	0.089 (0.0300)
Median	0.084	0.088
Min, max	0.02, 0.16	0.02, 0.16
Subjects receiving, n (%)		
0.01-0.04mg/kg	10 (6.3)	13 (8.3)
0.05-0.08mg/kg	71 (44.9)	60 (38.2)
0.09-0.12mg/kg	66 (41.8)	66 (42.0)
0.13-0.16mg/kg	11 (7.0)	18 (11.5)

Note: Endpoint is the visit with the last valid ADHD-RS-IV assessment post-baseline (Visit 2) within the open-label phase.
[a] Optimal dose is the dose at Visit 13.
[b] Weight-adjusted optimal dose is calculated as dose at Visit 13 divided by weight at baseline (Visit 2).
ADHD-RS-IV=; SD=standard deviation

Source: Study Report Body page 130/4553

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The maintenance of efficacy of SPD503 was demonstrated for the primary endpoint, key secondary endpoint, and for symptom measures (ADHD-RS-IV) and clinicians' assessments of global and ADHD functioning (CGI-S, WFIRS-P [Learning and School Domain]) when compared with placebo.

6.1.10 Additional Efficacy Issues/Analyses

No additional safety analysis.

Efficacy analyses of **Study SPD503-315** in subjects aged 6-17 years showed that treatment with SPD503 was efficacious in improving the symptoms of ADHD in children and adolescents, as demonstrated by the results on the primary endpoint, ADHD-RS-IV Total Score.

None of the treatment-by-subgroup interaction terms (sex and race) were statistically significant.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review is focused on Study SPD503-315. This safety review is focused on the Subjects who met the protocol-defined response criteria at both Weeks 12 and 13 (Visits 12/Week 12 and 13/Week 13) entered into a 26-week (6-month), Double-blind Randomized-withdrawal Phase.

7.1.2 Categorization of Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

A SAE was any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a cancer
- Is a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Is an important medical event (including pregnancy or overdose)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the Open-label phase there were During the Open-label Phase, the mean (SD) length of exposure to SPD503 (N=526) was 79.8 (24.86) days. Of note, the duration of the

Open-label Phase was planned to be a 7-week Optimization Period followed by a 6-week Maintenance Period; for a total duration of 91 days. Due to allowed visit windows and certain logistical issues, the duration of participation in the Open-label Phase was >91 days for some (165/526 [31.4%]) subjects. This was not considered to be a significant protocol deviation by the sponsor.

In the Open-label phase the mean (SD) optimal SPD503 dose during the Open-label Phase was 3.5 (1.10)mg. The mean (SD) weight-adjusted optimal dose was 0.090 (0.0305) mg/kg, with most (80.9%) subjects optimized at either 0.05-0.08mg/kg (171/440 [38.9%]) or 0.09-0.12mg/kg (185/440 [42.0%]).

The mean weight-adjusted dose (0.05-0.12mg/kg) was consistent with the range found to be efficacious in previous placebo-controlled pivotal studies (eg, Studies SPD503-301 and SPD503-304).

Table 9: Summary of Optimal Dose of SPD503 in Open-label Phase (Open-label Safety Population)

	Subjects Aged 6-12 Years (N=391)	Subjects Aged 13-17 Years (N=135)	SPD503 Total (N=526)
Optimal dose, mg [a]			
n	332	108	440
Mean (SD)	3.2 (0.85)	4.4 (1.28)	3.5 (1.10)
Median	3.0	4.0	4.0
Min, max	1, 4	1, 7	1, 7
Subjects receiving, n (%)			
1mg	15 (4.5)	1 (0.9)	16 (3.6)
2mg	46 (13.9)	4 (3.7)	50 (11.4)
3mg	120 (36.1)	25 (23.1)	145 (33.0)
4mg	151 (45.5)	25 (23.1)	176 (40.0)
5mg	0	30 (27.8)	30 (6.8)
6mg	0	19 (17.6)	19 (4.3)
7mg	0	4 (3.7)	4 (0.9)
Weight-adjusted optimal dose, mg/kg [b]			
Mean (SD)	0.095 (0.0314)	0.077 (0.0228)	0.090 (0.0305)
Median	0.095	0.079	0.089
Min, max	0.02, 0.16	0.02, 0.12	0.02, 0.16
Subjects receiving, n (%)			
0.01-0.04mg/kg	19 (5.7)	9 (8.3)	28 (6.4)
0.05-0.08mg/kg	112 (33.7)	59 (54.6)	171 (38.9)
0.09-0.12mg/kg	145 (43.7)	40 (37.0)	185 (42.0)
0.13-0.16mg/kg	56 (16.9)	0	56 (12.7)

Note: Percentages are based on the number of subjects in Safety Population in each group with dosing data at Visit 9.
[a] Optimal dose is the dose at Visit 9.
[b] Weight-adjusted optimal dose is calculated as dose at Visit 9 divided by weight at baseline (Visit 2).
max=maximum; min=minimum; SD=standard deviation

In the Double-blind Randomized-withdrawal phase there were a total of 157 subjects who received SPD503, and 158 subjects who received placebo in the Safety Population in Study SPD503-315.

In the Double-blind Randomized-withdrawal phase the mean (SD) length of exposure to SPD503 (N=157) was 114.7 (75.23) days and the mean (SD) length of exposure to placebo was 90.5 (73.06) days.

In Double-blind Randomized-withdrawal phase the mean optimal dose for the SPD503 treatment group was 3.5 mg. The mean (SD) weight-adjusted optimal dose was 0.089 (0.0300) mg/kg, with most (80.3%) subjects optimized at either 0.05-0.08 mg/kg (60/157 [38.2%]) or 0.09-0.12 mg/kg (66/157 [42.0%]). The mean weight-adjusted optimal dose was 0.05-0.12mg/kg, which was consistent with the range found to be efficacious in previous placebo-controlled pivotal studies (SPD503-301 and SPD503-304). The optimized dose of placebo subjects was the optimal dose determined during the Open-label Phase.

