CLINICAL REVIEW

Application Type	sNDA
Application Number	022037/Supplement 010
Priority or Standard	Priority
Application Submit Date Application Received Date User Fee Received Date	April 22, 2014 April 22, 2014 May 19, 2014
PDUFA Goal Date	November 19, 2014
Division/Office	DPP/ODE1
Reviewer Name	Jenn Sellers, MD, Ph.D.
Review Completion Date	October 6, 2014
Established Name	Guanfacine
Trade Name	Intuniv®
Therapeutic Class	Selective α_2 Agonist
Applicant	Shire Development, Inc.
Formulations	Extended-release Tablets (1 mg, 2 mg, 3 mg and 4 mg)
Dosing Regimen	1- 4 mg for children and 1-7mg for adolescents, Once Daily
Indication	Monotherapy for Attention Deficit Hyperactivity Disorder
Intended Population	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 010, is supported by Study SPD503-312 and Study SPD503-316. Both were Phase 3, double-blind, randomized, multicenter, placebo-controlled studies conducted to evaluate the efficacy, safety, and tolerability of SPD503 in pediatric patients.

Based on the available data obtained from these 2 studies, in which both efficacy and safety have been demonstrated, we recommend an approval of this sNDA.

1.2 Risk Benefit Assessment

The efficacy of once daily dosing with SPD503 in pediatric patients with a diagnosis of ADHD was demonstrated by the positive results from both Study SPD503-312 and Study SPD503-316.

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

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

This review identified no new major risks that would merit a Risk Evaluation and Mitigation Strategy (REMS).

1.4 Recommendations for Post-market 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 HCI) 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

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 US for the treatment of ADHD.

2.4 Important Safety Issues with Consideration to Related Drugs

Both guanfacine and clonidine are central α_2 adrenergic receptor agonists that are approved by FDA for the treatment of ADHD.

Clonidine is the prototypic α_2 adrenergic receptor agonist. It stimulates alpha$_2$-adrenergic receptors in the brain stem and reduces sympathetic outflow from the central nervous system and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

The most common adverse events (AEs) reported with clonidine treatment 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, 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.

The package insert (PI) for clonidine includes the following language regarding overdose with clonidine: "Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression; hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. 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 Pre-submission Regulatory Activity Related to Submission

Guanfacine was approved in 1986 for the treatment of hypertension in patients > 12 years old. Shire opened [redacted] (b) (4)
IND 63,551 (SPD503 - guanfacine HCl ER) on 10/26/2001 to support the treatment of ADHD. Highlights of regulatory interactions between Shire and FDA (DNPDP and DPP) are described below:

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.

04/20/2012: Shire submitted sNDA (Supplement 08) to revise the Prescribing Information (PI) to provide information to clinicians regarding the efficacy and tolerability of once daily dosing with Intuniv (1, 2, 3, 4 mg/day) administered either in the morning or evening when given as monotherapy in children aged 13-17 years with a diagnosis of ADHD.

2.6 Other Relevant Background Information

The New Drug Submission (NDS) for Intuniv was filed in Canada on October 17, 2011 for both monotherapy and adjunctive therapy in children and adolescents (6-17 years old).

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 016-0016 and Subject Identifier 031-0017) 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.

(b) (4) study sites are being inspected. These sites had relatively higher enrollments. 20, (b) (4) and 18 subjects were enrolled in the study site of Dr. John Turnbow (Study SPD503-312), (b) (4) and Dr. Linda S. Harper (Study SPD503-312); respectively. The clinical inspection summary is pending at this time.

3.2 Compliance with Good Clinical Practices

Study SPD503-312 and Study SPD503-316 were 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 3 in Study SPD503-312 claimed nothing to disclose. Three investigators who disclosed financial arrangements by sponsor addressed the potential conflict of interest on the SPD503-312 study by claiming that they were not part of the protocol design; not be privy to the blinded status of subjects and they would not write up publications without peer review.

Furthermore, the sites of these 3 investigators only entered (b) (6) subjects. A total of 314 subjects were randomized in Study SPD503-312. Since the number of subjects enrolled by these 3 investigators was relatively small and since Study SPD503-312 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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This submission includes 2 studies: **Study SPD503-312** and **Study SPD503-316**.

Study SPD503-312 was intended to satisfy post marketing requirement (PMR) 1538-2 (a deferred pediatric study under Pediatric Research Equity Act (PREA) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adolescent patients ages 13 to 17) and the pediatric written request. It was a Phase 3, double-blind, randomized, multicenter, placebo-controlled study.

Study SPD503-316 (additional short-term data in children and adolescents) was a Phase 3, double-blind, randomized, multicenter, placebo- and active-reference study conducted to evaluate the safety and efficacy of SPD503 in children and adolescents with a diagnosis of ADHD when given doses up to 7mg per day (dependent on age) using a flexible dose optimization design.

The following table summarizes these 2 studies.

Table 1: Summary of the ADHD Studies in Children and Adolescents: SPD503-312 and SPD503-316

Study SPD503-312	
Number of Study Sites	52 sites in the US
Study Dates	09/19/2011 – 05/16/2013
Study Design	Randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy and tolerability of once-daily dosing of SPD503 in adolescents aged 13-17 years when given at doses up to 7mg (dosed once daily) using a flexible dose-optimization design
Study Drugs	SPD503 (guanfacine HCl ER)
Randomized/Treated	314/ 312
Gender/Mean Age (years)	Male (63.9%) female (34.4 %)/mean age: 14.5 (13-17)
Endpoints Primary Key Secondary	 Change from baseline on the ADHD-RS-IV total score CGI-S, Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) Report and WFIRS-P Family Score
Study SPD503-316	
Number of Study Sites	Total 58 sites, including 11 sites in US, 2 sites in Canada, and 45 sites in Europe
Study Dates	01/17/2011 – 05/01/2013
Study Design	Randomized, double-blind, multicenter, parallel-group, Placebo and active-controlled (Strattera), dose-optimization, efficacy and safety study to assess the efficacy and tolerability of once-daily dosing with optimized SPD503 in male and female children and adolescents from 6 years to 17 years with a diagnosis of ADHD
Study Drugs	SPD503 (guanfacine HCl ER)
Randomized/Treated	338/337
Gender/Mean Age (years)	Male (73.9%) female (26.1%)/mean age: 10.8 (6-17)
Endpoints Primary Key Secondary	 Change from baseline on the ADHD-RS-IV total score CGI-I, WFIRS-P (Learning and School Domain and Family Domain)

5.2 Review Strategy

I have reviewed the Clinical Study Report (CSR) of Study SPD503-312 and Study SPD503-316, 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 conclusions.

5.3 Discussion of Individual Studies/Clinical Trials

Study SPD503-312 assessed the efficacy and safety of once daily dosing, monotherapy of SPD503 compared to placebo in the treatment of ADHD in children aged 13-17 years. **Study SPD503-316** assessed the efficacy and safety of once daily dosing, monotherapy of SPD503 compared to placebo in the treatment of ADHD in children aged 6-17 years. **SPD503-316** was an additional study which was not required by FDA. Therefore, the review will focus on **Study SPD503-312**.

6 Review of Efficacy

6.1 Rationale for Selection of Studies for Review

The clinical review for efficacy included review of two trials - Study SPD503-312 and Study SPD503-316.

6.2 Study Summary of Study SPD503-312 – Adolescents

6.2.1 Method/Study Design/Analysis Plan of Study SPD503-312

Study SPD503-312 was conducted from 09/19/2011 to 05/16/2013 at 52 sites in the US.

Overall Study Design

Study SPD503-312 was phase 3, multicenter, randomized, double-blind, placebo-controlled, flexible dose optimization study designed to assess the efficacy and tolerability of once daily dosing with SPD503 at doses up to 7mg per day as monotherapy compared with placebo in children aged 13-17 years with diagnosis of ADHD.

All eligible subjects were randomized 1:1 to SPD503 or placebo. Allocation of treatment was to be balanced within each weight group (34.0-41.4, 41.5-49.4, 49.5-58.4, and 58.5-91.0 kg). Subjects were assigned to a weight group at the Baseline Visit (Visit 2) and were maintained in that weight group regardless of weight loss/gain experienced during the study.

This study consisted of the following 5 periods:

Screening Period: 3-35 days

Dose Optimization Period
After randomization, all subjects 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.

Investigators titrated subjects up to the maximum dose permitted for the subject's respective weight group. Dosing was to initiate with 1mg/day starting the morning after the Baseline Visit (Visit 2) and the dose may have been increased by 1mg after a minimum of 1 week on the current dose to a maximum dose according to weight.

Subjects who achieved at least 30% reduction in ADHDRS-IV total score from Baseline Visit (Visit 2) and a CGI-I of 1 or 2 at a given tolerated dose were considered to be at an optimal dose. All subjects initially received 1mg/day of SPD503 or placebo.

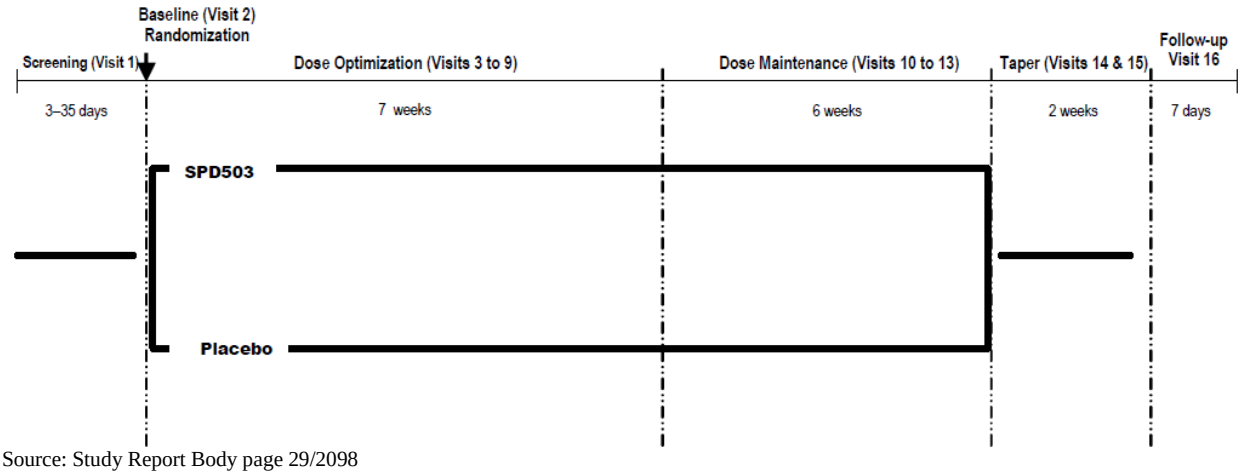
Dose Maintenance Period
All subjects who completed the double-blind Dose Optimization Period entered the double-blind Dose Maintenance Period and were treated for 6 weeks at their optimal dose.

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).

The study design flow chart is shown in **Figure 1.**

Figure 1: Study Design Schematic - Study SPD503-312



Source: Study Report Body page 29/2098

Selection of Study Population

Key Inclusion Criteria:

1. Male or female, aged 13-17 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 [ODD]), 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 outcome measure was the mean change from baseline (Visit 2) to endpoint in the clinician completed ADHD-RS-IV total score.

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 secondary efficacy outcome measure included the clinical global impressions (CGI-S) Scale and Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) Learning and School Domain and Family Domain at the endpoint.

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 questions in the WFIRS-P are framed to assess the degree that a child's behavior or emotional problems have impacted various domains of functioning. The WFIRS-P domains include family, learning and school, life skills, self-concept, social activities, and risky activities. The scale was completed by a parent/LAR and was used to evaluate the functional impairment associated with ADHD. The scale has 50 questions and each question was scored on a 4-point scale ranging from 0 (never or not at all) to 3 (very often or very much). The WFIRS-P is a functional outcome measure that was designed to specifically examine the functional impairment associated with ADHD.

Statistical Methods

The **Enrolled Population** included all subjects who were dispensed study medication at the Baseline visit.

The **Safety Population** included all subjects who took at least one randomized dose of study medication during this trial. The safety assessment used this population dataset.

The **Full Analysis Set (FAS)** included all subjects who took at least one randomized dose of study medication during this trial and had a valid Baseline and at least one post-Baseline follow-up assessment of the primary outcome measure - ADHD-RS-IV Total Score. The efficacy assessment used this data set.

In this trial, 314 subjects were randomized. 2 did not receive at least 1 randomized dose of investigational product. Therefore, FAS included 312 subjects.

The primary efficacy measurement - the ADHD-RS-IV total score was analyzed by a last observation carried forward (LOCF) ANCOVA. The ADHD-RS-IV total score was also analyzed separately for sex, and race.

6.2.2 Results of Study SPD503-312

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 (64.7%), not Hispanic or Latino (78.8%), and white (72.8%). 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 14.5 years (range 13-17 years). The BMI was comparable among all treatment groups.

Table 2: Demographic Characteristics (Safety Population of Study SPD503-312)

	Placebo (N = 155)	SPD503 (N = 157)	Total (N = 312)
n	155	157	312
Age, years			
Mean (SD)	14.6 (1.44)	14.5 (1.35)	14.5 (1.39)
Median	14.0	14.0	14.0
Min, Max	13, 17	13, 17	13, 17
n	155	157	312
Sex, n (%)			
Male	99 (63.9)	103 (65.6)	202 (64.7)
Female	56 (36.1)	54 (34.4)	110 (35.3)
n	155	157	312
Ethnicity			
Hispanic or Latino, n (%)	26 (16.8)	40 (25.5)	66 (21.2)
Not Hispanic or Latino, n (%)	129 (83.2)	117 (74.5)	246 (78.8)
n	155	157	312
Race, n (%)			
White	114 (73.5)	113 (72.0)	227 (72.8)
Black or African American	29 (18.7)	24 (15.3)	53 (17.0)
Asian	3 (1.9)	2 (1.3)	5 (1.6)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (0.6)
Other [a]	8 (5.2)	17 (10.8)	25 (8.0)
n	155	157	312
BMI (kg/m^2)			
Mean (SD)	21.69 (3.239)	22.00 (3.343)	21.85 (3.290)
Median	21.46	21.42	21.44
Min, Max	14.7, 34.1	15.2, 31.1	14.7, 34.1

a Other included biracial, more than 1 race, Ethiopian, and unknown
Note: Percentages are based on the number of subjects with data in each treatment group and total.
BMI=body mass index; Max=maximum; Min=minimum; SD=standard deviation
Source: body report page 76/2098

Baseline Disease Characteristics

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 majority of subjects had the combined subtype of ADHD (67.9%); 29.2% of subjects had the predominantly inattentive subtype and 2.9% had the predominantly hyperactive-impulsive subtype. The mean time since diagnosis of ADHD was 5.1 years and the mean ADHD-RS-IV total score at baseline was 39.9. All subjects were at least moderately ill as defined by the CGI-S score at baseline. Overall, 11.5% of subjects had a current diagnosis of Oppositional Defiant

Disorder at baseline and approximately half (47.4%) exhibited significant oppositional symptoms. They were summarized in the following table.

