This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:
- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
### STUDY SYNOPSIS

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**Title of the study:**
A Phase 3, Double-blind, Randomized, Multi-center, Placebo-controlled, Dose-optimization Study Evaluating the Safety, Efficacy, and Tolerability of Once-daily Dosing with Extended-release Guanfacine Hydrochloride in Adolescents Aged 13-17 Years Diagnosed With Attention-deficit/Hyperactivity Disorder (ADHD)

**Coordinating principal investigator:**
United States

**Study center(s):**
This was a multicenter study conducted at 52 sites in the United States (US).

**Publications (references):** Not applicable.

**Study period:**
- First subject consented: 19 Sep 2011
- Last subject’s last visit: 16 May 2013

**Phase of development:**
3

**Objectives:**

**Primary Objective:**
The primary objective of this study was to assess the efficacy of optimized SPD503 compared with placebo in the treatment of adolescents aged 13-17 years with a diagnosis of attention-deficit/hyperactivity disorder (ADHD) as measured by the ADHD Rating Scale-IV (ADHD-RS-IV).

**Key Secondary Objectives:**
1. To evaluate the effect on the clinician’s global impressions of ADHD severity with optimized SPD503 compared with placebo as measured by the Clinical Global Impressions-Severity (CGI-S) Scale.
2. To evaluate the changes in functional impairment associated with ADHD with optimized SPD503 compared with placebo as measured by 2 separate domains of the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P): the Learning and School Domain and the Family Domain.

**Other Secondary Objectives:**

Additional secondary objectives of this study were:
1. To evaluate the effect on the clinician’s global impressions of ADHD improvement with optimized SPD503 compared with placebo as measured by the Clinical Global Impressions-Improvement (CGI-I) Scale.
Name of sponsor/company: Shire Development LLC
Name of finished product: SPD503
Name of active ingredient: Extended-release Guanfacine HCl

Other Secondary Objectives (continued):
2. To evaluate the changes in functional impairment associated with ADHD of optimized SPD503 compared with placebo as measured by the WFIRS-P global score and individual domains.
3. To evaluate the safety and tolerability of optimized SPD503 compared with placebo based on treatment-emergent adverse events (TEAEs), clinical laboratory results, electrocardiogram (ECG) results, vital signs, and results from the Brief Psychiatric Rating Scale for Children (BPRS-C), a structured side-effect questionnaire (SSEQ), and Columbia Suicide Severity Rating Scale (C-SSRS).
4. To evaluate the tolerability of optimized SPD503 compared with placebo based on the Pediatric Daytime Sleepiness Scale (PDSS).
5. To collect blood samples to aid in the development of a population pharmacokinetic model of SPD503.
   Note: pharmacokinetic data and methods are summarized in a separate report, which is provided as an Appendix to the SPD503-312 Clinical Study Report.
6. To assess the impact on executive functioning and behavioral regulation through the Behavior Rating Inventory of Executive Function (BRIEF) – Parent Form.

Methodology:
This study was a double-blind, placebo-controlled, randomized study conducted 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.

Eligible subjects were randomized using a 1:1 ratio 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 58.5-91.0kg). 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.

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. Dosing was to be flexibly optimized to maximize the potential benefits while minimizing the risk of adverse events (AEs). Investigators could titrate 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. The investigator was to consider the efficacy, safety, and tolerability profile when determining the optimal dose for each subject. Subjects who achieved at least ≥30% reduction in ADHD-RS-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.

This study consisted of 5 periods:
1. Screening and Washout: 3-35 days.
2. Dose Optimization Period: the double-blind evaluation of SPD503 and placebo initiated with a Dose Optimization Period of 7 weeks.
3. 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.
4. Dose Tapering Period: 2 weeks.
5. Follow-up: 1 week (Visit 16) after the last dose of investigational product (window of 7-9 days after last dose).

**Number of subjects (planned and analyzed):**

The original sample size calculation required that 280 subjects (140 subjects in each of the SPD503 and placebo groups) be randomized into the study. The primary efficacy variable was the change from the Baseline Visit (Visit 2) at Week 13 (Visit 13) for the ADHD-RS-IV total score.

A blinded review of the sample size, in terms of the overall (blinded) standard deviation (SD) of the change from baseline to endpoint for the primary efficacy variable, was planned after 80% of subjects were enrolled into the study. The sample size was increased after the blinded sample size review was performed.

The revised sample size calculation required that 310 subjects aged 13 to less than 18 years of age with ADHD (155 subjects in each of the SPD503 and placebo groups) were required to be randomized into the study. It was also required that at least 25% of randomized subjects be female.