Table 10: Summary of Optimal Dose of SPD503 in Randomized-withdrawal Phase (Safety Population of Study SPD503-315)

	Placebo (N=158)	SPD503 (N=157)
Optimal dose, mg [a]		
n	158	157
Mean (SD)	3.5 (1.12)	3.5 (1.06)
Median	3.5	4.0
Min, max	1, 7	1, 7
Subjects receiving, n (%)		
1mg	6 (3.8)	6 (3.8)
2mg	15 (9.5)	19 (12.1)
3mg	58 (36.7)	52 (33.1)
4mg	58 (36.7)	62 (39.5)
5mg	12 (7.6)	13 (8.3)
6mg	7 (4.4)	4 (2.5)
7mg	2 (1.3)	1 (0.6)
Weight-adjusted optimal dose, mg/kg [b]		
Mean (SD)	0.086 (0.0287)	0.089 (0.0300)
Median	0.084	0.088
Min, max	0.02, 0.16	0.02, 0.16
Subjects receiving, n (%)		
0.01-0.04mg/kg	10 (6.3)	13 (8.3)
0.05-0.08mg/kg	71 (44.9)	60 (38.2)
0.09-0.12mg/kg	66 (41.8)	66 (42.0)
0.13-0.16mg/kg	11 (7.0)	18 (11.5)

Note: Endpoint is the visit with the last valid ADHD-RS-IV assessment post-baseline (Visit 2) within the open-label phase.
[a] Optimal dose is the dose at Visit 13.
[b] Weight-adjusted optimal dose is calculated as dose at Visit 13 divided by weight at baseline (Visit 2).
ADHD-RS-IV=; SD=standard deviation

Source: study body report 130/4553

7.2.2 Explorations for Dose Response

Since this Study 315 was a dose optimization study, the dose response of AEs interpretation is limited. The study report did note that there were small increases in the percentages of subjects with treatment-emergent events overall with increasing doses of SPD503 between 1 and 4mg. This trend continued at the higher doses (5-7mg), however there were too few subjects to make an assessment.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *In Vitro* testing was conducted in study.

7.2.4 Routine Clinical Testing

Routine clinical testing includes deaths, adverse events (AEs) which include serious AEs and common AEs, safety laboratory tests (hematology, clinical chemistry, urinalysis and serum beta HCG pregnancy test for females), vital signs including systolic blood pressure (SBP) and diastolic blood pressure (DBP), body weight, height and EKG.

These routine clinical testing was felt to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance, and interaction workup was conducted in study.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In general, the monitoring for important AEs seen in the class of selective α2-adrenergic receptor agonists, such as orthostasis, hypotension, and bradycardia was adequate.

7.3 Major Safety Results

Study SPD503-315

An overview of Treatment-Emergent Adverse Events (TEAEs) that occurred during Study SPD503-315 is summarized in the following tables.

No deaths occurred during Study SPD503-315.

In the Open-label phase there were 448 (85.2%) subjects who reported a total of 2195 treatment emergent adverse events. The majority of the TEAE's were categorized as mild or moderate intensity, and 31 subjects reported 44 severe TEAE's. There were 6 subjects that reported a total of 6 serious adverse events. The Open-label phase SAE's included, aggression (1 event/1 subject), syncope (3 events/3 subjects), sinus bradycardia (1event, 1 subject), and somnolence (1 event/1 subject). All of the SAE's in the Open-label phase resolved.

During the Open-label phase, 50 TEAE's reported by 42 subjects (8%) led to discontinuation. 80.4% of the sedative TEAE's resolved prior to the start of the taper period. There were 16 out of the 526 subjects that experienced mild or moderate intensity TEAE's that did not resolve at the end of the Open-label phase. Of these 16 subjects, 8 continued into the Double-blind Randomized-withdrawal phase, and all 8 subjects completed or discontinued from the Double-blind Randomized-withdrawal phase with TEAE's unresolved. The reasons for withdrawal from the 16 subjects were somnolence (9) and sedation (5). Of those events, 1 event was considered a serious sedative event and was the only serious sedative event reported during the study in both the Open-label and Double-blind Randomized-withdrawal phase.

Table 11: Overall Summary of Treatment-emergent Adverse Events in Open-label Phase (Open-label Safety Population)

	Subjects Aged 6-12 Years (N=391)		Subjects Aged 13-17 Years (N=135)		Total (N=526)	
	Subjects (%)	# AEs	Subjects (%)	# AEs	Subjects (%)	# AEs
Any TEAE	333 (85.2)	1615	115 (85.2)	580	448 (85.2)	2195
Severe	23 (5.9)	32	8 (5.9)	12	31 (5.9)	44
Serious	3 (0.8)	3	2 (1.5)	2	5 (1.0)	5
Related [a]	307 (78.5)	1034	100 (74.1)	326	407 (77.4)	1360
Leading to termination	32 (8.2)	39	10 (7.4)	11	42 (8.0)	50
Leading to dose reduction	54 (13.8)	80	13 (9.6)	19	67 (12.7)	99
Leading to death	0	0	0	0	0	0

Note: Percentages were based on the number of subjects in the Open-label Safety Population in each group.
Note: Adverse events were coded using MedDRA Version 12.1.
Note: Treatment-emergent adverse events were defined as AEs which start or worsen during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after treatment is stopped.
[a] Relatedness was determined by the investigator.
AEs=adverse events; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event

In the Double-blind Randomized-withdrawal phase there were 76/158 (48%) placebo subjects who reported a total of 192 TEAEs and 89/157 (56.7%) SPD503 subjects who reported a total of 287 TEAEs. The majority of TEAEs were mild to moderate in intensity with 2/158 (1.3%) placebo subjects and 5/157 SPD503 subjects reporting a severe TEAE.

During the Double-blind Randomized-withdrawal phase two subjects (1.3%) receiving SPD503 and four subjects (1.9%) receiving placebo experienced a serious Adverse

Event (SAE). The reported events included nephrolithiasis, aggression, family stress, abdominal pain, syncope, conduct disorder and a grand mal convulsion.

During the Double-blind Randomized-withdrawal phase three subjects (1.91%) receiving SPD503 and two subjects (1.2%) receiving placebo had a TEAE(s) leading to discontinuation from the study.

Table 12: Overall Summary of Treatment-Emergent Adverse Events Randomized-withdrawal Phase (Safety Population of Study SPD503-315)

	Placebo (N=158)		SPD503 (N=157)	
Preferred Term	**Subjects (%)**	**# AEs**	**Subjects (%)**	**# AEs**
Any TEAE leading to discontinuation	2 (1.3)	6	3 (1.9)	3
Grand mal convulsion	0	0	1 (0.6)	1
Sedation	0	0	1 (0.6)	1
Somnolence	0	0	1 (0.6)	1
Chest pain	1 (0.6)	1	0	0
Dizziness	1 (0.6)	1	0	0
Dyspnoea	1 (0.6)	1	0	0
Irritability	1 (0.6)	1	0	0
Nausea	1 (0.6)	1	0	0
Tremor	1 (0.6)	1	0	0

Note: Adverse events were coded using MedDRA Version 12.1. Percentages were based on the number of subjects in the Randomized Safety Population. Treatment-emergent AEs were defined as AEs that started or worsened during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after treatment was stopped.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Source: Study Body Report 131/4553

7.3.1 Deaths

No deaths were reported during the conduct of Study SPD503-315.

7.3.2 Nonfatal Serious Adverse Events

During the Open-label phase there were 6 subjects that reported serious but nonfatal TEAE's. Those events were listed as syncope (3 subjects), aggression (1 subject), sinus bradycardia (1 subject) and somnolence (1 subject). The dosages, and start day of the events are listed in detail in the following table.