Table 3: Baseline Disease Characteristics (Safety Population of Study SPD503-312)

	Placebo (N = 155)	SPD503 (N = 157)	Total (N = 312)
ADHD subtype, n (%)			
Predominately inattentive	45 (29.0)	46 (29.3)	91 (29.2)
Predominately hyperactive-impulsive	4 (2.6)	5 (3.2)	9 (2.9)
Combined subtype	106 (68.4)	106 (67.5)	212 (67.9)
Time since ADHD diagnosis (yrs)			
Mean (SD)	5.4 (3.83)	4.8 (3.92)	5.1 (3.88)
Median	6.0	5.0	6.0
Min, Max	0, 15	0, 14	0, 15
Baseline ADHD-RS-IV total score			
Mean (SD)	40.0 (6.11)	39.9 (5.57)	39.9 (5.83)
Median	38.0	39.0	39.0
Min, Max	32, 54	32, 53	32, 54
Baseline CGI-S, n (%)			
Normal, not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	0	0
Moderately ill	83 (53.5)	87 (55.4)	170 (54.5)
Markedly ill	67 (43.2)	67 (42.7)	134 (42.9)
Severely ill	5 (3.2)	3 (1.9)	8 (2.6)
Among the most extremely ill subjects	0	0	0
Current psychiatric comorbidities, n (%)			
None	136 (87.7)	133 (84.7)	269 (86.2)
Diagnosis of ODD [a]	16 (10.3)	20 (12.7)	36 (11.5)
Other	5 (3.2)	6 (3.8)	11 (3.5)
Significant oppositional symptoms[b], n (%)			
Yes	69 (44.5)	79 (50.3)	148 (47.4)
No	86 (55.5)	78 (49.7)	164 (52.6)

a Diagnosis of ODD per psychiatric history electronic case report form comes from the diagnosis of ODD in the current psychiatric comorbidities section.
b Defined as a CPRS-R:L oppositional subscale score at the Baseline Visit (Visit 2) of ≥9 for males and ≥8 for females.
Note: Percentages are based on the number of subjects with data in each treatment group and total. Subjects may have more than one other psychiatric comorbidity
ADHD=attention-deficit/hyperactivity disorder; CPRS-R:L=Conners' Parent Rating Scale-Revised: Long Form
CGI-S=Clinical Global Impressions–Severity; ODD=oppositional defiant disorder; SD=standard deviation
Source: body report page 77/2098

Subject Disposition

A total of 314 subjects were randomized; 209 completed to the end of the Taper Period, 207 completed the study, and 312 were included in the full analysis set. The completion rate at visit 13 (the endpoint, the last visit before taper) was 74.5% and 70.1% for SPD503 and placebo, respectively.

The number of subjects who withdrew by themselves was higher in the SPD503 treatment group (7%) than placebo (2.5%).

Table 4: Disposition of All Subjects in Study SPD503-312

	Placebo (N = 157) n (%)	SPD503 (N = 157) n (%)	Total (N = 314) n (%)
Subjects who were:			401
Screened	157 (100.0)	157 (100.0)	314 (100.0)
Randomized	155 (98.7)	157 (100.0)	312 (99.4)
Safety Population [a]	155 (98.7)	157 (100.0)	312 (99.4)
Full Analysis Set [a]	110 (70.1)	117 (74.5)	227 (72.3)
Completed through Visit 13 [b]	103 (65.6)	106 (67.5)	209 (66.6)
Completed through Visit 15 [c]	102 (65.0)	105 (66.9)	207 (65.9)
Completed through Visit 16 [d]	55 (35.0)	52 (33.1)	107 (34.1)
Early Termination [e]			
Reasons for Early Termination	3 (1.9)	9 (5.7)	12 (3.8)
Adverse event	3 (1.9)	1 (0.6)	4 (1.3)
Protocol violation	13 (8.3)	16 (10.2)	29 (9.2)
Withdrawal by subject	4 (2.5)	11 (7.0)	15 (4.8)
Lost to follow-up	25 (15.9)	9 (5.7)	34 (10.8)
Lack of efficacy	7 (4.5)	6 (3.8)	13 (4.1)
Other			

a Includes all subjects who received at least 1 dose of investigational product during this study.
b Visit 13 was the last visit before taper and is considered the endpoint for statistical purposes, provided that subjects were still on investigational product.
c Visit 15 includes the Taper Period.
e Early termination includes any subject that was randomized but discontinued before Visit 16 (Week 16).
Note: Percentages are based on the number of enrolled (randomized) subjects in each treatment group and total
Source: body report page 74/2098

Concomitant Medication Use

Listings of concomitant medications (Safety Population) in the submission (Section 14, Table 1.3.8) were reviewed. The prohibited medications that were used and might have confounded the evaluation of efficacy included: dexmethylphenidate hydrochloride (2 in placebo), hydrocodone (1 in placebo and 2 in SPD503), hydrocortisone (2 in SPD503), lisdexamfetamine mesilate (2 in placebo and 1 in SPD503), lorazepam (1 in SPD503), methylphenidate (1 in placebo), methylphenidate hydrochloride (4 in placebo), morphine (1 in placebo), prednisone (1 in placebo and 1 in SPD503), and promethazine (2 in SPD503).

Given the robust efficacy observed in this trial, it is unlikely that the prohibited medication use in these subjects would have substantially changed the efficacy result.

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

Protocol Deviations

Four subjects were discontinued from the study for protocol violations: Three subjects in the placebo group were withdrawn due to failure to meet eligibility criteria. One subject in the SPD503 group was withdrawn because of violation of Inclusion Criterion 6 (functioning at age appropriate level) and Exclusion Criterion 9 (BMI > 95th percentile)

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

These protocol deviations would probably not have biased efficacy in favor of the drug.

Table 5: Summary of Protocol Deviations (Safety Population of Study SPD503-312)

	Placebo (N=155) n (%)	SPD503 (N=157) n (%)	Total (N=312) n (%)
Any violation or significant deviation	60 (38.7)	64 (40.8)	124 (39.7)
Failed to meet inclusion/exclusion criteria	14 (9.0)	8 (5.1)	22 (7.1)
Took prohibited medication	26 (16.8)	25 (15.9)	51 (16.3)
Insufficient washout	1 (0.6)	2 (1.3)	3 (1.0)
Became pregnant	0	0 (0.0)	0 (0.0)
Overdosed, abused or misused investigational product	23 (14.8)	34 (21.7)	57 (18.3)
Received incorrect investigational product	7 (4.5)	2 (1.3)	9 (2.9)
Treatment compliance	0	0 (0.0)	0 (0.0)
Other	3 (1.9)[a]	2 (1.3)[b]	5 (1.6)

a Informed consent irregularities (did not sign updated version, did not sign all pages, single pharmacokinetic sample drawn but not consented.
b weight assessment not conducted properly, subject 7 weeks out of window for Visit 13
Source: Study Report Body page 81/2098

Efficacy Findings

Primary Efficacy Endpoint

The primary endpoint for each subject was the mean change from baseline to endpoint on the ADHD-RS-IV total score.

There was a statistically significant difference between the treatment groups in favor of SPD503 ($p<0.001$) in the adjusted mean change from baseline to endpoint in the ADHD-RS-IV total score.

The analysis results of LS Mean (SE) change from baseline in the ADHD-RS-IV Total score for placebo and SPD503 treatment groups at endpoint were shown in the following table.

Table 6: Summary of MMRM Analysis of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Week 13 (FAS) - Study SPD503-312

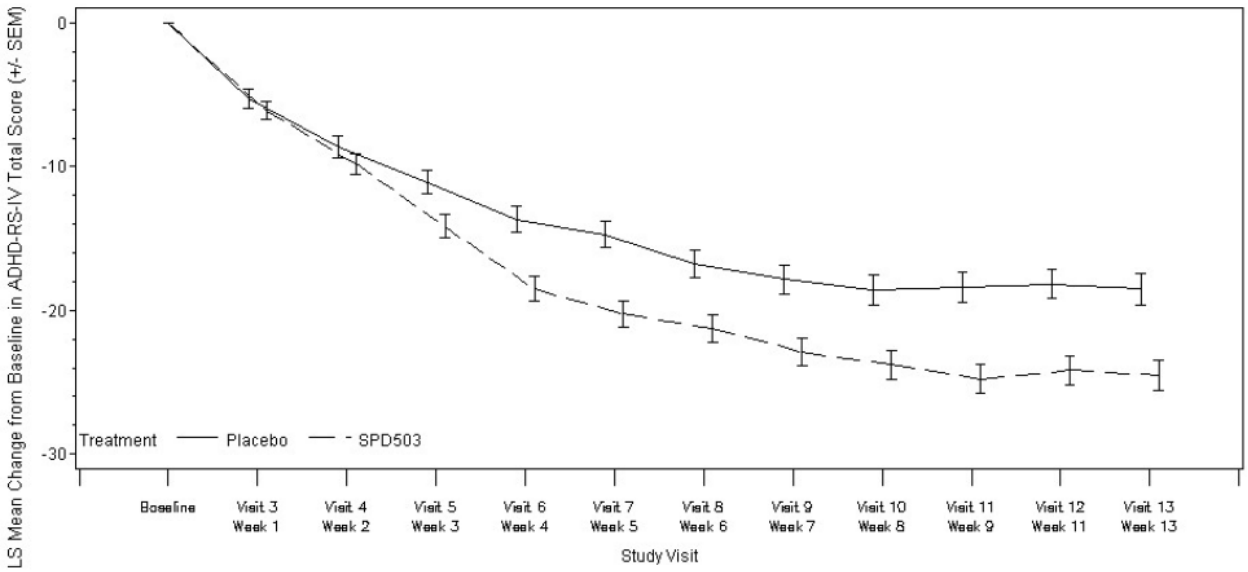
	Placebo (N=155)	**SPD503** (N=157)
Baseline		
N	155	157
Mean (SD)	40.0 (6.11)	39.9 (5.57)
Visit 13		
N	106	109
Mean (SD)	20.3 (13.35)	14.1 (9.38)
Change from baseline		
Mean (SD)	-19.5 (12.63)	-25.7 (10.09)
Comparison to placebo [a]		
LS mean	-18.527	-24.552
Difference in LS means	NA	-6.026
(95% CI)	NA	-8.865, -3.187
Effect Size	NA	0.52
p-value		<0.001

a LS Mean, standard error (SE), effect size, and p-value are based on repeated measures analysis for the change from baseline scores at Visits 3-13 (Weeks 1-13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (11 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including baseline and base line by- time as covariates. Note: A negative difference in LS Mean (SPD503 - placebo) indicates a positive effect of the active treatment over the placebo.
ADHD-RS-IV=Attention deficit/Hyperactivity Disorder Rating Scale-IV; CI=confidence interval; FAS=Full Analysis Set; LS=least squares; MMRM=mixed model repeated measures; NA=not applicable; SD=standard deviation
Source: Study Report Body page 83/2098

The following figure demonstrated the Attention-deficit/Hyperactivity Disorder Rating Scale-IV total score over time.

From Visit 9 through Visit 13 (Weeks 7-13), improvements measured by LS Mean Change From Baseline in ADHD-RS-IV Total Score were statistically significant (p<0.001).

Figure 2: LS Mean Change from Baseline in ADHD-RS-IV Total Score - MMRM Analysis (FAS) - Study SPD503-312



ADHD-RS-IV=Attention deficit/Hyperactivity Disorder Rating Scale-IV; FAS=Full Analysis Set; LS=least squares; MMRM=mixed model repeated measures
Source: Study Report Body page 84/2098

The following table summarized the mean ADHD-RS-IV total score by weight-adjusted dose. The mean reductions at Visit 13 (Week 13) from baseline (indicating improvement) in ADHD-RS-IV total score were greater for each SPD503 weight-adjusted dose compared with placebo.

Table 7: Summary of ADHD-RS-IV Total Score by Weight-adjusted Dose (FAS) - Study SPD503-312

	Placebo	**All Active SPD503**	**SPD503** 0.01-0.04mg/kg	**SPD503** 0.05-0.08mg/kg	**SPD503** 0.09-0.12mg/kg
Baseline					
n	155	157			
Mean (SD)	40.0 (6.11)	39.9 (5.57)			
Visit 13					
n	106	109	19	58	32
Mean (SD)	20.3 (13.35)	14.1 (9.38)	12.4 (7.63)	11.9 (7.71)	19.0 (11.32)
Change from baseline					
Mean (SD)	-19.5 (12.63)	-25.7 (10.09)	-25.3 (9.38)	-27.9 (9.02)	-22.1 (11.45)

Note: Subjects are not assigned to a weight-adjusted dose at baseline, but are tabulated under SPD503 All Active for SPD503 for subjects randomized to SPD503.
ADHD-RS-IV=Attention deficit/Hyperactivity Disorder Rating Scale-IV; FAS=Full Analysis Set; SD=standard deviation
Source: Study Report Body page 86/2098

The mean change at Visit 13 (Week 13) from baseline in ADHD-RS-IV total scores was greater for all SPD503 doses (0.01- 0.12mg/kg) compared with placebo. However, the interpretation of dose response is limited due to dose-optimization study design and the small sample sizes.