A total of 314 subjects were randomized: 157 to receive SPD503, 157 to receive placebo. Of the 314 randomized subjects, 312 received at least 1 dose of investigational product and were included in the Full Analysis Set and Safety Population. Of the 312 subjects in the Safety Population, 99 (63.9%) were male and 54 (34.4%) were female.

**Diagnosis and main criteria for inclusion:**

Eligible subjects were male or female aged 13-17 years at the time of consent/assent and met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (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 Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version (K-SADS-PL) at the Screening Visit (Visit 1). Subjects were to have a minimum ADHD-RS-IV total score of 32 at the Baseline Visit (Visit 2), a minimum CGI-S score of 4 at the Baseline Visit (Visit 2), and supine and standing blood pressure (BP) measurement within the 95th percentile for age, sex, and height.

**Main criteria for exclusion:**

Subjects were ineligible if they had any current, controlled (requiring a prohibited medication or behavioral modification program) or uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder [ODD]), including any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder (PTSD), bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder (OCD), 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 might have confounded efficacy or safety assessments. In addition, subjects with a medical history of cardiac abnormalities or disease were ineligible.
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**Investigational product, dose, mode of administration, and batch number(s):**

SPD503 is an extended-release tablet formulation containing guanfacine hydrochloride designed for once-daily oral administration. Investigational product was manufactured by Shire US Manufacturing; Inc (Owings Mills MD) The sponsor supplied SPD503 in 1, 2, 3, and 4mg tablets. The sponsor also supplied placebo in matching 1, 2, 3, and 4mg tablets. Batch numbers for SPD503 were: **1mg**, **2mg**, **3mg** and **4mg**. Batch numbers for matching SPD503 placebo were: **1mg**, **2mg**, **3mg**, and **4mg**.

**Reference product(s), dose, mode of administration, and batch number(s):** Not applicable.

**Duration of treatment:**

- Planned duration of Screening Period: 3-35 days
- Planned duration of the Treatment Period: 15 weeks (7-week dose-optimization, 6-week dose-maintenance, and 2-week dose tapering)
- Planned duration of Post-treatment Follow-up Period: 7 days (+2 days) after the last dose of investigational product

**Criteria for evaluation:**

**Efficacy:**

The primary efficacy measure was the change from the Baseline Visit (Visit 2) for the ADHD-RS-IV total score at Visit 13 (Week 13). Efficacy was assessed using the ADHD–RS-IV, CGI-S, CGI-I, BRIEF - Parent Form, and WFIRS-P.

**Safety:**

Safety assessments included BPRS-C, C-SSRS, PDSS, AEs, SSEQ, clinical laboratory tests, vital signs, ECG measurements, and physical examinations.

**Statistical methods:**

**Primary Efficacy Analysis:**

The primary efficacy analysis was performed on the observed change from the Baseline Visit (Visit 2) in the ADHD-RS-IV total score at Week 13 (Visit 13) for the Full Analysis Set (FAS). A mixed model repeated measures (MMRM) was used to analyze the observed change from the Baseline Visit (Visit 2) scores at all post-baseline, pre-taper, on-treatment visits (Visits 3-13). The mean ADHD-RS-IV score and change from baseline score was summarized for each visit by treatment group for the observed data.

**Key Secondary Analyses:**

A dichotomized CGI-S value was a key secondary efficacy endpoint. The CGI-S responses were dichotomized into 2 categories, with CGI-S of 1 or 2 combined into 1 category (normal/borderline mentally ill) and CGI-S>2 the other category (mild mentally ill or greater). For all visits from the Baseline Visit (Visit 2) through Visit 13 and last on-treatment assessment (LOTA) with a valid CGI-S, the CGI-S dichotomized response was summarized and analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by weight group to examine treatment group effects.

The Learning and School Domain, and the Family Domain of WFIRS-P change from the Baseline Visit (Visit 2) to Visit 13 were also defined as key secondary endpoints and these data were analyzed using a MMRM using similar methodology as for the primary efficacy analysis.
Name of sponsor/company: Shire Development LLC  
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**Secondary Efficacy Analyses:**

The change from the Baseline Visit (Visit 2) to Visits 3-13 for the hyperactivity-impulsivity subscale total score and inattention (“inattentiveness”) subscale total score of the ADHD-RS-IV were summarized by treatment group and analyzed using a MMRM, using similar methodology to that described for the primary efficacy analysis.