Table 13: Subjects who reported serious treatment-emergent adverse events in Open-label phase

Subject Number	Sex/Age/ Race	Adverse Event / Preferred Term	Onset Dose (mg)	Start Day	Severity	Relationship / Outcome	Action Taken
103-0002	M/13/W	Aggression towards mother / Aggression	1	6	Moderate	Not related/ Recovered/ resolved	Not applicable [a]
108-0013	M/9/B	Syncope / Syncope	4	39	Moderate	Related/ Recovered/ resolved	Drug withdrawn
305-0005[b]	F/14/W	Syncope / Syncope	4	46	Moderate	Related/ Recovered/ Resolved	Dose Not Changed
801-0016	M/6/O	Sinus Bradycardia / Sinus bradycardia	4	56	Severe	Related/ Recovered/ resolved	Drug withdrawn
802-0002	F/15/W	Syncope / Syncope	6	60	Moderate	Related/ Recovered/ resolved	Dose not changed
907-0001	M/8/W	Somnolence / Somnolence	3	38	Severe	Related/ Recovered/ resolved	Drug withdrawn

Note: Adverse events were coded using MedDRA Version 12.1. Treatment-emergent AEs were defined as AEs that started or worsened during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after treatment was stopped.
Note: Start Day is the number of days from the first dose of investigational product to the start of the AE.
[a] Not applicable because the subject had ceased dosing with investigational product 3 days prior to start of the SAE, which was still within the treatment-emergent window.
[b] Syncope, per protocol, was required to be captured as an SAE. However, this event was not captured as serious in the clinical database. Subsequently, an errata has been added and this event is considered to be serious by the sponsor.
AEs=adverse events; B=Black or African American; F=Female; M=Male; MedDRA=Medical Dictionary for Regulatory Activities; O=Other; SAE=serious adverse event; W=White

Source: Section 14 Table 4.4.7 Study Report Body

During the Double-blind Randomized-withdrawal phase two subjects receiving SPD503 and four subjects receiving placebo experienced a total of 7 SAEs during the conduct of Study SPD503-315 including aggression, nephrolithiasis, family stress, abdominal pain, syncope, conduct disorder and grand mal convulsion.

Three of these cases are reviewed below.

Subject Identifier 104-0022

Subject 104-0022 was an 11-year-olds white male with ADHD (combined subtype) who had no relevant medical history and was not receiving concomitant medication. He received his first dose of SPD503 1mg on 24 May 2011 (Day 1). His dose of SPD503 was titrated up to 3mg on 08 June 2011 (Day 16) and he remained at that dose through

the open-label phase. The subject completed the open-label phase and began the randomized-withdrawal taper on 23 August 2011 (Day 92), receiving SPD503 2mg (Days 92-100) and 1mg (Days 101-107). He continued into the randomized-withdrawal phase, receiving his first dose of placebo on 08 September 2011 (Day 108).

On (b) (4) while receiving placebo, the subject presented with blood in his urine and was hospitalized for testing, which included a CT scan of the kidney and x-rays of the chest and lower abdomen. He was diagnosed with a kidney stone on his left side and reported with a serious treatment-emergent adverse event of sever nephrolithiasis.

The subject had a family history of nephrolithiasis. The subject received treatment with normal saline, morphine hydrochloride, and Solpadine; and a stent was placed in his ureter. The kidney stone was removed in (b) (4). The nephrolithiasis was resolved on (b) (4)). The subject continued receiving investigational product and completed the randomized-withdrawal phase. Investigational product was tapered as per the protocol. His last dose of investigational product was on 05 March 2012 (Day 287). Given his family history of nephrolithiasis and resolution of symptoms this reviewer does not consider this event to be related to investigational product.

Subject Identifier 802-0002

Subject 802-0002 was a 15-year-old white female with ADHD (inattentive subtype) who had ongoing mild asthma (since 2008) and ongoing menorrhagia (since 2009) and was receiving eugynon for menorrhagia. She received her first dose of SPD503 1mg on 11 May 2012 (Day 1). Her dose of SPD503 was titrated up to 6mg on 20 July 2012 (Day 41) and she remained at that dose throughout the open-label phase. The subject completed the open-label phase and began the randomized-withdrawal taper period on 14 August 2012 (Day 96), receiving SPD503 5mg (Days 96-104), 4mg (Days 105-106), 3mg (Days 107-110), and 2mg (Days 111-113). She continued into the randomized-withdrawal phase with her first dose of placebo on 01 September 2012 (Day 114).

On 13 June 2012 (Day 34), while receiving SPD503 5mg, the subject experienced non-serious treatment-emergent adverse events of mild blurred vision and mild dizziness. On (b) (4)), while receiving SPD503 6mg, the subject experienced a serious treatment-emergent adverse event of moderate syncope. Blood pressure measurements were not available for that date, and her previously recorded vitals supine and standing were 108/68 mmHg to 90/56 mmHg on Visit 8, 110/70 mmHg to 85/55 mmHg on Visit 9, and 108/64 mmHg to 86/40 mmHg on Visit 10.

On 21 August 2012 (Day 103) while receiving SPD503 5mg, the subject experienced dizziness that resolved on that day, and on (b) (4) while taking placebo, the subject experienced syncope. The syncope had been immediately preceded by nausea and dark vision and resulted in mild physical injuries. The subject

was sent to the hospital for an ECG, vital signs and blood tests which were normal. The investigational product was withdrawn on 9 October 2012 (Day 152) due to the treatment failure criteria being met. Her last dose of investigational product was on 23 October 2013 (Day 166). This reviewer considers the syncopal episodes to be related to the investigational product.

Subject Identifier: 402-0003

Subject 402-0003 was a 13-year-old white male with ADHD (combined subtype) who had no relevant medical history and was not receiving concomitant medication. He received his first dose of SPD503 1mg on 29 Feb 2012 (Day 1). His dose of SPD503 was titrated up to 3mg on 14 Mar 2012 (Day 15) and he remained at that dose throughout the open-label phase. The subject completed the open-label phase and the randomized-withdrawal taper phase and continued into the randomized-withdrawal phase where he was randomized to SPD503 with his first dose of SPD503 3mg on 13 Jun 2012 (Day 106).

On (b) (4), while receiving SPD503 3mg, the subject was admitted to the hospital from the emergency room following a serious treatment-emergent adverse event of grand mal convulsion (grand mal epileptic seizure), which was considered by the investigator to be related to investigational product. No treatment was provided for the event. Investigational product was withdrawn due to the grand mal convulsion the same day (b) (4) Investigational product was not tapered per the protocol. The subject was discharged from the hospital on (b) (4) and the event was considered resolved without sequelae (note that the end date of the grand mal convulsion in the clinical database, (b) (4) was incorrect). Note that the investigator reported the subject had 1 fever-related seizure as a child that was possibly Blitz-Nick-Salaam epilepsy.

With regard to the grand mal seizure, given that the child experienced one seizure previously (before the age of 3), the grand mal seizure may or may not be directly related to the study medication.