Key Secondary Efficacy Endpoint

Clinical Global Impressions-Severity (CGI-S)

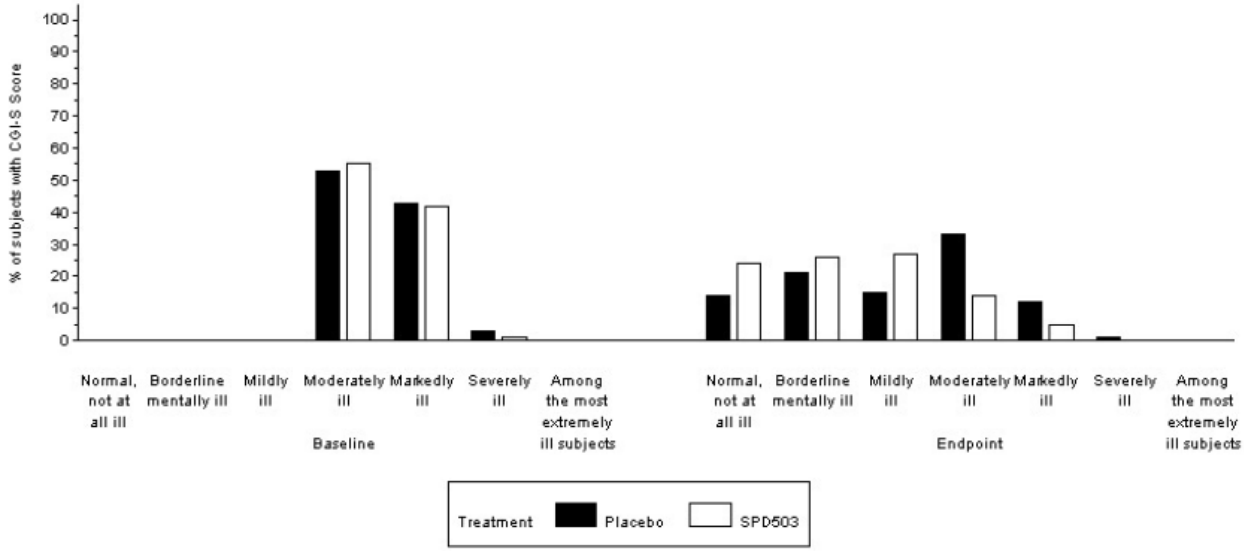
A significantly larger proportion of subjects in the SPD503 group achieved a CGI-S of normal or borderline mentally ill compared with placebo (p=0.01)

Table 8: Summary and Analysis of CGI-S at the Last On-treatment Assessment (FAS) - Study SPD503-312

	Placebo (N=155)	SPD503 (N=157)
Last on-treatment assessment [a], n	155	154
Normal/borderline mentally ill	56 (36.1)	78 (50.6)
Mildly ill or greater p-value [b]	99 (63.9)	76 (49.4) 0.010

a Last on-treatment assessment is the last valid assessment obtained after baseline whilst on investigational product and before first dose taper medication.
b p-value is based on Cochran-Mantel-Haenszel statistic comparing the treatment groups with weight included as a stratification factor.
CGI-S=Clinical Global Impressions–Severity; FAS=Full Analysis Set
Note: Percentages are based on the number of subjects with data at that visit in each treatment group.
Source: Study Report Body page 88/2098

Figure 3: CGI-S at Baseline and the Last On-treatment Assessment (FAS) - Study SPD503-312



Last On-treatment Assessment/Endpoint is the last valid assessment obtained after baseline while on investigational product and before first dose taper medication
Source: Study Report Body page 95/2098

Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) Report

The change from baseline in the WFIRS-P Learning and School Domain score was not statistically significant between the SPD503 group and placebo.

Table 9: Summary of MMRM Analysis of WFIRS-P Learning and School Domain Scores and Change from Baseline at Week 13 (FAS) - Study SPD503-312

	Placebo (N=155)	SPD503 (N=157)
Baseline		
n	147	150
Mean (SD)	1.302 (0.6877)	1.286 (0.6461)
Visit 13		
n	103	103
Mean (SD)	0.806 (0.6156)	0.708 (0.5297)
Change from baseline		
n	101	97
Mean (SD)	-0.448 (0.6107)	-0.565 (0.6784)
Comparison to placebo [a]		
LS mean	-0.457	-0.572
Difference in LS means	NA	-0.115
95% CI	NA	(-0.254, 0.024)
Effect size	NA	0.22
p-value	NA	0.104

a LS Mean, standard error (SE), effect size and P-Value is based on repeated measures analysis for the change from Baseline scores at Visits 9, 11 and 13 (Weeks 7, 9, and 13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (3 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including Baseline and baseline-by-time as covariates
CI=confidence interval; FAS=Full Analysis Set; LS=least squares; MMRM=mixed model repeated measures; NA=not applicable; SD=standard deviation; WFIRS-P=Weiss Functional Impairment Rating Scale-Parent Report
Source: Study Report Body page 89/2098

WFIRS-P Family Score

The change from baseline in the WFIRS-P family score was not statistically significant either between the SPD503 group and placebo.

Table 10: Summary of MMRM Analysis of WFIRS-P Family Domain Scores and Change from Baseline at Week 13 (FAS) - Study SPD503-312

	Placebo (N=155)	**SPD503** (N=157)
Baseline		
n	152	155
Mean (SD)	0.911 (0.7101)	1.005 (0.6902)
Visit 13 (Week 13)		
n	103	106
Mean (SD)	0.605 (0.6702)	0.632 (0.6519)
Change from baseline		
n	101	105
Mean (SD)	-0.342 (0.5780)	-0.415 (0.6029)
Comparison to placebo [a]		
LS mean	-0.314	-0.371
Difference in LS means	NA	-0.057
95% CI	NA	(-0.192, 0.078)
Effect size	NA	0.11
p-value	NA	0.408

a LS Mean, standard error (SE), effect size and p-value are based on repeated measures analysis for the change from baseline scores at Visit 13 (Week13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (3 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including baseline and baseline-by-time as covariates.
CI=confidence interval; FAS=Full Analysis Set; LS=least squares; MMRM=mixed model repeated measures; NA=not applicable; SD=standard deviation; WFIRS-P=Weiss Functional Impairment Rating Scale-Parent Report
Source: Study Report Body page 90/2098

6.2.3 Efficacy Conclusion of Study SPD503-312

SPD503 was effective compared with placebo in the treatment of ADHD symptoms in subjects aged 13-17 years as measured by the change from baseline score on the ADHD-RS-IV total score at endpoint (Visit 13, Week 13) and by the change from baseline score on CGI-S at endpoint.

At Visit 13 (Week 13), subjects who received SPD503 did not show significantly greater improvement from baseline on either the WFIRS-P Learning and School Domain score or the WFIRS-P Family Domain score compared with subjects who received placebo.

6.2.4 Crosscutting Issues of Study SPD503-312

I. Subgroup Analyses
The sponsor did exploratory subgroup analyses of ADHD-RS-IV Total Score.

Sex
Consistent with the primary efficacy result, the mean changes (SD) of ADHD-RS-IV Total score at Endpoint [Visit 13 (Week 13)] from baseline for both males and females were males: SPD503 -25.4±10.26, placebo -20.5±12.94; females: SPD503 -26.5±9.81, placebo -18.0±13.23, demonstrating improvement in both sexes relative to placebo.

Race
At Endpoint, the mean changes ± SD from Baseline in ADHD-RS-IV Total score for white subjects was -25.7 ± 9.87 for the SPD503 group, compared to -19.2 ± 13 for placebo. The results observed for non-white subjects were -25.8 ± 10.68, and -20.3 ± 11.77 for SPD503 and placebo groups, respectively.

ADHD-RS-IV Hyperactivity/Impulsivity Score
Similar to the results for the ADHD-RS-IV Total score, the mean reduction from Baseline in the ADHD-RS-IV Hyperactivity/Impulsivity subscale score for SPD503 treatment group was statistically significantly different from placebo at endpoint.

ADHD-RS-IV Inattention Score
Similar to the results for the ADHD-RS-IV Total score, the mean reduction from Baseline in the ADHD-RS-IV Inattention subscale score for SPD503 treatment group was statistically significantly different from placebo at endpoint.

II. Dose Response
Since this was a dose optimization study, the interpretation of dose response is limited and the sample sizes in some dose groups are relatively small. The mean change (SD) from baseline was -25.3 (9.38); -27.9 (9.02); -22.1 (11.45) for weight-adjusted dose group 0.01-0.04mg/kg; 0.05-0.08mg/kg; 0.09-0.12mg/kg, respectively, compared to placebo -19.5 (12.63).

III. Effect Size
The effect size of all SPD503 treatment groups at endpoint is shown in the previous table**.** Adjusted effect size was calculated as LS mean difference/square root of mean square error and 95% CI of the effect size was based on the normal distribution of the estimators of effect size. A negative difference in LS Mean (Active - Placebo) indicated a positive effect of the active treatment over the placebo.

6.3 Study Summary of Study SPD503-316

6.3.1 Method/Study Design/Analysis Plan of Study SPD503-316

Study SPD503-316 was conducted from Jan 17, 2011 to May 01, 2013 at 58 sites, including 11 sites in the United States (US), 2 sites in Canada, and 45 sites in Europe (Austria, France, Germany, Ireland, Italy, Poland, Romania, Spain, Sweden, Ukraine, and United Kingdom).

Overall Study Design
This was a Phase 3, randomized, double-blind, multicenter, parallel-group, placebo and active (Strattera) controlled, dose-optimization study to assess the efficacy and tolerability of once-daily dosing with optimized SPD503 in children and adolescents ages 6 years to 17 years with ADHD.

Eligible subjects were randomized 1:1:1 ratio to placebo, SPD503, or Strattera. Allocation to treatment was stratified within age group (6 to 12 years and 13 to 17 years) and country.

The duration of Double-blind Evaluation Period:

- Maximum of 10 weeks for children aged 6-12 years, including a 4-week Dose-optimization and 6-week Dose-maintenance Period

- Maximum of 13 weeks for adolescents aged 13-17 years, including a 7-week Dose-optimization and a 6-week Dose-maintenance Period

Dose Optimization Period
After randomization, all subjects underwent a 4-week (subjects aged 6-12 years) or 7-week (subjects aged 13-17 years) double-blind Dose Optimization Period to allow subjects to titrate to their optimal dose.

The maximum dose was 4mg/day for children aged 6-12 years. See the table below.

Table 11: Dose-optimization Schedule for Children Aged 6-12 Years - Study SPD503-316

Weight Group	Week 1	Week 2	Week 3	Week 4
≥25.0kg Max Dose=4mg	1mg	2mg	3mg	4mg

Source: body report page 40/2899 Study SPD503-316

The maximum dose was 4-7mg/day for adolescents aged 13-17 years, depending on the subject's baseline weight. The dose-optimization schedule is shown in the table below.

Table 12: Dose-optimization Schedule for Adolescents Aged 13-17 Years - Study SPD503-316

Weight Group [a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
34.0 – 41.4kg Max Dose=4mg	1mg	2mg	3mg	4mg	Optimize [b]	Optimize [b]	Optimize [b]
41.5 – 49.4kg Max Dose=5mg	1mg	2mg	3mg	4mg	5mg	Optimize [b]	Optimize [b]
49.5 – 58.4kg Max Dose=6mg	1mg	2mg	3mg	4mg	5mg	6mg	Optimize [b]
58.5 – 91.0kg Max Dose=7mg	1mg	2mg	3mg	4mg	5mg	6mg	7mg [c]

a Adolescent subjects had to weigh at least 34.0kg and not more than 91.0kg for inclusion in the study.

b A dose was considered optimal if a subject achieved at least a 30% reduction from the Baseline Visit (Visit 2/Week 0) in the ADHD-RS-IV total score and a CGI-I score of 1 or 2 with tolerable side effects.

c Subjects weighing 58 5-91.0kg may have been titrated to a 7mg/day dose after the subject completed a minimum of 1 week of therapy on a 6mg/day dose and after the investigator performed a thorough review of tolerability and efficacy. In addition, prior to increasing the dose above 6mg, the investigator was required to consult with the PRA medical monitor.

Source: body report page 41/2899 Study SPD503-316

Subjects who achieved at least a 30% reduction in ADHD-RS-IV total score from the

Baseline Visit (Visit 2/Week 0) and a CGI-I of 1 or 2 at a given tolerated dose were considered to be at an optimal dose. Subjects who did not achieve this level of reduction at a given tolerated dose could have been titrated to a higher dose at the investigator's discretion. Further, if a ≥30% reduction in ADHD-RS-IV total score from the Baseline Visit (Visit 2/Week 0) was achieved, the optimal dose was well tolerated, and, in the opinion of the investigator, the subject could have potentially received additional symptom reduction, the dose could have been increased to the next dosage strength.

For Strattera, dosing was based upon weight at the Baseline Visit (Visit 2/Week 0). In children aged 6-12 years and adolescents aged 13-17 years <70kg, dosing was initiated with approximately 0.5mg/kg/day. The dose may have been increased to the target of approximately 1.2mg/kg/day, if well tolerated, after a minimum of 1 week on the current dose. The total daily dose did not exceed 1.4mg/kg/day. Permitted doses of Strattera for subjects weighing <70kg were 10, 18, 25, 40, 60, and 80mg/day depending on the weight of the subject at the Baseline Visit (Visit 2/Week 0). See the table below.

Table 13: Dosing of Strattera for Subjects <70kg by Weight at the Baseline Visit (Visit 2/Week 0) - Study SPD503-316

Weight Range (kg)	STRATTERA First Dose 0.5mg/kg	STRATTERA Up-titration 1.2mg/kg
25.0-29.9	10mg	25mg
30.0-44.5	18mg	40mg
44.6-64.5	25mg	60mg
64.6-69.9	40mg	80mg

Source: body report page 42/2899 Study SPD503-316

Dosing in children and adolescents ≥ 70kg at the Baseline Visit (Visit 2/Week 0) was initiated at 40mg/day and may have been increased, if well tolerated, after a minimum of 1 week on the current dose to 80mg/day. After 1 week at 80mg/day, the dose may have been increased to 100mg/day, if required. The total daily dose in children and adolescents ≥ 70kg was not permitted to exceed 100mg/day. See table below.

Table 14: Dosing of Strattera for Subjects ≥ 70kg at the Baseline Visit (Visit 2/Week 0) - Study SPD503-316

Weight Range (kg)	STRATTERA First Dose	STRATTERA First Up-titration	STRATTERA Second Up-titration
≥70	40mg	80mg	100mg

Source: body report page 42/2899 Study SPD503-316

Dose-maintenance Period
On completion of the Dose-optimization Period, all subjects entered a 6-week Dose-maintenance Period and returned to the site for weekly visits.

Taper Period
The subjects in SPD503 group were required to taper their SPD503 dose downward over a 2-week period. No taper period was required for Strattera or placebo.

Follow-up:
1 week after the last dose of investigational product (window of 7-9 days after last dose). See the table below for taper schedule.