7.3.3 Dropouts and/or Discontinuations

During the Open-label phase there were a total of 50 TEAE's reported by 42 out of the 526 subjects (8%) that led to discontinuation. In the Open-label phase the frequency of TEAE's were similar between age groups (32/391 [8.2%] subjects 6-12 years reporting 39 events; 10/135 [7.4%] subjects 13-17 years reporting 11 events). Treatment-emergent AEs leading to discontinuation that were reported by more than 1 subject included somnolence (9/526 [1.7%]), fatigue (5/526 [1.0%]), sedation (5/526 [1.0%]), dizziness (3/526 [0.6%]), hypotension (3/526 [0.6%]), irritability (2/526 [0.4%]), affect lability (2/526 [0.4%]), and ODD (2/526 [0.4%]). In the Open-label phase all other TEAEs leading to discontinuation were reported by single subjects.

Table 14: Summary of Treatment-Emergent Adverse Events in Open-label Safety Population

	Placebo (N=159)		SPD503 (N=526)	
	#(%) Subj	# AEs	#(%) Subj	# AEs
Any Treatment-Emergent Adverse Events (TEAEs)	76 (47.8%)	192	455 (86.5%)	2482
Severe TEAEs	2 (1.3%)	3	36 (6.8%)	49
Serious TEAEs	4 (2.5%)	5	7 (1.3%)	7
Related TEAEs	20 (12.6%)	36	411 (78.1%)	1436
TEAEs leading to Discontinuation	2 (1.3%)	6	45 (8.6%)	53
TEAEs Requiring Dose Reduction	0 (0.0%)	0	67 (12.7%)	99
TEAEs leading to Death	0 (0.0%)	0	0 (0.0%)	0

Percentages are based on the number of subjects in the Open-label Safety Population in each group.
Subjects entering randomised-withdrawal phase and randomised to placebo will appear in both columns - in the SPD503 column for the open-label phase, and in the placebo column for the randomised-withdrawal phase.
Adverse events were coded using MedDRA Version 12.1.
Treatment-Emergent Adverse Events are defined as adverse events which start or worsen during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after their treatment is stopped.

Source: Listing 7

Program: t_oae.sas, Output: t_oae-1.rtf, Generated on: 20AUG2013 04:38, Page 1 of 1

During the Double-blind Randomized-withdrawal phase during the three subjects (1.91%) receiving SPD503 and two subjects (1.2%) receiving placebo had a TEAE(s) leading to discontinuation from the study.

Among the 3 SPD503 subjects who had TEAEs leading to discontinuation, events included: grand mal convulsion (1 subject), sedation (1 subject), and somnolence (1 subject).

Table 15: Summary of Treatment-emergent Adverse Events Leading to Discontinuation (Double-blind Randomized-withdrawal Phase)

	Placebo (N=158)		SPD503 (N=157)	
Preferred Term	**Subjects (%)**	**# AEs**	**Subjects (%)**	**# AEs**
Any TEAE leading to discontinuation	2 (1.3)	6	3 (1.9)	3
Grand mal convulsion	0	0	1 (0.6)	1
Sedation	0	0	1 (0.6)	1
Somnolence	0	0	1 (0.6)	1
Chest pain	1 (0.6)	1	0	0
Dizziness	1 (0.6)	1	0	0
Dyspnoea	1 (0.6)	1	0	0
Irritability	1 (0.6)	1	0	0
Nausea	1 (0.6)	1	0	0
Tremor	1 (0.6)	1	0	0

Note: Adverse events were coded using MedDRA Version 12.1. Percentages were based on the number of subjects in the Randomized Safety Population. Treatment-emergent AEs were defined as AEs that started or worsened during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after treatment was stopped.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Source: Study Body Report 137/4553

7.3.4 Significant Adverse Events

The significant AEs in this trial were consistent with what has been labeled.

7.3.5 Submission Specific Primary Safety Concerns

The analysis of sedative events included the following preferred terms: somnolence, sedation, and hypersomnia. The three reports of treatment emergent syncopal events are listed in Table 15.

During the Open-label Phase a total of 448 sedative events were reported in 282/526 (53.6%) subjects and the frequency of sedative events was similar between age groups (212/391 [54.2%] subjects 6-12 years reporting 328 events; 70/135 [51.9% subjects 13-17 years reporting 120 events). The majority of events were mild to moderate in intensity (307/448 [68.5%] mild; 136/448 [30.4%] moderate). Overall, there were 5 severe sedative events (3 in the 6-12 year group; 2 in the 13-17 year group). Among severe TEAEs of somnolence, 1 event (reported by 1 subject) was considered to be an SAE.

During the Double-blind Randomized-withdrawal Phase sedative events were reported in 29 subjects (12.7%) receiving SPD503 compared with of no subjects who were receiving placebo.

Table 16: Summary of Onset and Duration of Treatment-emergent Syncopal Events

Subject Number	Sex/Age/ Race	Adverse Event / Preferred Term	Onset Dose SPD503 (mg)	Severity	Relationship / Outcome	Action Taken	Serious (yes/no)
Placebo							
802-0002	F/15/W	Fainting attack / syncope	0	Moderate	Not related/ Recovered/ resolved	Dose not changed	Yes
SPD503							
203-0009	M/13/W	Pre-syncope / Presyncope	5	Mild	Related/ Not recovered/ not resolved	Dose not changed	No [a]
605-0006	M/12/W	Vaso-vagal episode without loss consciousness / Presyncope	3	Mild	Not related/ Recovered/ resolved	Dose not changed	No [a]

[a] Per protocol, only events of syncope (ie, not presyncope) were considered to be serious and thus events of presyncope were not considered to be SAEs.
Note: Adverse events were coded using MedDRA Version 12.1. Treatment-emergent AEs were defined as AEs that started or worsened during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after treatment was stopped.
AEs=adverse events; B=Black or African American; F=Female; M=Male; MedDRA=Medical Dictionary for Regulatory Activities: O=Other: SAE=serious adverse event: W=White

Source: Study Body Report 139/4553

There was a higher incidence (%) of sedative events in SPD503 subjects compared with placebo throughout the study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the Open-label phase somnolence was the most frequently reported TEAE and occurred in 255/526 (48.5%) subjects reporting 387 TEAEs. Other TEAEs occurring in >10% of all subjects included headache (27.4%), fatigue (24.7%), and abdominal pain upper (11.4%). Of these events, only abdominal pain upper was reported with a 2-fold difference in frequency between age groups with 5.9% of subjects aged 13-17 years reporting this TEAE compared with 13.3% of subjects aged 6-12 years.

Table 17: Summary of Common Treatment-emergent Adverse Events Occurring in ≥ 5% of subjects in Open-label Phase

Preferred Term	Subjects Aged 6-12 Years (N=391)		Subjects Aged 13-17 Years (N=135)		Total (N=526)	
	Subjects (%)	# AEs	Subjects (%)	# AEs	Subjects (%)	# AEs
Any TEAE	333 (85.2)	1615	115 (85.2)	580	448 (85.2)	2195
Somnolence	190 (48.6)	281	65 (48.1)	106	255 (48.5)	387
Headache	101 (25.8)	169	43 (31.9)	73	144 (27.4)	242
Fatigue	92 (23.5)	130	38 (28.1)	56	130 (24.7)	186
Abdominal pain upper	52 (13.3)	62	8 (5.9)	8	60 (11.4)	70
Dizziness	30 (7.7)	38	20 (14.8)	24	50 (9.5)	62
Sedation	35 (9.0)	47	12 (8.9)	14	47 (8.9)	61
Diarrhoea	31 (7.9)	39	6 (4.4)	7	37 (7.0)	46
Irritability	31 (7.9)	35	6 (4.4)	6	37 (7.0)	41
Nasopharyngitis	22 (5.6)	24	14 (10.4)	15	36 (6.8)	39
Nausea	25 (6.4)	34	8 (5.9)	8	33 (6.3)	42

This reviewer summarized the most common AEs which has occurred ≥5% and at least twice placebo rate) in Study SPD503-315 according to Table 34 of the study report in this submission: a summary of TEAEs occurring in ≥ 5% of subjects in any treatment group. The most common AEs included headache, somnolence, nasopharyngitis, pyrexia, fatigue, upper respiratory tract infection, cough and abdominal pain upper.

Table 18: Summary of Treatment - Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group in Randomized-withdrawal Phase (Randomized Safety Population)

Preferred Term	Placebo (N=158)		SPD503 (N=157)	
	Subjects (%)	# AEs	Subjects (%)	# AEs
Any TEAE	76 (48.1)	192	89 (56.7)	287
Headache	18 (11.4)	24	25 (15.9)	34
Somnolence	0	0	19 (12.1)	27
Nasopharyngitis	13 (8.2)	14	11 (7.0)	14
Pyrexia	5 (3.2)	5	10 (6.4)	10
Fatigue	2 (1.3)	2	8 (5.1)	11
Upper respiratory tract infection	10 (6.3)	10	8 (5.1)	8
Cough	9 (5.7)	11	5 (3.2)	6
Abdominal pain upper	8 (5.1)	10	3 (1.9)	4

Note: Percentages were based on the number of subjects in the Randomized Safety Population of each treatment group.

Note: Adverse Events were coded using MedDRA Version 12.1.

Note: Treatment-emergent adverse events were defined as AEs which start or worsen during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after treatment is stopped.

AEs=adverse events; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event

Source: Study Body Report 133/4553

7.4.2 Laboratory Findings

In summary, there were no clinically meaningful differences between the treatment groups with regard to laboratory findings (hematology, serum chemistry and urinalysis). There were no dropouts due to Abnormal Laboratory Findings.

Hematology
This reviewer has examined Section 14, Table 4.6.22: the List of Outlier Clinical Laboratory Tests: Hematology (Safety Population). There were no clinically meaningful differences between the treatment groups with regard to clinical hematology results.

Serum Chemistry
In terms of outliers, no clinical laboratory test results for clinical chemistry were reported as a TEAE in the SPD503 group, and 1 TEAE of alanine aminotransferase increased in 1 placebo subject. Overall the incidences of outliers were similar between SPD503 and placebo and there were no clinically meaningful differences between SPD503 and placebo regarding clinical chemistry results.

Urinalysis
No clinical laboratory test results for urinalysis (SOC of Investigations) met the criteria of a TEAE and there were no clinically meaningful differences between SPD503 and placebo.

7.4.3 Vital Signs

The vital sign changes seen in Study SPD503-315 were consistent with the known effects of guanfacine.

a. Vital Sign Assessments

Systolic blood pressure (BP), diastolic BP, orthostatic BP, and pulse rate were measured at screening, baseline, dose optimization, dose maintenance and endpoint/early term visit and post- dose taper visit during this double-blind child ADHD trial. Baseline was defined as the last available measurement prior to the first dose of investigational product.

b. Mean Change from Baseline in Vital Sign Measures

In summary, a greater mean change (decrease) from baseline was seen in pulse rate, systolic blood pressure, and diastolic blood pressure in SPD503 treatment group at the endpoint compared to placebo. The lowest point of pulse rate, systolic BP and diastolic BP tended to occur around treatment Week 3 and the values tended to return back to Baseline at the post-dose taper visits.

Pulse Rate

Consistent with the known effects of guanfacine, in the Open label Subjects in the 2 age groups had similar supine pulse rates at baseline (age 6-12 years: 77.5±10.31bpm; age 13-17 years: 72.4±10.41bpm). At endpoint (LOTA) subjects had a -5.9±13.52bpm mean decrease from baseline in supine pulse; results were similar between age groups (age 6-12 years: -5.9±13.04bpm; age 13-17 years: -5.9±14.91bpm). This decrease from baseline is consistent with the known effects of SPD503. When supine pulse rate was examined across visits, it tended to reach its lowest point around Visit 9/Week 7, which coincided with the end of the 7-week Dose-optimization Phase.

Similar results were noted in the Double-blind Randomized-withdrawal phase, subjects receiving SPD503 had 3.8 bpm mean decrease from Baseline in supine pulse compared with a 0.6 bpm mean increase in subjects receiving placebo. Similar results were seen in standing pulse. (See tables below)

Table 19: Summary of Supine Pulse by Age Group in Open-label Phase

	Subjects Aged 6-12 Years (N=391)	Subjects Aged 13-17 Years (N=135)	SPD503 Total (N=526)
Supine Pulse, bpm			
Baseline mean (SD)	77.5 (10.31)	72.4 (10.41)	76.2 (10.57)
Mean change from baseline at endpoint (SD) (LOTA)	-5.9 (13.04)	-5.9 (14.91)	-5.9 (13.52)
Mean change from baseline at follow-up (SD)	3.5 (14.08)	4.1 (12.59)	3.7 (13.68)
Standing Pulse, bpm			
Baseline mean (SD)	85.6 (13.74)	81.7 (13.93)	84.6 (13.88)
Mean change from baseline at endpoint (SD) (LOTA)	-3.6 (14.58)	-3.3 (17.57)	-3.5 (15.38)
Mean change from baseline at follow-up (SD)	2.3 (17.85)	6.0 (16.48)	3.2 (17.53)

Note: Endpoint is the last valid assessment obtained after the Open-label Baseline Visit (Visit 2/Week 0) while on investigational product in Open-label Phase and on or before last dose of non-taper medication.
Note: Follow-up is Visit 25 assessment value or any other assessment value from any other visit which is ≥5 days after the last dose of investigational product (if earlier than Visit 25).
bpm=beats per minute; LOTA=last on-treatment assessment; SD=standard deviation

Table 20: Summary of Pulse by Double-blind Treatment Group

	Placebo N=158	SPD503 N=157
Standing Pulse, bpm		
n	156	156
Baseline (Visit 2/Week 0) mean (SD)	84.7 (13.67)	83.0 (11.52)
n	156	155
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	1.4 (15.01)	0.6 (12..59)
n	134	134
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	2.5 (15.81)	5.7 (15.06)

Note: Endpoint is the last valid assessment obtained after Baseline (Visit 2) whilst on investigational product in the Double-blind Randomized-withdrawal Phase and on or before last dose of non-taper medication.
Note: Follow-up is the earliest of an assessment done at Visit 25 or any other assessment at any other visit which is ≥5 days after the last dose of investigational product
bpm=beats per minute, SD=standard deviation

Source: Study Report Body, page 142/4553

Systolic Blood Pressure

Consistent with the known effects of guanfacine, in the Open-label phase, subjects in the 2 age groups had similar supine systolic blood pressure values at baseline, and a similar decrease from baseline in supine systolic blood pressure; results were similar between age groups (age 6-12 years: -2.9±9.89mmHg; age 13-17 years: -2.3 ± 11.17mmHg.)