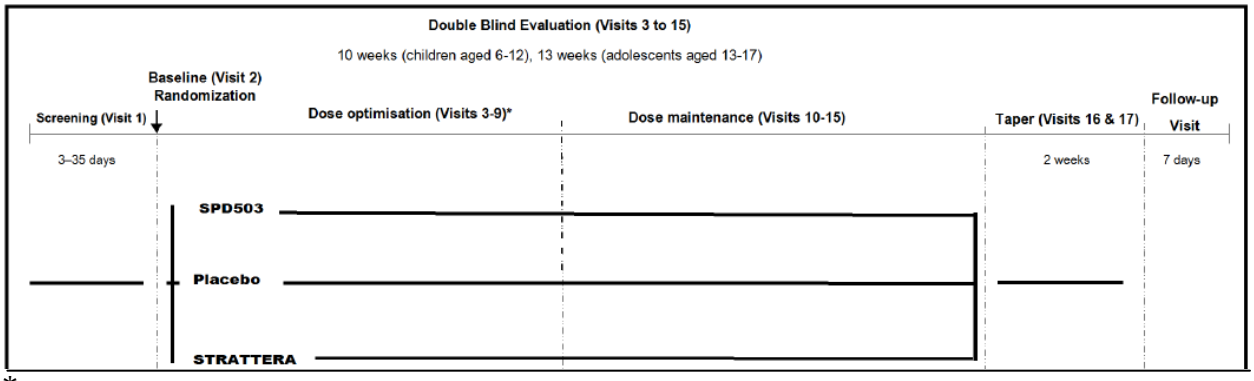
Table 15: Taper Schedule for Study SPD503-316

Last Maintenance Dose	Visit 15/ Week 10 (Children Aged 6-12 Years) Visit 15/ Week 13 (Adolescents Aged 13-17 Years)		Visit 16 / Week 11 (Children Aged 6-12 Years) Visit 16 / Week 14 (Adolescents Aged 13-17 Years)	
	Days 1-4	Days 5-7	Days 8-11	Days 12-14
1mg	1mg	1mg	1mg	1mg
2mg	2mg	2mg	1mg	1mg
3mg	2mg	2mg	1mg	1mg
4mg	3mg	2mg	1mg	1mg
5mg	4mg	3mg	2mg	1mg
6mg	5mg	4mg	3mg	2mg
7mg	6mg	5mg	3mg	2mg

Source: body report page 43/2899 Study SPD503-316

The design is shown in the following figure.

Figure 4: Study Design Schematic - Study SPD503-316



* Dose optimization visits 7-9 for adolescents aged 13-17 years only. Source: body report page 31/2899 for study 316

Selection of Study Population

Key Inclusion Criteria:

- Male or female, aged 6-17 years at the time of consent/assent at the Screening Visit (Visit 1)

- Subject met DSM-IV-TR criteria for a primary diagnosis of ADHD, combined subtype, hyperactive/impulsive subtype, or inattentive subtype based on a detailed psychiatric evaluation using the K-SADS-PL

- Subject had a minimum ADHD-RS-IV total score of 32 at the Baseline Visit (Visit 2/Week 0)

- Subject had a minimum CGI-S score of 4 at the Baseline Visit (Visit 2/Week 0)

- Female subject of child-bearing potential, defined as ≥9 years of age or <9 years of age and post-menarchal, had to have a negative serum β-hCG pregnancy test at the Screening Visit (Visit 1) and a negative urine pregnancy test at the Baseline Visit (Visit 2/Week 0) and agreed to comply with any applicable contraceptive requirements of the protocol

- Subject had a supine and standing blood pressure measurement within the 95th percentile for age, sex, and height

Key Exclusion Criteria:

- Subject had a current, controlled (requiring a prohibited medication or behavioral modification program) or uncontrolled, comorbid psychiatric diagnosis (except ODD), including 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 or lifetime history of bipolar illness, psychosis, or conduct disorder that, in the opinion of the investigator, contraindicated treatment with SPD503 or Strattera or confounded efficacy or safety assessments

- Subject had any condition or illness including clinically significant abnormal Screening Visit (Visit 1) laboratory values which, in the opinion of the investigator, represented an inappropriate risk to the subject and/or could have confounded the interpretation of the study. Mild stable asthma treated without the use of a β-2 agonist was not exclusionary

- Subject had a known history or presence of structural cardiac abnormalities, cardiovascular or cerebrovascular disease, serious heart rhythm abnormalities, syncope, tachycardia, cardiac conduction problems (e.g., clinically significant heart block or QT interval prolongation), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia

- Subject had a known family history of sudden cardiac death, ventricular arrhythmia, or QT prolongation

- Subject had orthostatic hypotension or a known history of hypertension

- Subject had glaucoma

- Subject had clinically significant ECG findings as judged by the investigator with consideration of the central ECG laboratory's interpretation

- Subject had a history of a seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years) or the presence of a serious tic disorder including Tourette's Syndrome

- Subject had a BMI > 95th percentile

- Children aged 6-12 years with a body weight of <25.0kg or adolescents aged 13-17 years had a body weight of <34.0kg or >91.0kg at the Screening Visit (Visit 1)

- Subject was considered a suicide risk in the opinion of the investigator, had previously made a suicide attempt, or had a prior history of, or was demonstrating active suicide ideation. Subjects with intermittent passive suicidal ideation were not necessarily excluded, based on the assessment of the investigator

- Subjects with renal or hepatic insufficiency

The Primary and Secondary Efficacy Endpoints

The primary efficacy outcome measure was the mean change from baseline to endpoint in the clinician completed ADHD-RS-IV total score.

The secondary efficacy outcome measure included the clinical global impressions (CGI) Scale and the WFIRS-P functionality assessment at the endpoint.

Statistical Methods

The **Safety Population** included all subjects who took at least one randomized dose of study medication during this trial. The safety assessment used this population dataset.

The **Full Analysis Set (FAS):** In this trial, 338 subjects were randomized. 337 received at least 1 dose of investigational product and were included in the Safety Population and Full Analysis Set (FAS) (placebo: 111; SPD503: 114; STRATTERA: 112).

The primary efficacy measurement - the ADHD-RS-IV total score was analyzed by a last observation carried forward (LOCF) ANCOVA.

6.3.2 Results of Study SPD503-316

Demographics
There were no clinically significant differences between the treatment groups for demographic characteristics.

Of the 337 subjects in the FAS/Safety Population, 71.8% were in the 6-12 year age group and 28.2% were in the 13-17 year age group. The mean age of subjects was 10.8 years (range 6-17 years).

The majority of subjects was male (73.9%), not Hispanic or Latino (95.5%), and white (93.7%). 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 majority of subjects had the combined subtype of ADHD (85.2%); 10.7% of subjects had the predominantly inattentive subtype and 4.2% had the predominantly hyperactive-impulsive subtype. The mean time since diagnosis was 2.2 years and the mean ADHD-RS-IV score at baseline was 43.3. All subjects were at least moderately ill as defined by the CGI-S score at baseline.

The BMI was comparable among all the treatment groups.

Table 16: Demographic Characteristics (FAS/Safety Population): Study SPD503-316

	Placebo (N = 111)	**SPD503** (N = 114)	**STRATTERA** (N = 112)	**Total** (N = 337)
n	111	114	112	337
Age, years				
Mean (SD)	11.0 (2.76)	10.9 (2.77)	10.5 (2.81)	10.8 (2.78)
Median	11.0	11.0	10.0	11.0
Min, Max	6, 17	6, 17	6, 16	6, 17
Age group, n (%)				
6-12 years	79 (71.2)	81 (71.1)	82 (73.2)	242 (71.8)
13-17 years	32 (28.8)	33 (28.9)	30 (26.8)	95 (28.2)
n	111	114	112	337
Sex, n (%)				
Male	86 (77.5)	76 (66.7)	87 (77.7)	249 (73.9)
Female	25 (22.5)	38 (33.3)	25 (22.3)	88 (26.1)
n	109	112	110	331
Ethnicity				
Hispanic or Latino, n (%)	6 (5.5)	6 (5.4)	3 (2.7)	15 (4.5)
Not Hispanic or Latino, n (%)	103 (94.5)	106 (94.6)	107 (97.3)	316 (95.5)
Missing, n	2	2	2	6
n	109	112	110	331
Race, n (%)				
White	104 (95.4)	105 (93.8)	101 (91.8)	310 (93.7)
Black or African American,	3 (2.8)	5 (4.5)	7 (6.4)	15 (4.5)
American Indian or Alaska Native	0	1 (0.9)	0	1 (0.3)
Other	2 (1.8)	1 (0.9)	2 (1.8)	5 (1.5)
Missing, n	2	2	2	6
n	111	114	112	334
BMI (kg/m^2)				
Mean (SD)	18.78 (2.76)	18.79 (3.02)	18.74 (2.95)	18.77 (2.91)
Median	18.09	18.30	18.20	18.14
Min, Max	14.3, 26.7	13.5, 27.6	14.0, 27.4	13.5, 27.6

Note: Percentages are based on the number of subjects with data in each treatment group and total.
BMI=body mass index; FAS=Full Analysis Set; SD=standard deviation
Source: Study Report Body page 79/2899

Baseline Disease Characteristics

The baseline disease characteristics, which were demonstrated in ADHD subtypes, time since diagnosis, Baseline ADHD-RS-IV total score and Baseline CGI severity rating (CGI-S) and current psychiatric comorbidities and significant oppositional symptoms, were comparable among all treatment groups. They were summarized in the following table.

Table 17: Baseline Disease Characteristics (FAS/Safety Population): Study SPD503-316

	Placebo (N = 111)	SPD503 (N = 114)	STRATTERA (N = 112)	Total (N = 337)
ADHD subtype, n (%)				
Predominantly inattentive	11 (9.9)	15 (13.2)	10 (8.9)	36 (10.7)
Predominantly hyperactive-impulsive	5 (4.5)	6 (5.3)	3 (2.7)	14 (4.2)
Combined subtype	95 (85.6)	93 (81.6)	99 (88.4)	287 (85.2)
Time since ADHD diagnosis (yrs)				
Mean (SD)	2.1 (2.57)	2.3 (2.67)	2.0 (2.27)	2.2 (2.51)
Median	1.0	1.0	1.0	1.0
Min, Max	0, 12	0, 9	0, 10	0, 12
Baseline ADHD-RS-IV				
Mean (SD)	43.2 (5.60)	43.1 (5.47)	43.7 (5.86)	43.3 (5.63)
Median	44.0	43.0	45.0	44.0
Min, Max	32, 54	33, 54	30, 54	30, 54
Baseline CGI-S, n (%)				
Normal, not at all ill	0	0	0	0
Borderline mentally ill	0	0	0	0
Mildly ill	0	0	0	0
Moderately ill	33 (29.7)	21 (18.4)	23 (20.5)	77 (22.8)
Markedly ill	49 (44.1)	60 (52.6)	53 (47.3)	162 (48.1)
Severely ill	27 (24.3)	30 (26.3)	33 (29.5)	90 (26.7)
Among the most extremely ill subjects	2 (1.8)	3 (2.6)	3 (2.7)	8 (2.4)
Current psychiatric comorbidities, n (%)				
None	96 (86.5)	97 (85.1)	101 (90.2)	294 (87.2)
Diagnosis of ODD [a]	14 (12.6)	17 (14.9)	10 (8.9)	41 (12.2)
Other	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.9)
n	111	113	110	334
Significant oppositional symptoms [b], n (%)				
Yes	60 (54.1)	60 (53.1)	68 (61.8)	188 (56.3)
No	51 (45.9)	53 (46.9)	42 (38.2)	146 (43.7)

Note: Percentages are based on the number of subjects with data in each treatment group and total. a Diagnosis of ODD per psychiatric history case report form comes from the diagnosis of ODD in the current psychiatric comorbidities section.
b Defined as a CPRS-R:L oppositional subscale score at the Baseline Visit (Visit 2/Week 0) of ≥14 for males and ≥12 for females.
ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-IV=ADHD Rating Scale-IV; CGI-S=Clinical Global Impression-Severity; CPRS-R:L= Conners' Parent Rating Scale-Revised: Long Form; FAS=Full Analysis Set;
ODD=oppositional defiant disorder; SD=standard deviation
Source: Study Report Body page 81/2899

Subject Disposition

A total of 338 subjects were enrolled into the study at 58 sites including 11 sites in the US, 2 sites in Canada and 45 sites in Europe (77.5% of subjects came from European sites, and 22.5% came from North American sites).

There were 337 subjects in the Safety Population and 337 subjects in the FAS. A total of 272 subjects completed the study through Visit 15 (Week 10/13) (placebo: 92 [82.9%]; SPD503: 91 [79.1%]; Strattera: 89 [79.5%]).

As expected, the number of subjects who withdrew prematurely due to lack of efficacy was higher in the placebo group and the number of subjects who withdrew prematurely due to AEs was higher in the SPD503 treatment group.

Table 18: Disposition of All Enrolled Subjects in Study SPD503-316

	Placebo (N = 111)	**SPD503** (N = 115)	**STRATTERA** (N = 112)	**Total** (N = 338)
Subjects who were:				
Screened				404
Randomized	111 (100)	115 (100)	112 (100)	338 (100)
Safety Population [a]	111 (100)	114 (99.1)	112 (100)	337 (99.7)
Full Analysis Set [a]	111 (100)	114 (99.1)	112 (100)	337 (99.7)
Completed through Visit 15 (Week 10/13) [b]	92 (82.9)	91 (79.1)	89 (79.5)	272 (80.5)
Completed through Visit 17 (Week 12/15) [c]	92 (82.9)	91 (79.1)	89 (79.5)	272 (80.5)
Completed through Visit 18 (Week 13/16) [d]	92 (82.9)	90 (78.3)	87 (77.7)	269 (79.6)
Early termination [e]	19 (17.1)	24 (20.9)	23 (20.5)	66 (19.5)
Reasons for early termination				
Adverse event(s)	1 (0.9)	9 (7.8)	5 (4.5)	15 (4.4)
Protocol violation	0	0	0	0
Withdrawal by subject	4 (3.6)	4 (3.5)	9 (8.0)	17 (5.0)
Lost to follow-up	0	6 (5.2)	3 (2.7)	9 (2.7)
Lack of efficacy	14 (12.6)	5 (4.3)	5 (4.5)	24 (7.1)
Other	0	0	1 (0.9)	1 (0.3)

a Includes all subjects who received at least 1 dose of any investigational product during this study (excludes Subject 804-0003, who was randomized to but did not receive SPD503 due to being lost to follow-up)

b Visit 15 (Week 10/13) was the last visit before taper and is considered the endpoint for statistical purposes, provided that subjects were still on investigational product

c Visit 17 (Week 12/15) includes the Taper Period

d Visit 18 (Week 13/16) includes the Follow-up Visit

e Early termination includes any subject who did not complete all visits through Visit 15 (Week 10/13)

Note: Percentages are based on the number of enrolled (randomized) subjects in each treatment group and total

Source: Study Report Body page 77/2899

Concomitant Medication Use

Overall, the concomitant treatment medications received were: placebo: 35 [31.5%]; SPD503: 36 [31.6%]; and Strattera: 28 [25.0%]. The most common concomitant medications (used by >5% of subjects) were ibuprofen (placebo: 16 [14.4%]; SPD503: 11 [9.6%]; Strattera: 9 [8.0%]) and acetaminophen (placebo: 11 [9.9%]; SPD503: 16 [14.0%]; Strattera: 8 [7.1%]).