Also, consistent with the known effects of guanfacine, subjects receiving SPD503 during the Double-blind Randomized-withdrawal phase had a mean decrease 0.2mmHg from Baseline in supine systolic BP compared with a mean increase 3.2mmHg in supine systolic BP in subjects receiving placebo.

Table 21: Summary of Systolic Blood Pressure by Age Group in Open-label phase

	Subjects Aged 6-12 Years (N=391)	Subjects Aged 13-17 Years (N=135)	SPD503 Total (N=526)
Supine systolic blood pressure, mmHg			
Baseline mean (SD)	102.7 (8.81)	110.4 (9.38)	104.7 (9.55)
Mean change from baseline at endpoint (SD) (LOTA)	-2.9 (9.89)	-2.3 (11.17)	-2.7 (10.22)
Mean change from baseline at follow-up (SD)	4.0 (11.05)	4.7 (10.19)	4.2 (10.81)
Standing systolic blood pressure, mmHg			
Baseline mean (SD)	104.1 (9.82)	112.4 (8.84)	106.3 (10.23)
Mean change from baseline at endpoint (SD) (LOTA)	-4.3 (10.98)	-6.6 (12.63)	-4.9 (11.46)
Mean change from baseline at follow-up (SD)	3.8 (11.14)	2.5 (10.64)	3.4 (11.00)

Note: Endpoint is the last valid assessment obtained after the Open-label Baseline Visit (Visit 2/Week 0) while on investigational product in Open-label Phase and on or before last dose of non-taper medication.
Note: Follow-up is Visit 25 assessment value or any other assessment value from any other visit which is ≥5 days after the last dose of investigational product (if earlier than Visit 25).
LOTA=last on-treatment assessment; SD=standard deviation

Source: Study report body section 14, table 4.7.2

Table 22: Summary of Systolic Blood Pressure by Treatment Group (Safety Population of Study SPD503-315)

	Placebo N=158	SPD503 N=157
Supine Systolic Blood Pressure, (mmHg)		
n	158	157
Baseline (Visit 2/Week 0) mean (SD)	105.4 (9.28)	104.9 (9.40)
n	158	156
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	3.2 (8.69)	-0.2 (10.50)
n	136	135
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	3.3 (11.30)	6.5 (10.62)
Standing Systolic Blood Pressure, (mmHg)		
n	157	156
Baseline (Visit 2/Week 0) mean (SD)	106.4 (9.97)	106.2 (9.70)
n	157	155
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	2.7 (9.59)	-1.5 (10.76)
n	135	134
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	1.9 (10.92)	5.0 (11.79)

Note: Endpoint is the last valid assessment obtained after Baseline (Visit 2) whilst on investigational product in the Double-blind Randomized-withdrawal Phase and on or before last dose of non-taper medication.
Note: Follow-up is the earliest of an assessment done at Visit 25 or any other assessment at any other visit which is ≥5 days after the last dose of investigational product
SD=standard deviation

Source: Study Report Body, page 143/4553

Diastolic Blood Pressure

During the Open-label Randomized-withdrawal phase, subjects in the 2 age groups had similar supine diastolic blood pressure values at baseline, and similar mean decrease from baseline in the 2 age groups. When supine diastolic blood pressure was examined across visits, it tended to reach its lowest points around Visits 4 and 5/Weeks 2 and 3,

which was during the Dose-optimization Phase (-2.1 mmHg: Ages 6-12, -2.5mmHg:Ages 13-17).

Table 23: Summary of Diastolic Blood Pressure by Age Group in Open-label Phase

	Subjects Aged 6-12 Years (N=391)	Subjects Aged 13-17 Years (N=135)	SPD503 Total (N=526)
Supine diastolic blood pressure, mmHg			
Baseline mean (SD)	62.2 (7.66)	63.8 (8.20)	62.7 (7.82)
Mean change from baseline at endpoint (SD) (LOTA)	-2.1 (9.63)	-2.5 (9.27)	-2.2 (9.54)
Mean change from baseline at follow-up (SD)	2.1 (10.15)	3.2 (8.74)	2.4 (9.79)
Standing diastolic blood pressure, mmHg			
Baseline mean (SD)	65.2 (7.85)	69.0 (8.50)	66.2 (8.18)
Mean change from baseline at endpoint (SD) (LOTA)	-2.7 (10.11)	-4.9 (10.46)	-3.3 (10.24)
Mean change from baseline at follow-up (SD)	3.4 (10.13)	2.8 (11.01)	3.3 (10.33)

Note: Endpoint is the last valid assessment obtained after the Open-label Baseline Visit (Visit 2/Week 0) while on investigational product in Open-label Phase and on or before last dose of non-taper medication.
Note: Follow-up is Visit 25 assessment value or any other assessment value from any other visit which is ≥5 days after the last dose of investigational product (if earlier than Visit 25).
LOTA=last on-treatment assessment; SD=standard deviation

During the Double-blind Randomized-withdrawal phase, consistent with the known effects of guanfacine, subjects receiving SPD503 had 0.9 mmHg mean decrease (-0.9 mmHg) from Baseline in supine diastolic BP compared with a 1.2 mmHg mean increase (1.2 mmHg) in subjects receiving placebo.

Table 24: Summary of Diastolic Blood Pressure by Treatment Group (Safety Population of Study SPD503-315)

	Placebo N=158	SPD503 N=157
Supine Diastolic Blood Pressure, (mmHg)		
n	158	157
Baseline (Visit 2/Week 0) mean (SD)	63.2 (7.85)	61.8 (7.64)
n	158	156
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	1.2 (8.56)	-0.9 (10.29)
n	136	135
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	0.2 (9.09)	5.2 (10.76)
Standing Diastolic Blood Pressure, (mmHg)		
n	157	156
Baseline (Visit 2/Week 0) mean (SD)	66.9 (8.40)	65.1 (7.28)
n	157	155
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	1.8 (8.31)	-1.3 (9.80)
n	135	134
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	0.7 (9.69)	4.7 (11.04)

Note: Endpoint is the last valid assessment obtained after Baseline (Visit 2) whilst on investigational product in Double-blind Randomized-withdrawal Phase and on or before last dose of non-taper medication.
Note: Follow-up is the earliest of an assessment done at Visit 25 or any other assessment at any other visit which is ≥5 days after the last dose of investigational product
SD=standard deviation

Source: Study Report Body, page 143/4553

Postural Orthostatic Blood Pressure

During the Open-label phase At endpoint (LOTA) subjects had a -2.2±10.54mmHg mean decrease from baseline in postural orthostatic blood pressure. This decrease from baseline is consistent with the known effects of SPD503. When postural orthostatic blood pressure was examined across visits, it tended to reach its lowest points around Visits 6 and 7/Weeks 4 and 5, which was during the Dose-optimization Phase.

Table 25: Summary of Postural Orthostatic Blood Pressure by Age Group in the Open-label Phase

	Subjects Aged 6-12 Years (N=391)	Subjects Aged 13-17 Years (N=135)	SPD503 Total (N=526)
Orthostatic systolic blood pressure, mmHg			
Baseline mean (SD)	1.5 (8.11)	1.9 (7.29)	1.6 (7.90)
Mean change from baseline at endpoint (SD) (LOTA)	-1.5 (10.13)	-4.2 (11.49)	-2.2 (10.54)
Mean change from baseline at follow-up (SD)	-0.2 (10.24)	-2.2 (9.63)	-0.7 (10.09)
Orthostatic diastolic blood pressure, mmHg			
Baseline mean (SD)	3.0 (7.56)	5.1 (7.69)	3.5 (7.64)
Mean change from baseline at endpoint (SD) (LOTA)	-0.5 (10.96)	-2.4 (8.54)	-1.0 (10.43)
Mean change from baseline at follow-up (SD)	1.4 (10.65)	-0.2 (9.30)	1.0 (10.32)

Note: Endpoint is the last valid assessment obtained after the Open-label Baseline Visit (Visit 2/Week 0) while on investigational product in Open-label Phase and on or before last dose of non-taper medication.
Note: Follow-up is Visit 25 assessment value or any other assessment value from any other visit which is ≥5 days after the last dose of investigational product (if earlier than Visit 25).
Note: Postural orthostatic blood pressure is defined as the difference from last supine blood pressure measurement to first standing blood pressure measurement.
LOTA=last on-treatment assessment; SD=standard deviation

During the Double-blind Randomized-withdrawal phase, at the endpoint, the SPD503 treatment group had greater changes in both postural orthostatic systolic BP and diastolic BP compared to placebo. See table below.

Table 26: Summary of Postural Orthostatic Blood Pressure (Change from Supine to Standing and Change from Baseline to Endpoint) by Treatment Group (Safety Population of Study SPD503-315)

	Placebo N=158	SPD503 N=157
Orthostatic Systolic Blood Pressure, (mmHg)		
n	157	156
Baseline (Visit 2/Week 0) mean (SD)	1.1 (7.04)	1.4 (7.73)
n	157	155
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	-0.5 (9.64)	-1.4 (10.67)
n	135	134
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	-1.3 (10.41)	-1.4 (10.64)
Orthostatic Diastolic Blood Pressure, (mmHg)		
n	157	156
Baseline (Visit 2/Week 0) mean (SD)	3.7 (7.04)	3.4 (7.14)
n	157	155
Mean change from baseline (Visit 2/Week 0) at endpoint (SD)	0.7 (8.48)	-0.4 (9.83)
n	135	134
Mean change from baseline (Visit 2/Week 0) at follow-up (SD)	0.5 (10.43)	-0.5 (11.76)

Note: Endpoint is the last valid assessment obtained after Baseline (Visit 2) whilst on investigational product in the Double-blind Randomized-withdrawal Phase and on or before last dose of non-taper medication.
Note: Follow-up is the earliest of an assessment done at Visit 25 or any other assessment at any other visit which is ≥5 days after the last dose of investigational product
SD=standard deviation

Source: Study Report Body, page 145/4553

c. Potentially Clinically Significant Vital Sign Changes

In summary, subjects receiving SPD503 were more likely than placebo to have a lower supine pulse, a lower supine systolic and supine diastolic blood pressure. Postural orthostatic blood pressure, a decrease of ≥ 25mmHg in systolic BP was reported more often in SPD503 group than in placebo (8.4% vs.1.9%).

Table 27: Vital Sign Outliers at any Time While Receiving Treatment

Timepoint Vital sign	Statistic	Placebo (N=158)	SPD503 (N=157)
Overall-On-Treatment			
Supine Pulse	n	158	156
<=50bpm	n (%)	3 (1.9)	12 (7.7)
>=100bpm	n (%)	21 (13.3)	17 (10.9)
Standing Pulse	n	158	156
<=50bpm	n (%)	1 (0.6)	1 (0.6)
>=100bpm	n (%)	79 (50.0)	62 (39.7)
Body Weight	n	158	156
Increase from Baseline >=10%	n (%)	77 (48.7)	92 (59.0)
Decrease from Baseline >=10%	n (%)	2 (1.3)	0 (0.0)
Postural orthostatic[1] BP			
Diastolic BP	n	158	156
Decrease >=15mmHg	n (%)	12 (7.6)	14 (9.0)
Systolic BP	n	158	156
Decrease >=25mmHg	n (%)	1 (0.6)	0 (0.0)

[1] Postural orthostatic BP is defined as the difference from last supine BP measurement to first standing BP measurement. BP=Blood Pressure. Subjects may appear in more than 1 category.
Overall-On-Treatment includes all measurements taken while on the investigational product in randomised-withdrawal phase (including tapering).
Endpoint is the last valid assessment obtained after Baseline (Visit 2) whilst on investigational product in randomised-withdrawal phase and on or before last dose of non-taper medication.
On-Taper-Medication is the last valid assessment on or after the date of the first dose of taper medication and on or before the date of the last dose of taper medication.
Follow-up is the earliest of an assessment done at Visit 25 or any other assessment at any other visit which is >=5 days after the last dose of investigational product.

Source: Study Report Body Table 4.7.13, page 3349/4553

d. Dropouts due to Vital Sign Abnormalities

During the Open-label phase, treatment-emergent AEs leading to discontinuation that were reported were hypotension (3/526 [0.6%]), and 1 subject (108-0013) discontinued during the Open-label phase for a syncopal event.

During the Double-blind Randomized-withdrawal Phase two subjects discontinued the study due to cardiac-related TEAEs. One subject discontinued the study due to an SAE of severe, related sinus bradycardia and 1 subject discontinued due to TEAEs of non-serious, related, moderate hypotension and non-serious, mild, related bradycardia.

All events that led to discontinuation resolved.

7.4.4.1 Weight

There were no significant differences in weight changes in SPD503 treatment group and placebo.

Weight Assessments
Weight was measured at screening and weekly and the endpoint/early termination visit.