Listings of concomitant medications (Safety Population) in the submission (Section 14, Table 1.3.7) were reviewed. The prohibited medications that were used and might have confounded the evaluation of efficacy included: codeine (1 in placebo), chlorcyclizine (1 in placebo), levocabastine (1 in placebo), loperamide hydrochloride, an opioid drug (2 in SPD503) and

caffeine (1 in Strattera). The prohibited medications such as antipsychotics, SSRIs/SNRIs, psychostimulants were not listed in the Table 1.3.7.

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

Protocol Deviations

There were no protocol violations that led to the withdrawal of any subject from the study.

There were subjects who had protocol violations occurring across inclusion and exclusion criteria, taking of prohibited medication, insufficient washout, and incorrect dosing of investigational product; but these subjects continued into the study and these violations occurred across all 3 treatment groups. These protocol deviations probably would not have biased efficacy in favor of the drug.

Efficacy Findings

Primary Efficacy Endpoint

The primary endpoint for each subject was the mean change from baseline to endpoint: Visit 15 (Week 10/13) on the ADHD-RS-IV total score. It was analyzed by an LOCF ANCOVA.

There was a statistically significant difference between the treatment group of SPD503 ($p<0.001$) and placebo in the adjusted mean change from baseline to endpoint in the ADHD-RS-IV total score. Strattera also had a greater improvement from baseline compared with placebo (nominal $p=0.017$). The difference in LS mean change from baseline in ADHD-RS-IV total score at Visit 15 (Week 10/13) compared with placebo was -8.9 (95% CI: -11.9, -5.8) for SPD503 and -3.8 (95% CI: -6.8, -0.7) for Strattera.

Table 19: Summary of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Visit 15 (Week 10/13) (LOCF) (FAS) - Study SPD503-316

	Placebo (N=111)	**SPD503** (N=114)	**STRATTERA** (N=112)
Baseline			
n	111	114	112
Mean (SD)	43.2 (5.60)	43.1 (5.47)	43.7 (5.86)
Visit 15 (Week 10/13)			
n	111	112	112
Mean (SD)	28.1 (14.13)	19.2 (11.85)	25.0 (12.97)
Change from baseline			
Mean (SD)	-15.0 (13.07)	-23.9 (12.41)	-18.6 (11.91)
Comparison to placebo [a]			
LS mean	-15.0	-23.9	-18.8
Difference in LS means	NA	-8.9	-3.8
95% CI	NA	-11.9, -5.8	-6.8, -0.7
Effect size	NA	0.76	0.32
p-value		<0.001	0.017 [b]

a LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as fixed effects, and baseline value as a covariate.

b Nominal p-value uncorrected for multiplicity.

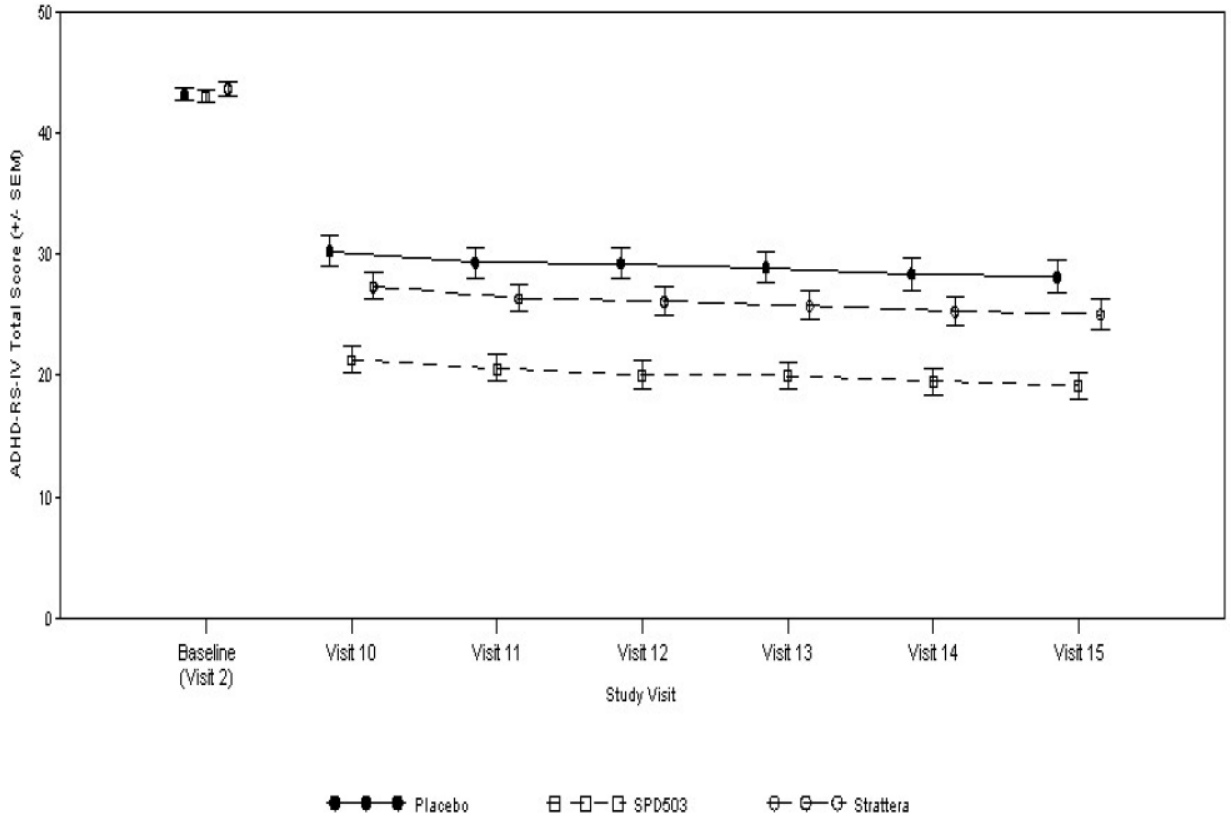
Note: A negative difference in LS Mean (active treatment - placebo) indicates a positive effect of the active treatment over the placebo. The primary analysis is the SPD503 vs. placebo comparison at Visit 15 (Week 10/13).

ADHD-RS-IV=Attention-deficit/Hyperactivity Disorder Rating Scale IV; ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; NA=not applicable; SD=standard deviation.
Source: Study Report Body page 87/2899

Attention-deficit/Hyperactivity Disorder-RS-IV Total Score Over Time

SPD503 demonstrated consistent improvements from baseline in ADHD-RS-IV total score throughout the Dose-maintenance Period, from Visit 10 (Week 5/8) through Visit 15 (Week 10/13) (LOCF) (nominal $p<0.001$) as shown in the following figure.

Figure 5: Mean ADHD-RS-IV Total Score by Visit (LOCF) (FAS) - Study SPD503-316



Source: Study Report Body page 88/2899

Key Secondary Efficacy Results

I. Clinical Global Impressions Scale – Categorical Analysis of Global Improvement

A categorical analysis of the CGI-I assessment by visit is summarized in the table below. At FOTA (Week 10/13) (LOCF), a greater proportion of subjects who received SPD503 were much improved or very much improved on the CGI-I (67.9%) compared with subjects who received placebo (44.1%) and the difference was statistically significant ($p<0.001$)

Table 20: Summary and Analysis of Dichotomized CGI-I at Visit 15 (Week 10/13 (LOCF) (FAS) - Study SPD503-316

		Placebo (N=111)	SPD503 (N=114)	STRATTERA (N=112)
n		111	112	112
Improvement [a]	n (%)	49 (44.1)	76 (67.9)	63 (56.3)
No improvement [a]	n (%)	62 (55.9)	36 (32.1)	49 (43.8)
	95% CI for % improved	34.9, 53.4	59.2, 76.5	47.1, 65.4
	Difference in % improved from placebo		23.7	12.1
	95% CI for % improved		11.1, 36.4	-0.9, 25.1
	Comparison to placebo p-value [b]		<0.001	0.024 [c]

a Improvement includes CGI-I categories 'very much improved' and 'much improved.' No improvement includes all other categories.
b p-value is based on Cochran-Mantel-Haenszel statistic comparing the respective treatment group to placebo with country and age group included as stratification factors.
c Nominal p-value uncorrected for multiplicity.
CGI-I=Clinical Global Impression-Improvement; FAS=Full Analysis Set; LOCF=last observation carried forward
Source: Study Report Body page 90/2899

II. Overall Clinical Global Impressions – Improvement

Subjects in SPD503 group demonstrated statistically significant improvement in overall of the individual categories of CGI-I. See table below.

Table 21: Summary and Analysis of CGI-I at Visit 15 (Week 10/13) (LOCF) (FAS) - Study SPD503-316

	Placebo (N=111)	SPD503 (N=114)	STRATTERA (N=112)
n	111	112	112
Very much improved, n (%)	19 (17.1)	34 (30.4)	24 (21.4)
Much improved, n (%)	30 (27.0)	42 (37.5)	39 (34.8)
Minimally improved, n (%)	27 (24.3)	20 (17.9)	22 (19.6)
No change, n (%)	30 (27.0)	12 (10.7)	22 (19.6)
Minimally worse, n (%)	4 (3.6)	3 (2.7)	3 (2.7)
Much worse, n (%)	1 (0.9)	1 (0.9)	2 (1.8)
Very much worse, n (%)	0	0	0
p-value [a]		<0.001 [b]	0.071 [b]

a p-value is based on Cochran-Mantel-Haenszel statistic comparing the respective treatment group to placebo with country and age group included as stratification factors.
b Nominal p-value uncorrected for multiplicity.
CGI-I=Clinical Global Impression-Improvement; FAS=Full Analysis Set; LOCF=last observation carried forward
Source: Study Report Body page 92/2899

III. Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P), Learning and School Domain Score

Subjects in SPD503 group showed greater improvement from baseline on the WFIRS-P Learning and School Domain score compared with placebo and the difference was statistically significant (p=0.003). Subjects who received Strattera also had improvements compared with placebo (nominal p=0.026).

Table 22: Summary of WFIRS-P Learning and School Domain Scores and Change from Baseline at Visit 15 (Week 10/13) (LOCF) (FAS) - Study SPD503-316

	Placebo (N=111)	**SPD503** (N=114)	**STRATTERA** (N=112)
Baseline			
n	106	108	106
Mean (SD)	1.370 (0.6235)	1.389 (0.6096)	1.400 (0.6284)
Visit 15 (Week 10/13) (LOCF)			
n	104	109	102
Mean (SD)	0.965 (0.6870)	0.769 (0.5777)	0.851 (0.5498)
Change from baseline			
n	100	103	100
Mean (SD)	-0.378 (0.5489)	-0.610 (0.6695)	-0.571 (0.6367)
Comparison to placebo [a]			
LS mean	-0.419	-0.636	-0.581
Difference in LS means	NA	-0.217	-0.162
95% CI	NA	-0.358, -0.076	-0.305, -0.019
Effect size	NA	0.42	0.32
p-value		0.003	0.026 [b]

a LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as a fixed effect, and baseline value as a covariate.
b Nominal p-value uncorrected for multiplicity.
ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; NA=not applicable; SD=standard deviation; WFIRS-P=Weiss Functional Impairment Rating Scale-Parent.
Note: A negative difference in LS Mean (Treatment - Placebo) indicates a positive effect of the active treatment over the placebo.
Source: Study Report Body page 93/2899

IV. WFIRS-P Family Domain Score

At Visit 15 (Week 10/13) (LOCF), subjects in SPD503 group demonstrated statistically significant improvement from baseline on the WFIRS-P Family Domain score compared with placebo (p=0.006). See table below.

Table 23: Summary of WFIRS-P Family Domain Scores and Change from Baseline at Visit 15 (Week 10/13) (LOCF) (FAS) - Study SPD503-316

	Placebo (N=111)	**SPD503** (N=114)	**STRATTERA** (N=112)
Baseline			
n	111	112	110
Mean (SD)	1.439 (0.8134)	1.405 (0.7505)	1.483 (0.7816)
Visit 15 (Week 10/13) (LOCF)			
n	106	111	106
Mean (SD)	1.040 (0.7962)	0.823 (0.6208)	0.994 (0.6632)
Change from baseline			
n	106	109	105
Mean (SD)	-0.387 (0.6091)	-0.596 (0.7706)	-0.507 (0.6893)
Comparison to placebo [a]			
LS mean	-0.409	-0.617	-0.499
Difference in LS means	NA	-0.209	-0.090
95% CI	NA	-0.358, -0.059	-0.241, 0.061
Effect size	NA	0.38	0.16
p-value		0.006	0.242 [b]

a LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as a fixed effect, and baseline value as a covariate.
b Nominal p-value uncorrected for multiplicity.
ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; NA=not applicable; SD=standard deviation; WFIRS-P=Weiss Functional Impairment Rating Scale-Parent
Note: A negative difference in LS Mean (active treatment - placebo) indicates a positive effect of the active treatment over the placebo
Source: Study Report Body page 93/2899

6.3.3 Efficacy Conclusion of Study SPD503-316

SPD503 was effective in the treatment of ADHD symptoms in subjects aged 6-17 years demonstrated by the change from baseline score on the ADHD-RS-IV total score at endpoint. Subjects receiving SPD503 showed statistically significant improvement on the ADHD-RS-IV total score compared with placebo.

Subjects receiving SPD503 also showed statistically significant improvement from baseline in CGI-I and WFIRS-P (Learning and School Domain score and the Family Domain) at endpoint compared to placebo.

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

II. Key Secondary Endpoints
The sponsor also analyzed the results of CGI-I. Subjects who received SPD503 were more improved compared with subjects who received placebo.

IV. Pediatric Development
The pediatric study requirement for ages 0 to 5 years of age was waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group according to Intuniv approval letter dated September 2, 2009.

6.4 Efficacy Conclusions

Efficacy analyses of **Study SPD503-312** in subjects aged 13-17 years and **Study SPD503-316** 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

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review is focus mainly on Study SPD503-312. Since Study SPD503-316 was not required by FDA and its safety profile was not expected to be different from Study SPD503-312 and the previous studies in children, the safety review of Study SPD503-316 will be brief, which the Team Leader Dr. Jing Zhang has agreed.

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)

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

All safety data were from Study SPD503-312 and Study SPD503-316. No pooling of safety data was performed due to flexible dosing design of these two trials.

7.2 Adequacy of Safety Assessments

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

7.2.1.1 Overall Exposure for Study SPD503-312

There were a total of 157 subjects who received SPD503, and 155 subjects who received placebo in the Safety Population in Study SPD503-312.

The mean (SD) length of exposure was 87.9 (29.77) days among placebo subjects and 89.9 (28.23) days among SPD503 subjects.

Table 24: Summary of Drug Exposure (Safety Population of Study SPD503-312)

	Placebo (N=155)	SPD503 (N=157)	Total (N=312)
Length of exposure (days)			
Mean (SD)	87.9 (29.77)	89.9 (28.23)	88.9 (28.98)
Median	105.0	105.0	105.0
Min, Max	7, 124	1, 132	1, 132
Days exposed, n (%)			
1-7	1 (0.6)	3 (1.9)	4 (1.3)
8-14	4 (2.6)	1 (0.6)	5 (1.6)
15-21	3 (1.9)	0	3 (1.0)
22-28	3 (1.9)	4 (2.5)	7 (2.2)
29-35	2 (1.3)	7 (4.5)	9 (2.9)
36-42	9 (5.8)	3 (1.9)	12 (3.8)
43-49	4 (2.6)	2 (1.3)	6 (1.9)
50-56	6 (3.9)	7 (4.5)	13 (4.2)
57-63	5 (3.2)	3 (1.9)	8 (2.6)
64-70	3 (1.9)	4 (2.5)	7 (2.2)
71-77	3 (1.9)	5 (3.2)	8 (2.6)
78-84	1 (0.6)	2 (1.3)	3 (1.0)
85-91	3 (1.9)	1 (0.6)	4 (1.3)
92-98	3 (1.9)	5 (3.2)	8 (2.6)
99-105	66 (42.6)	74 (47.1)	140 (44.9)
>105	39 (25.2)	36 (22.9)	75 (24.0)
Total days exposed	13618	14120	27738
Total years exposed	37.3	38.7	75.9

Note: Length of exposure = last dose date - first dose date + 1. Total number of days exposed is the total number of days over all subjects. Total number of years exposed is the total number of years over all subjects. Percentages were based on the number of subjects in Safety Population in each treatment group.
Max=maximum; Min=minimum; SD=standard deviation
Source: body report 109/2098

The mean optimal dose for the SPD503 treatment group was 4.3mg. Fewer than 20% of subjects received an optimal dose of 1mg (2 subjects [1.5%]), 2mg (12 subjects [9.2%]), or 7mg (10 subjects [7.6%]), with the majority receiving optimal doses of 3, 4, 5, or 6mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] subjects, respectively). The mean weight-adjusted optimal dose was 0.073mg/kg, with most subjects optimized at 0.05-0.08mg/kg (49.6%) or 0.09-0.12mg/kg (35.9%). See table below.

Table 25: Summary of Optimal Dose of SPD503 (Safety Population of Study SPD503-312)

	SPD503 (N=157)
Optimal dose, mg [a]	
N	131
Mean (SD)	4.3 (1.50)
Median	4.0
Min, Max	1, 7
Subjects receiving, n (%)	
1mg	2 (1.5)
2mg	12 (9.2)
3mg	30 (22.9)
4mg	26 (19.8)
5mg	27 (20.6)
6mg	24 (18.3)
7mg	10 (7.6)
Weight-adjusted optimal dose, mg/kg [b]	
Mean (SD)	0.073 (0.0248)
Median	0.073
Min, Max	0.02, 0.12
Subjects receiving, n (%)	
0.01-0.04mg/kg	19 (14.5)
0.05-0.08mg/kg	65 (49.6)
0.09-0.12mg/kg	47 (35.9)

Note: Percentages are based on the number of subjects in Safety Population in each group with dosing data at Visit 9 (Week 7).
a Optimal dose is the dose at Visit 9 (Week 7).
b Weight-adjusted optimal dose is calculated as dose at Visit 9 (Week 7) divided by weight at baseline (Visit 2).
Max=maximum; Min=minimum; SD=standard deviation
Source: body report 110/2098

Summary statistics of the final dose before taper are summarized in the table below. The mean (SD) SPD503 dose before taper was 4.2 (1.48) mg and the mean weight-adjusted dose was 0.071mg/kg with most subjects in the range of 0.05-0.08mg/kg (38.2%) or 0.09-0.12mg/kg (24.2%) at the final dose before taper.

Table 26: Summary of Final Dose before Taper (Safety Population of Study SPD503-312)

	SPD503 (N=157)
Final dose, mg	
N	118
Mean (SD)	4.2 (1.48)
Median	4.0
Min, Max	1, 7
Subjects receiving, n (%)	
1mg	2 (1.3)
2mg	12 (7.6)
3mg	31 (19.7)
4mg	25 (15.9)
5mg	20 (12.7)
6mg	22 (14.0)
7mg	6 (3.8)
Weight-adjusted final dose before taper, mg/kg	
Mean (SD)	0.071 (0.0249)
Median	0.070
Min, max	0.02, 0.12
Subjects receiving, n (%)	
0.01-0.04mg/kg	20 (12.7)
0.05-0.08mg/kg	60 (38.2)
0.09-0.12mg/kg	38 (24.2)

Source: body report 111/2098

7.2.1.2 Overall Exposure for Study SPD503-316

The Safety Population was the same as the FAS, and was defined as all randomized subjects who took at least 1 dose of investigational product. A total of 337 subjects were in the Safety Population: 111 subjects in placebo; 114 subjects in SPD503 and 112 subjects in Strattera group in Study SPD503-316.

The following table summarizes the duration of exposure to investigational product for this study. The majority of subjects remained in the study >77 days, with most having exposure of 78-84 days (placebo: 47.7%; SPD503: 38.6%; STRATTERA: 41.1%).

Table 27: Summary of Drug Exposure (Safety Population of Study SPD503-316)

	Placebo (N=111)	SPD503 (N=114)	STRATTERA (N=112)
Length of exposure (days)			
Mean (SD)	82.5 (22.26)	81.6 (22.06)	80.9 (22.96)
Median	84.0	84.0	84.0
Min, Max	8, 113	1, 113	6, 114
Days exposed, n (%)			
1-7	0	2 (1.8)	3 (2.7)
8-14	5 (4.5)	2 (1.8)	0
15-21	0	0	3 (2.7)
22-28	1 (0.9)	0	1 (0.9)
29-35	1 (0.9)	3 (2.6)	1 (0.9)
36-42	3 (2.7)	2 (1.8)	0
43-49	2 (1.8)	1 (0.9)	3 (2.7)
50-56	0	3 (2.6)	2 (1.8)
57-63	1 (0.9)	5 (4.4)	6 (5.4)
64-70	3 (2.7)	3 (2.6)	4 (3.6)
71-77	2 (1.8)	3 (2.6)	0
78-84	53 (47.7)	44 (38.6)	46 (41.1)
85-91	12 (10.8)	19 (16.7)	16 (14.3)
92-98	1 (0.9)	0	1 (0.9)
99-105	20 (18.0)	24 (21.1)	21 (18.8)
>105	7 (6.3)	3 (2.6)	5 (4.5)
Total days exposed	9161	9308	9060
Total years exposed	25.1	25.5	24.8

Note: Length of exposure = last dose date - first dose date + 1. Total number of days exposed is the total number of days over all subjects. Total number of years exposed is the total number of years over all subjects. Percentages were based on the number of subjects in Safety Population in each treatment group.
Max=maximum; Min=minimum; SD=standard deviation
Source: body report 113/2899

The following table summarizes the optimal dose of SPD503 and STRATTERA in the Safety Population in Study SPD503-316. The mean optimal dose for the SPD503 group was 3.6mg, with over half of the subjects optimized at 3mg (28.8%) or 4mg (30.8%). The mean weight-adjusted optimal dose was 0.09mg/kg, with most subjects optimized at 0.05-0.08 mg/kg (35.6%) or 0.09-0.12 mg/kg(44.2%).

Table 28: Summary of Optimal Dose of SPD503 and STRATTERA (Safety Population of Study SPD503-316)

	SPD503 (N=114)		STRATTERA (N=112)	
Optimal dose, mg [a]				
n	104		100	
Mean (SD)	3.6 (1.31)		42.1 (20.09)	
Median	3.5		40.0	
Min, max	1, 7		10, 100	
Subjects receiving, n (%)	1mg	3 (2.9)	10mg	3 (3.0)
	2mg	19 (18.3)	18mg	0
	3mg	30 (28.8)	25mg	36 (36.0)
	4mg	32 (30.8)	40mg	31 (31.0)
	5mg	9 (8.7)	60mg	22 (22.0)
	6mg	9 (8.7)	80mg	4 (4.0)
	7mg	2 (1.9)	100mg	4 (4.0)
Weight-adjusted optimal dose, mg/kg [b]				
Mean (SD)	0.090 (0.0301)		1.03 (0.205)	
Median	0.090		1.01	
Min, max	0.03, 0.16		0.4, 1.4	
Subjects receiving, n (%)	0.01-0.04mg/kg	9 (8.7)	0.3-<0.8mg/kg	6 (6.0)
	0.05-0.08mg/kg	37 (35.6)	0.8-<1.2mg/kg	73 (73.0)
	0.09-0.12mg/kg	46 (44.2)	1.2-<1.4mg/kg	21 (21.0)
	0.13-0.16mg/kg	12 (11.5)		

a Optimal dose is the dose at Visit 10 (Week 5/8).
b Weight-adjusted optimal dose is calculated as optimal dose divided by weight at baseline.
Max=maximum; Min=minimum; SD=standard deviation
Percentages are based on the numbers with an optimal dose in the Safety Population in each treatment group.
Source: body report 115/2899

Summary statistics of the final dose before taper are summarized in the table below. The mean (SD) SPD503 dose before taper was 4.2 (1.48) mg and the mean weight-adjusted dose was 0.071mg/kg with most subjects in the range of 0.05-0.08mg/kg (38.2%) or 0.09-0.12mg/kg (24.2%) at the final dose before taper.

The mean optimal dose for the STRATTERA group was 42mg.

The following table shows the dose at the Visit 15, the final dose before the tapering. For subjects with an ADHD-RS-IV total score at Visit 15 (Week 10/13) (LOCF), the mean dose was 3.5mg for the SPD503 group and the mean weight-adjusted dose was 0.087mg/kg.

Table 29: Summary of Dose at Visit 15 for Subjects with an ADHD-RS-IV Assessment at Visit 15 (Week 10/13) (LOCF), (Safety Population of Study SPD503-316)

	SPD503 (N=114)		STRATTERA (N=112)	
Visit 15 (Week 10/13) (LOCF) dose, mg				
n	112		112	
Mean (SD)	3.5 (1.33)		41.7 (20.52)	
Median	3.0		40.0	
Min, max	1, 7		10, 100	
Subjects receiving, n (%)	1mg	5 (4.5)	10mg	4 (3.6)
	2mg	20 (17.9)	18mg	0
	3mg	33 (29.5)	25mg	42 (37.5)
	4mg	33 (29.5)	40mg	33 (29.5)
	5mg	10 (8.9)	60mg	24 (21.4)
	6mg	9 (8.0)	80mg	4 (3.6)
	7mg	2 (1.8)	100mg	5 (4.5)
Weight-adjusted Visit 15 (Week 10/13) (LOCF) dose, mg/kg [a]				
Mean (SD)	0.087 (0.0311)		1.01 (0.234)	
Median	0.088		1.00	
Min, max	0.03, 0.16		0.4, 1.4	
Subjects receiving, n (%)	0.01-0.04mg/kg	13 (11.6)	0.3-<0.8mg/kg	11 (9.8)
	0.05-0.08mg/kg	40 (35.7)	0.8-<1.2mg/kg	78 (69.6)
	0.09-0.12mg/kg	47 (42.0)	1.2-<1.4mg/kg	23 (20.5)
	0.13-0.16mg/kg	12 (10.7)		

a Weight-adjusted dose is calculated as dose at ADHD-RS-IV Visit 15 (Week 10/13) (LOCF) divided by weight at baseline.
SD=standard deviation
Source: body report 116/2899

7.2.2 Explorations for Dose Response

Since these Study 312 and Study 316 were dose optimization studies, the dose response of AEs cannot be appropriately interpreted.

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 SPD503-312

An overview of Treatment-Emergent Adverse Events (TEAEs) that occurred during Study SPD503-312 is summarized in the following table.

No deaths occurred during Study SPD503-312. Four subjects (2.5%) receiving SPD503 and 2 subjects (1.3%) receiving placebo experienced a serious Adverse Event (SAE). Nine subjects (5.7%) receiving SPD503 and 3 subjects (1.9%) receiving placebo had a TEAE(s) leading to discontinuation from the study. Twenty one subjects (13.4%) receiving SPD503 and 8 subjects (5.2%) receiving placebo had a TEAE(s) leading to dose reduction.

Table 30: Overall Summary of Treatment-Emergent Adverse Events (Safety Population of Study SPD503-312)

	Placebo (N=155)		**SPD503 (N=157)**	
	Subjects (%)	# AEs	Subjects (%)	# AEs
Any TEAE	120 (77.4)	413	147 (93.6)	667
Severe	5 (3.2)	9	15 (9.6)	23
Serious	2 (1.3)	3	4 (2.5)	7
Related [a]	80 (51.6)	176	125 (79.6)	372
Leading to termination	3 (1.9)	3	9 (5.7)	15
Leading to dose reduction	8 (5.2)	11	21 (13.4)	27
Leading to death	0	0	0	0

Note: Percentages were based on the number of subjects in the Safety Population in each treatment group.
Note: Adverse events were coded using MedDRA Version 12.1.
Note: 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.
a Relatedness was determined by the investigator.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Source: body report 112/2098

7.3.1.1 Deaths

No death was reported during the conduct of Study SPD503-312.

7.3.2.1 Nonfatal Serious Adverse Events (SAEs)

Four (4) subjects receiving SPD503 experienced a total of 7 SAEs during the conduct of Study SPD503-312 including vomiting and withdrawal hypertension (**Subject Identifier 016-0016**); cholecystitis chronic and abdominal pain (**Subject Identifier 031-0017**); homicidal ideation (**Subject Identifier 004-0006**); loss of consciousness and concussion (**Subject Identifier 004-0009**). These cases are reviewed below.

Subject Identifier 016-0016

Subject 016-0016 was a 14-year-old black male with ADHD (inattentive subtype) with no relevant medical history/concomitant medications. He received his first dose of SPD503 1mg on (b) (6) (Day 1). The subject's dose was titrated according to protocol to the final of 7mg beginning (b) (6) (Day 45). No TEAEs were reported for this subject during the treatment period. The subject completed the treatment period on (b) (6) (Day 93) and began the taper period according to the protocol.