Mean Weight Changes from Baseline
There were no clinically meaningful differences in mean weight between SPD503 treatment group at Baseline or Endpoint. At Endpoint, the mean change from Baseline was similar among treatment groups ([+4.40kg ± 3.609] and [+3.63kg ±3.413] for the SPD503 and placebo, respectively).

Potentially Clinically Significant Weight Changes
There was no significant difference in the rate of weight increase or decrease from baseline ≥7% between SPD503 group and placebo. See the table below.

Table 28: Weight Outliers at any Time While Receiving SPD503 Treatment (Safety Population of Study SPD503-315)

Body weight		Placebo (N=158)	SPD503 (N=157)
Increase from baseline ≥ 10%	n (%)	77 (48.7.0)	92 (59.0)
Decrease from baseline ≥ 10%	n (%)	2 (1.3)	0 (0.0)

Source: Study Body Report Table 4.7.13, page 3349/4553

Dropouts due to Weight Gain
There were no dropouts due to weight gain.

7.4.5.1 Electrocardiograms (ECGs)

During the Open-label phase, there were no clinically meaningful trends in ECG values across doses. There was 1 subject that had a clinically significant ECG interpretation of first degree AV block. Upon further examination, subject 801-0008, had an abnormal and not clinically significant baseline ECG which was also interpreted as AV block. During the Open-label phase the most frequently reported cardiac-related TEAE was bradycardia, with a total of 7/526 (1.3%) subjects reporting a total of 8 events. There were two subjects who discontinued the study due to cardiac-related TEAE's during the Open-label phase, subject 801-0016 experienced severe sinus bradycardia, related to the use of SPD503-315, and subject 103-0003 discontinued due to hypotension, and mild related bradycardia.

Table 29: ECG QT Outliers at Any Time by Age Group in the Open-label Phase

QT interval		Subjects Aged 6-12 Years (N=391)	Subjects Aged 13-17 Years (N=135)	Total (N=526)
Overall	n	330	115	445
QT Interval ≥480msec	n (%)	1 (0.3)	0	1 (0.2)
QTcF ≥500msec	n (%)	0	0	0
QTcB ≥500msec	n (%)	0	0	0
Change from baseline				
QT ≥30msec-<60msec	n (%)	86 (26.1)	26 (22.6)	112 (25.2)
QT ≥60msec	n (%)	24 (7.3)	12 (10.4)	36 (8.1)
QTcF ≥30msec-<60msec	n (%)	15 (4.5)	8 (7.0)	23 (5.2)
QTcF ≥60msec	n (%)	0	0	0
QTcB ≥30msec-<60msec	n (%)	9 (2.7)	8 (7.0)	17 (3.8)
QTcB ≥60msec	n (%)	0	1 (0.9)	1 (0.2)

Note: Baseline is the average of electrocardiogram values at the Open-label Baseline Visit (Visit 2/Week 0).
Note: Endpoint is the last valid assessment obtained after the Open-label Baseline Visit (Visit 2/Week 0) while on investigational product in Open-label Phase and on or before last dose of non-taper medication.
QTcB= QT interval measured using Bazett's method; QTcF=QT interval measured using Fridericia's method

During the Double-blind Randomized-withdrawal Phase two subjects discontinued the study due to cardiac-related TEAEs. One subject discontinued the study due to an SAE of severe, related sinus bradycardia and 1 subject discontinued due to TEAEs of non-serious, related, moderate hypotension and non-serious, mild, related bradycardia. All events that led to discontinuation resolved.

No subjects experienced a change from baseline in QT interval ≥480msec, or a QTcF or QTcB interval ≥500msec. There were no clinically meaningful differences in mean ECG parameters between SPD503 and placebo. Electrocardiogram QT outliers at any time by treatment group in double-blind randomized-withdrawal phase (Randomized Safety Population)

Table 30: Electrocardiogram QT Outliers at Any Time While Receiving Treatment (Safety Population of Study SPD503-315)

QT interval		Placebo (N=158)	SPD503 (N=157)
Overall	n	123	127
QT Interval ≥480msec	n (%)	0	0
QTcF ≥500msec	n (%)	0	0
QTcB ≥500msec	n (%)	0	0
Change from baseline (Visit 2/Week 0)			
QT ≥30msec-<60msec	n (%)	12 (9.8)	32 (25.2)
QT ≥60msec	n (%)	3 (2.4)	7 (5.5)
QTcF ≥30msec-<60msec	n (%)	2 (1.6)	6 (4.7)
QTcF ≥60msec	n (%)	0	0
QTcB ≥30msec-<60msec	n (%)	6 (4.9)	9 (7.1)
QTcB ≥60msec	n (%)	1 (0.8)	0

Note: Baseline is the average of electrocardiogram values at the Open-label Baseline Visit (Visit 2/Week 0).
Note: Endpoint is the last valid assessment obtained after the Open-label Baseline Visit (Visit 2/Week 0) while on investigational product in the Double-blind Randomized-withdrawal Phase and on or before last dose of non-taper medication or last on-treatment assessment.
QTcB= QT interval measured using Bazett's method; QTcF=QT interval measured using Fridericia's method
Source: Study Report Body Table 44, page 151/4553

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this indication.

7.4.6 Immunogenicity

No immunogenicity study was conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Since this was a dose optimization study, the interpretation of dose response is limited.

7.5.2 Time Dependency for Adverse Events

The time dependency for adverse events was not studied.

7.5.3 Drug-Demographic Interactions

The drug-demographic interactions were not studied.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.

7.5.5 Drug-Drug Interactions

SPD503 is a marketed drug in the USA since 1986. Drug-drug interaction profile had been established and is addressed in current approved Intuniv labeling. No drug-drug interaction studies were conducted in this trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity study has been conducted.

7.6.2 Human Reproduction and Pregnancy Data

The human reproduction and pregnancy were not studied in this trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

The effects on growth were not shown in this short term study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no new information on overdose, drug abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

The 4-month Safety Update to sNDA S-11 was submitted on May 19, 2014. The update included new safety information from the 3 ongoing studies: SPD503-318 and 2 Japanese Studies sponsored by Shinogi (1306A3122 and 1307A3131). There were no

deaths reported as of the cut-off date (May 31, 2014) for the reports of all 3 studies. The results of the studies have thus far been consistent with known results of SPD503. In addition, there have been no publications of studies that described potentially important new toxicological, clinical or epidemiological safety information in relation to SPD503. No new safety signals were identified in ongoing clinical studies, the literature, and post marketing experience.

8 Postmarket Experience

Intuniv has not been withdrawn from the market worldwide for any reason.

9 Appendices

9.1 Literature Review/References

The sponsor submitted a list of literature references and publications referenced in the report which appeared to be acceptable.

9.2 Labeling Recommendations

Multiple disciplines have submitted recommendations for labeling changes to the sponsor and they are being reviewed at this time.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this submission.

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/s/

AEVA N GAYMON-DOOMES
02/24/2015

JING ZHANG
02/24/2015