On (b) (6) (Day 106), while receiving SPD503 2mg, the subject experienced SAE of vomiting. He was suspected to have a viral infection since he didn't experience any symptoms the next day ((b) (6) , Day 107) when he finished his last dose. On (b) (6) (Day 108), the subject experienced severe vomiting and was hospitalized. His blood pressure ranged from 150-180/70-90 mmHg during hospitalization. His initial clinical laboratory tests revealed a significantly increased CPK level (>3000IU). A CT scan revealed no abnormalities. The subject was hydrated and treated with clonidine for hypertension and pantoprazole for vomiting. The vomiting and withdrawal hypertension resolved on (b) (6) (Day 114) and the subject was discharged from the hospital (no BP values available for this day). This reviewer believed that this SAE was related to the treatment of SPD503.

Subject Identifier 031-0017

Subject 031-0017 was a 13-year-old white female with ADHD (combined subtype) and with no relevant medical history/concomitant medications. She received her first dose of SPD503 1mg on (b) (6) (Day 1). On (b) (6) (Day 29), while receiving SPD503 4mg, the subject experienced a TEAE of abdominal symptoms, which was considered as cholecystitis and given omeprazole. She was then seen by a pediatric gastroenterologist and MRI and upper gastrointestinal endoscopy were performed which suggested the possibility of gall bladder disease. On (b) (6) (Day 55), while receiving SPD503 7mg, she was hospitalized for worsening abdominal symptoms. She had a laparoscopic cholecystectomy on (b) (6) (Day 57). On (b) (6) (Day 60), the subject experienced moderate abdominal tenderness, moderate decreased appetite, moderate epigastric discomfort, moderate nausea (intermittent), and moderate vomiting (intermittent) and was given ibuprofen, macrogol, vicodin, and ondansetron.

The subject decided to withdraw from the study on (b) (6) (Day 60). SPD503 was tapered per the protocol. On (b) (6) (Day 67), while receiving SPD503 3mg, her abdominal pain intensified to severe and she experienced moderate peripheral neuropathy. On (b) (6)

(Day 68), the severe abdominal pain, and intractable nausea and vomiting prompted an emergency room visit that led to readmission to the hospital for testing. The subject was treated with promethazine and pethidine hydrochloride for her abdominal pain and gabapentin for the peripheral neuropathy. Her last dose of SPD503 2mg was on (b) (6) (Day 74) when she was reported to have mild abdominal discomfort. The abdominal tenderness, decreased appetite, epigastric discomfort, nausea, and vomiting resolved on (b) (6) (Day 78), 4 days after the last dose. The peripheral neuropathy and abdominal discomfort were ongoing at the time of last dose.

This reviewer believes that the SAE of abdominal symptoms could possibly be related to the treatment of SPD503 because her abdominal symptoms did not resolve after laparoscopic cholecystectomy but those symptoms were resolved 4 days after the discontinuation of SPD503. Even though the peripheral neuropathy and abdominal discomfort were ongoing at the time of last dose, these symptoms might take longer to resolve.

Subject Identifier 004-0006

Subject 004-0006 was a 13-year-old white male with ADHD (combined subtype) with ODD, with no relevant medical history and no concomitant medications. He was reported to have experienced severe homicidal ideation on the treatment Day 1 of SPD503 1mg. He was hospitalized and SPD503 1mg was discontinued the same day. This reviewer did not believe this SAE was related to the treatment of SPD503.

Subject Identifier 004-0009

Subject 004-0009 was a 14-year-old male with ADHD (inattentive subtype) with no relevant medical history/concomitant medications. He experienced SAEs of severe loss of consciousness and severe concussion while playing football on the treatment of Day 37 of SPD503. This reviewer did not believe this SAE was related to the treatment of SPD503.

7.3.3.1 Dropouts and/or Discontinuations

Nine (9) (5.7%) subjects receiving SPD503 had treatment-emergent AEs leading to discontinuation while 3 subjects (1.9%) receiving placebo discontinued the study due to TEAEs.

Among the 9 SPD503 subjects who had TEAEs leading to discontinuation, events included: homicidal ideation (1 subject), irritability (1 subject), fatigue (2 subjects), orthostatic hypotension (1 subject), somnolence (1 subject), and Wolff-Parkinson-White syndrome (1 subject); diarrhea, headache, and nausea (1 subject); bradycardia, hypotension and dizziness (1 subject); and constipation, dizziness postural (1 subject)

Table 31: Summary of Treatment-emergent Adverse Events Leading to Discontinuation (Safety Population of Study SPD503-312)

	Placebo (N=155)		SPD503 (N=157)	
Preferred Term:	n (%)	Number of TEAEs	n (%)	Number of TEAEs
Any TEAE leading to discontinuation	3 (1.9)	3	9 (5.7)	15
Fatigue	0	0	2 (1.3)	2
Bradycardia	0	0	1 (0.6)	1
Constipation	0	0	1 (0.6)	1
Diarrhoea	0	0	1 (0.6)	1
Dizziness	0	0	1 (0.6)	1
Dizziness postural	0	0	1 (0.6)	1
Headache	0	0	1 (0.6)	1
Homicidal ideation	0	0	1 (0.6) [a]	1
Hypotension	0	0	1 (0.6)	1
Irritability	0	0	1 (0.6)	1
Nausea	0	0	1 (0.6)	1
Orthostatic hypotension	0	0	1 (0.6)	1
Somnolence	0	0	1 (0.6)	1
Wolff- Parkinson-White syndrome	0	0	1 (0.6)	1
Cognitive disorder	1 (0.6)	1	0	0
Depression	1 (0.6)	1	0	0
Pelvic fracture	1 (0.6) [a]	1	0	0

a Events were serious adverse events
Note: Percentages were based on the number of subjects in the Safety Population of each treatment group.
Note: Adverse events were coded using MedDRA Version 12.1.
Note: Treatment-emergent AEs were defined as AEs that start or worsen during the period between the day of a subject's first date of investigational product and the third day (inclusive) after their treatment is stopped.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Source: body report page 120/2098

7.3.4.1 Other Treat-emergent Adverse Events of Special Interest

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

7.3.4.1 Sedative Events

The analysis of sedative events included the following preferred terms: somnolence, sedation, and hypersomnia. Sedative events were reported in 85 subjects (54.1%) receiving SPD503 compared with of 35 subjects (22.6%) receiving placebo.

Table 32: Summary of Onset and Duration of Treatment-emergent Sedative Events (Safety Population of Study SPD503-312)

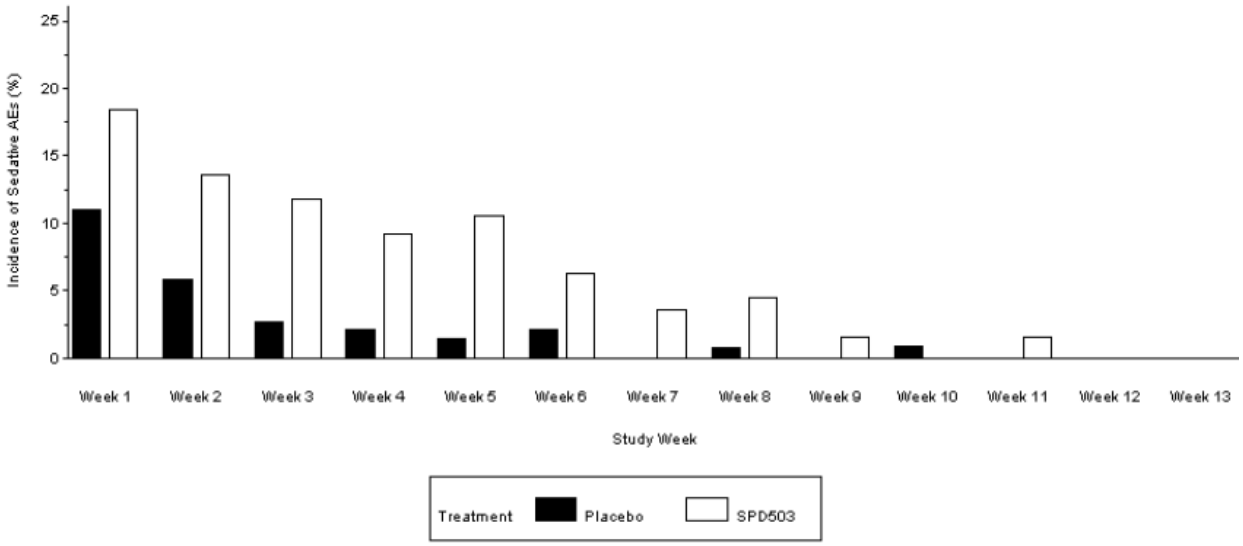
	Placebo (N=155)	SPD503 (N=157)
Subjects with at least 1 treatment-emergent sedative event [a]		
n (%)	35 (22.6)	85 (54.1)
Number of treatment-emergent sedative events	42	123
Number of treatment-emergent sedative events per subject		
Mean (SD)	1.2 (0.53)	1.4 (0.81)
Median	1.0	1.0
Min, max	1, 3	1, 5
Onset day of first event		
Mean (SD)	10.0 (10.25)	14.1 (11.94)
Median	8.0	12.0
Min, max	1, 40	1, 50
Duration (days) of individual events		
Mean (SD)	43.3 (37.52)	27.4 (26.94)
Median	33.0	17.0
Min, max	2, 105	1, 109
Duration (days) from start of first AE through end of last AEs		
Mean (SD)	51.7 (38.13)	38.4 (31.59)
Median	43.0	27.0
Min, max	2, 106	1, 109
Severity of TEAEs; n (%) [b]		
Mild	33 (78.6)	69 (56.1)
Moderate	8 (19.0)	51 (41.5)
Severe	1 (2.4)	3 (2.4)
Worst severity of TEAEs; n (%)[c]		
Mild	26 (74.3)	42 (49.4)
Moderate	8 (22.9)	41 (48.2)
Severe	1 (2.9)	2 (2.4)
TEAEs; n(%) [b]:		
Unresolved TEAEs	2 (4.8)	7 (5.7)
Resolved prior to start of the Taper Period	24 (57.1)	97 (78.9)
Resolved during the Taper Period	10 (23.8)	11 (8.9)
Resolved 1-3 days after last dose of investigational product	3 (7.1)	5 (4.1)
Resolved >3 days after last dose of investigational product	3 (7.1)	3 (2.4)
Drug withdrawn [b]	0	1 (0.8)
Dose reduced [b]	5 (11.9)	11 (8.9)

a Percentages are based on the number of subjects in the Safety Population in each treatment group.
b Percentages are based on the number of treatment-emergent sedative events.
c Percentages are based on the number of subjects with a treatment-emergent sedative event.
Note: Treatment-emergent AEs were defined as AEs that start or worsen during the period between the day of subject's first date of investigational product and the third day (inclusive) after treatment is stopped.

If an event onset day was missing but the month was present, then either the first day of the month or the first dose date was used, depending on which is later. If an event end day is missing but the month is present, then either the last day of the month or the last dose date is used, depending on which was earlier. Adverse events were coded using MedDRA 12.1.
Note: Sedative events include somnolence, sedation, and hypersomnia.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SD=standard deviation; TEAE=treatment emergent adverse event
Source: body report page 123/2098

There was a higher incidence (%) of sedative events in SPD503 subjects compared with placebo throughout the study and there was a trend for the incidence of sedative events to decrease over time. See figure below.

Figure 6: Incidence of Sedative Events by Week (Safety Population of Study SPD503-312)



Source: body report page 124/2098

7.3.5.1 Submission Specific Primary Safety Concerns

No submission specific primary safety concerns were identified.

Study SPD503-316

An overview of TEAEs that occurred during Study SPD503-316 is presented is summarized in the following table.

Since Study SPD503-316 is not a required study by FDA. The safety review will focus on SAEs and AEs that caused discontinuation or the AEs that were not labeled.

Table 33: Overall Summary of Treatment-emergent Adverse Events (Safety Population of Study SPD503-316)

	Placebo (N=111)		SPD503 (N=114)		STRATTERA (N=112)	
	Subjects (%)	**# AEs**	**Subjects (%)**	**# AEs**	**Subjects (%)**	**# AEs**
Any TEAE	73 (65.8)	322	88 (77.2)	509	76 (67.9)	424
Severe	3 (2.7)	4	8 (7.0)	11	2 (1.8)	2
Serious	1 (0.9)	1	1 (0.9)	1	0	0
Related [a]	44 (39.6)	136	70 (61.4)	277	62 (55.4)	278
Leading to termination	1 (0.9)	1	9 (7.9)	19	5 (4.5)	5
Leading to dose reduction	2 (1.8)	2	9 (7.9)	21	4 (3.6)	12
Leading to death	0	0	0	0	0	0

Note: Adverse events were coded using MedDRA Version 12.1. Percentages were based on the number of subjects in the Safety Population in each treatment group. Treatment-emergent adverse events 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.

a Relatedness was determined by the investigator.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE= treatment-emergent adverse event.

Source: body report of Study 316 page 118/2899

7.3.1.2 Deaths

No death was reported during the conduct of Study SPD503-316. See table above.

7.3.2.2 Nonfatal Serious Adverse Events (SAEs)

One subject (0.9%) receiving SPD503 experienced a SEA of syncope, which was labeled in the WARNINGS AND PRECAUTIONS.

7.3.3.2 Dropouts and/or Discontinuations

Nine subjects (7.9%) receiving SPD503, 5 subjects (4.5%) receiving Strattera and 1 subject (0.9%) receiving placebo experienced TEAE(s) that led to discontinuation. See table below.

Table 34: Summary of Treatment-emergent Adverse Events Leading to Discontinuation (Safety Population of Study SPD503-316)

System organ class Preferred term	Placebo (N=111)		SPD503 (N=114)		STRATTERA (N=112)	
	Subjects (%)	# AEs	Subjects (%)	# AEs	Subjects (%)	# AEs
Any TEAE leading to discontinuation	1 (0.9)	1	9 (7.9)	19	5 (4.5)	5
Psychiatric disorders	**0**	**0**	**5 (4.4)**	**8**	**1 (0.9)**	**1**
Affect lability	0	0	1 (0.9)	1	0	0
Aggression	0	0	1 (0.9)	1	0	0
Anxiety	0	0	1 (0.9)	1	0	0
Depressed mood	0	0	0	0	1 (0.9)	1
Insomnia	0	0	2 (1.8)	2	0	0
Obsessive thoughts	0	0	1 (0.9)	1	0	0
Persecutory delusion	0	0	1 (0.9)	1	0	0
Terminal insomnia	0	0	1 (0.9)	1	0	0
Nervous system disorders	**0**	**0**	**4 (3.5)**	**5**	**2 (1.8)**	**2**
Headache	0	0	1 (0.9)	1	0	0
Somnolence	0	0	3 (2.6)	3	2 (1.8)	2
Syncope	0	0	1 (0.9)	1	0	0
Vascular disorders	**1 (0.9)**	**1**	**0**	**0**	**0**	**0**
Hypotension	1 (0.9)	1	0	0	0	0
General disorders and administration site conditions	**0**	**0**	**3 (2.6)**	**3**	**1 (0.9)**	**1**
Fatigue	0	0	1 (0.9)	1	1 (0.9)	1
Irritability	0	0	2 (1.8)	2	0	0
Gastrointestinal disorders	**0**	**0**	**2 (1.8)**	**2**	**1 (0.9)**	**1**
Abdominal pain	0	0	1 (0.9)	1	0	0
Nausea	0	0	1 (0.9)	1	0	0
Vomiting	0	0	0	0	1 (0.9)	1
Metabolism and nutrition disorders	**0**	**0**	**1 (0.9)**	**1**	**0**	**0**
Decreased appetite	0	0	1 (0.9)	1	0	0

Note: Percentages were based on the number of subjects in the 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 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 their treatment was stopped.
Note: Termination defined as event that resulted in action taken of drug withdrawal.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Source: body report of Study 316 page 125/2899

The only TEAEs reported by more than 1 subject that led to discontinuation included: somnolence (SPD503: 3 subjects; STRATTERA: 2 subjects), insomnia (SPD503: 2 subjects,

with 1 additional SPD503 subject reported insomnia), irritability (SPD503: 2 subjects), and fatigue (SPD503: 1 subject; STRATTERA: 1 subject).

7.4 Supportive Safety Results

Study SPD503-312

7.4.1.1 Common Adverse Events

This reviewer summarized the most common AEs which has occurred ≥5% and at least twice placebo rate) in Study SPD503-312 according to Table 30 of the study report (report-body.pdf, page 113/2098) in this submission: a summary of TEAEs occurring in ≥ 5% of subjects in any treatment group. The most common AEs included somnolence, sedation, insomnia, dry mouth, and postural dizziness as shown in the table below, which insomnia and dry mouth were not labeled as the most common AEs.

Table 35: Summary of Treatment - Emergent Adverse Events Occurring in ≥ 5% and at Least Twice Placebo Rate in SPD503 (Safety Population of Study SPD503-312)

Preferred Term AE	Placebo (N=155) Subject n (%)	SPD503 (N=157) Subject n (%)
Somnolence	33 (21.3)	69 (43.9)
Sedation	3 (1.9)	18 (11.5)
Insomnia	6 (3.9)	14 (8.9)
Dry mouth	0	12 (7.6)
Dizziness postural	3 (1.9)	8 (5.1)

Note: Percentages were based on the number of subjects in the Safety Population of each treatment group.
Note: Adverse events were coded using MedDRA Version 12.1.
Note: Treatment-emergent AEs were defined as AEs that 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.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Source: compiled from Table 30 in Study Report Body, page 114/2098.

7.4.2.1 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 4.6.1: the List of Outlier Clinical Laboratory Tests: Hematology (Safety Population). It appears that all outliers occurred during Pre-Treatment of SPD503. 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 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.

7.4.3.1 Vital Sign Data

The vital sign changes seen in Study SPD503-312 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, subjects receiving SPD503 had 3.7 bpm mean decrease from Baseline in supine pulse compared with a 1.0 bpm mean increase in subjects receiving placebo. Similar results were seen in standing pulse. See table below.

Table 36: Summary of Pulse by Treatment Group (Safety Population of Study SPD503-312)

	Placebo (N=155)	SPD503 (N=157)
Supine Pulse, bpm		
Baseline mean (SD)	71.3 (10.03)	70.0 (10.31)
Mean (SD) change from baseline at endpoint	1.0 (10.94)	-3.7 (12.22)
Mean (SD) change from baseline at end of taper (Visit 15)	1.3 (11.09)	3.0 (12.67)
Standing Pulse, bpm		
Baseline mean (SD)	82.3 (13.16)	82.4 (12.21)
Mean (SD) change from baseline at endpoint	1.0 (11.65)	-2.0 (13.30)
Mean (SD) change from baseline at end of taper (Visit 15)	3.0 (12.89)	5.2 (14.35)

SD=standard deviation
Source: Study Report Body, page 126/2098

Systolic Blood Pressure

Consistent with the known effects of guanfacine, subjects receiving SPD503 had 1.6 mmHg mean decrease from Baseline in supine systolic BP compared with a 0.5 mmHg mean increase in subjects receiving placebo. There was even a greater mean decrease in standing systolic BP in SPD503 treatment groups (-4.4 mmHg).

Table 37: Summary of Systolic Blood Pressure by Treatment Group (Safety Population of Study SPD503-312)

	Placebo (N=155)	SPD503 (N=157)
Supine systolic blood pressure, mmHg		
Baseline mean (SD)	112.6 (9.31)	111.5 (8.32)
Mean (SD) change from baseline at endpoint	0.5 (8.81)	-1.6 (8.77)
Mean (SD) change from baseline at end of taper (Visit 15)	0.5 (9.46)	2.7 (8.98)
Standing systolic blood pressure, mmHg		
Baseline mean (SD)	113.4 (9.15)	111.8 (9.21)
Mean (SD) change from baseline at endpoint (SD)	0.5 (9.76)	-4.4 (10.45)
Mean (SD) change from baseline at end of taper	-0.3 (9.74)	2.2 (10.41)

Source: Study Report Body, page 127/2098

Diastolic Blood Pressure

Consistent with the known effects of guanfacine, subjects receiving SPD503 had 1.3 mmHg mean decrease (-1.3 mmHg) from Baseline in supine diastolic BP compared with a 0.1 mmHg mean decrease (-0.1 mmHg) in subjects receiving placebo. Subjects receiving SPD503 had 2.9 mmHg mean decrease (-2.9 mmHg) from Baseline in standing diastolic BP while Subjects in

placebo had 0.1 mmHg mean decrease (-0.1 mmHg). See table below. The supine diastolic blood pressure was observed to reach its lowest point around Visit 8 (Week 6).

Table 38: Summary of Diastolic Blood Pressure by Treatment Group (Safety Population of Study SPD503-312)

	Placebo (N=155)	SPD503 (N=157)
Supine diastolic blood pressure, mmHg		
Baseline mean (SD)	64.9 (7.30)	64.3 (7.52)
Mean (SD) change from baseline at endpoint	-0.1 (7.21)	-1.3 (9.31)
Mean (SD) change from baseline at end of taper (Visit 15)	0.4 (8.09)	1.5 (7.76)
Standing diastolic blood pressure, mmHg		
Baseline mean (SD)	70.2 (7.71)	69.6 (8.10)
Mean (SD) change from baseline at endpoint	-0.1 (7.67)	-2.9 (9.28)
Mean (SD) change from baseline at end of taper (Visit 15)	0.3 (8.28)	1.1 (7.78)

Source: Study Report Body, page 128/2098

Postural Orthostatic Blood Pressure

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 39: Summary of Postural Orthostatic Blood Pressure (Change from Supine to Standing and Change from Baseline to Endpoint) by Treatment Group (Safety Population of Study SPD503-312)

	Placebo (N=155)	SPD503 (N=157)
Postural orthostatic systolic BP [a], mmHg		
Baseline mean (SD)	0.8 (6.94)	0.4 (6.69)
Mean (SD) change from baseline at endpoint	-0.1 (9.25)	-2.8 (8.34)
Mean (SD) change from baseline at end of taper (Visit 15)	-0.8 (8.49)	-0.5 (9.50)
Postural orthostatic diastolic BP [a], mmHg		
Baseline mean (SD)	5.3 (6.62)	5.2 (6.97)
Mean (SD) change from baseline at endpoint	-0.0 (7.50)	-1.6 (7.97)
Mean (SD) change from baseline at end of taper (Visit 15)	-0.1 (7.64)	-0.4 (7.28)

Postural Orthostatic BP actual values refer to the change from supine to standing; changes from Baseline are the double delta change from Baseline change from supine to standing.
Source: Study Report Body, page 128/2098

c. Potentially Clinically Significant Vital Sign Changes

In summary, subjects receiving SPD503 were more likely than placebo to have a supine pulse ≤ 50bpm (26.6% vs. 7.1%), supine systolic BP < 100 mmHg (55.8% vs. 31.0%); and supine diastolic BP < 60mmHg (76.0% vs. 64.5%). In terms of postural orthostatic BP, a decrease of ≥ 25mmHg in systolic BP was reported more often in SPD503 group than in placebo (8.4% vs. 1.9%) and a decrease of ≥ 15mmHg in diastolic BP was reported more often in SPD503 group than in placebo (11.0% vs. 5.8%).

Table 40: Vital Sign Outliers at any Time While Receiving Treatment (Safety Population of Study SPD503-312)

Vital Sign		**Placebo (N=155)**	**SPD503 (N=157)**
Supine pulse	n	155	154
≤50bpm	n (%)	11 (7.1)	41 (26.6)
≥100bpm	n (%)	12 (7.7)	4 (2.6)
Standing pulse	n	155	154
≤50bpm	n (%)	1 (0.6)	5 (3.2)
≥100bpm	n (%)	69 (44.5)	51 (33.1)
Supine systolic blood pressure	n	155	154
<100 mmHg	n (%)	48 (31.0)	86 (55.8)
>140 mmHg	n (%)	1 (0.6)	1 (0.6)
Supine diastolic blood pressure	n	155	154
<60 mmHg	n (%)	100 (64.5)	117 (76.0)
>90 mmHg	n (%)	3 (1.9)	2 (1.3)
Postural Orthostatic blood pressure [a]			
Diastolic blood pressure	n	155	154
Decrease ≥15mmHg	n (%)	9 (5.8)	17 (11.0)
Systolic blood pressure	n	155	154
Decrease ≥25mmHg	n (%)	3 (1.9)	13 (8.4)

[a] Postural Orthostatic BP actual values refer to the change from supine to standing.
Source: body report table 38, page 131/2098

d. Dropouts due to Vital Sign Abnormalities

There was one SPD503 **subject (016-0016)** who reported an SAE of severe, related withdrawal hypertension on Day 106. This case was discussed in the SAE section. Two SPD503 subjects withdrew from the study as a result of non-serious TEAEs of hypotension; **Subject 005-0008** withdrew due to bradycardia and hypotension and **Subject 028-0010** withdrew due to orthostatic hypotension. The 2 cases are described below.

Subject 005-0008 was a 17-year-old white female with ADHD (inattentive subtype) with no relevant medical history and was not receiving concomitant medications. On SPD503 treatment Day 29, she experienced severe bradycardia, severe hypotension, and severe dizziness. Her vitals

were not available then. She withdrew from the study on SPD503 treatment Day 30 due to these symptoms. Her supine and standing SBP/DBP measurements on Day 30 (at Early Termination Visit) were 91/50 and 81/49mmHg, respectively; and her supine and standing heart rates were 42 and 44bpm, respectively. Her bradycardia and hypotension resolved on Day 37, when her supine and standing SBP/DBP measurements were 124/77 and 109/74mmHg, respectively, and her supine and standing heart rates were 72 and 108bpm, respectively. The dizziness resolved on Day 56.

Subject 028-0010
Subject 028-0010 was a 15-year-old white female with ADHD (inattentive subtype) with no relevant medical history and was not receiving concomitant medications.

On SPD503 treatment Day 31, while receiving SPD503 5mg, the subject experienced moderate orthostatic hypotension, mild fatigue, mild insomnia, and mild somnolence, but her vitals were not available then. Her supine and standing SBP/DPB were reported 98/52 and 94/52mmHg, respectively at Visit 6 (Day 28). She withdrew on Day 34. Her supine and standing SBP/DBP measurements on Day 35 were 100/68 and 75/48mmHg, respectively. Her orthostatic hypotension was reported to be resolved on Day 36; however, the blood pressure measurements were not available then. The fatigue, insomnia, and somnolence were reported to be resolved on Day 40.

7.4.4.1 Weight

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

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

b. 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 ([+1.61kg ± 2.494] and [+1.55kg ±2.329] for the SPD503 and placebo, respectively).

c. 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 41: Weight Outliers at any Time While Receiving SPD503 Treatment (Safety Population of Study SPD503-312)

Body weight		**Placebo (N=155)**	**SPD503 (N=154)**
Increase from baseline ≥ 7%	n (%)	31 (20.0)	34 (22.1)
Decrease from baseline ≥ 7%	n (%)	6 (3.9)	6 (3.9)

Source: body report table 38, page 131/2098

d. Dropouts due to Weight Gain

There was no dropout due to weight gain.

7.4.5.1 Electrocardiograms (ECGs)

There was no dropout due to ECG changes. This reviewer did not identify new findings.

This reviewer examined the list of subjects with ECG outliers in safety population in Section 14, Table 4.9.1 in the submission and did not find any clinically meaningful ECK changes in the SPD503 Treatment group except one subject experienced a change from baseline QTcF of >60msec. This subject had a QTcF of 357msec at baseline which increased to a maximum of 442msec at Week 13. No AE was reported that was associated with this QTcF increase and the subject withdrew at Week 13 for reasons other than a TEAE.

Table 42: Electrocardiogram QT Outliers at Any Time While Receiving Treatment (Safety Population of Study SPD503-312)

QT interval		Placebo (N=155)	SPD503 (N=157)
Overall	n		
QT interval ≥480msec	n (%)	0	0
QTcF ≥500msec	n (%)	0	0
QTcB ≥500msec	n (%)	1 (0.8)	0
Change from baseline			
QTcF ≥30msec-<60msec	n (%)	3 (2.3)	3 (2.3)
QTcF ≥60msec	n (%)	0	1 (0.8)
QTcB ≥30msec-<60msec	n (%)	6 (4.6)	5 (3.9)
QTcB ≥60msec	n (%)	0	0

Source: body report table 39, page 134/2098

7.4.6.1 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this indication.

7.4.7.1 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 Interaction

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

There are no additional submissions and safety issues.

8 Post-market 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

This reviewer has examined the proposed labeling changes dated 9/10/2014. This reviewer has the following recommendations:

- (b) (4)

9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENN W SELLERS
10/06/2014

JING ZHANG
10/06/2014