A further secondary efficacy endpoint of response was defined and analyzed. Response was defined as a percentage reduction from the Baseline Visit (Visit 2) in the ADHD-RS-IV total score of ≥30% and a CGI-I=1 or 2. The number and percentage of subjects in each category was summarized by treatment group at Visits 3-13 (Weeks 1-13) and last on-treatment assessment with a valid score/CGI-I, and treatment effects were examined using a CMH test stratified by weight group. The number and percentage of subjects with an ADHD-RS-IV total score ≤18 versus >18 were summarized by treatment group at Visits 3-13 and last on-treatment assessment with a valid score. Treatment effects were examined using a CMH test stratified by weight group. At all post-baseline visits through Visit 13 (Week 13) and last on-treatment assessment (LOTA) with a valid CGI-I or CGI-S, the CGI-I and CGI-S were summarized and analyzed using a CMH test stratified by weight group to examine treatment group effects.

The CGI-I analysis was repeated with the analysis variable dichotomized into 2 categories, with “very much improved” and “much improved” combined into 1 category (improved) and the remaining levels combined into the other (not improved). The Behavioral Rating Inventory of Executive Function (BRIEF) - Parent Form scores and changes from the Baseline Visit (Visit 2) were summarized at the Baseline Visit (Visit 2) and Visits 9, 11, and 13 (Weeks 7, 9, and 13). Analyses were performed on the change from baseline for the Global Executive Composite (GEC), Behavioral Regulation Index (BRI), and Metacognition Index (MI) subscale T-scores at Visits 9, 11, and 13 (Weeks 7, 9, and 13) using a MMRM using similar methodology as for the primary efficacy analysis. The WFIRS-P change from the Baseline Visit (Visit 2) for the global score and individual domain scores were summarized at the Baseline Visit (Visit 2) change from baseline at Visits 9, 11, and 13 (7, 9, and 13). Analyses were performed on the change from the Baseline Visit (Visit 2) for the WFIRS-P global score and each individual domain score at Visits 9, 11 and 13 (7, 9, and 13) using a MMRM using similar methodology as for the primary efficacy analysis.

**Safety Analyses:**

The safety and tolerability of SPD503 compared with placebo was based on treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), clinical laboratory assessments, Pediatric Daytime Sleepiness Scale (PDSS), Brief Psychiatric Rating Scale for Children (BPRS-C), Columbia Suicide Severity Rating Scale (C-SSRS), and Structure Side-Effect Questionnaire (SEQ).
Name of sponsor/company: Shire Development LLC
Name of finished product: SPD503
Name of active ingredient: Extended-release Guanfacine HCl

**Results:** A total of 314 subjects were randomized: placebo 157; SPD503 157. Safety Population: total 312; placebo 155; SPD503 157. Full Analysis Set: total 312; placebo 155; SPD503 157.

**Efficacy results:**

**Primary:**

SPD503 was effective compared with placebo in the treatment of ADHD symptoms in subjects aged 13-17 years of age with a diagnosis of ADHD as measured by the change from baseline score on the ADHD-RS-IV total score at Visit 13 (Week 13). At Visit 13 (Week 13), subjects receiving SPD503 showed statistically significant and clinically relevant improvement on the ADHD-RS-IV total score compared with subjects receiving placebo (p<0.001).

**Key Secondary:**

- At the LOTA (Visit 13/Week 13/LOCF), a significantly larger proportion of subjects in the SPD503 group achieved a CGI-S of normal or borderline mentally ill compared with placebo (p=0.010).
- At Visit 13 (Week 13) subjects who received SPD503 did not show significantly greater improvement from baseline on the WFIRS-P Learning and School Domain score compared with subjects who received placebo (p=0.104). At Visit 13 (Week 13), subjects who received SPD503 did not show significantly greater improvement from baseline on the WFIRS-P Family Domain score compared with subjects who received placebo (p=0.408). Although improvement was noted in both treatment groups, the mean change from baseline in the Learning and School Domain score was judged to be clinically meaningful as it exceeded the minimal important difference (MID) noted in the literature.

**Other Secondary:**

- Significant improvements in ADHD-RS-IV were consistently evident in the SPD503 treatment group throughout the Dose Maintenance Period using observed data.
- SPD503 demonstrated a treatment benefit over placebo on the ADHD-RS-IV subscales of hyperactivity/impulsivity and inattention.
- SPD503 demonstrated a treatment benefit over placebo on the proportion of subjects who showed improvement on the CGI-I at the LOTA.
- A greater treatment response (defined as a percentage reduction from baseline in the ADHD-RS-IV total score of ≥30% and a CGI-I of 1 or 2) was shown at endpoint for subjects receiving SPD503 compared with the placebo group.
- Symptomatic remission: At the LOTA 61.7% of subjects in the SPD503 group had an ADHD-RS-IV total score ≤18 compared with 41.3% of subjects in the placebo group.
- SPD503 did not show greater improvement from baseline at Visit 13 (Week 13) on the WFIRS-P secondary analyses for all domains and the global score.
- SPD503 did not show greater improvement from baseline at Visit 13 (Week 13) on the BRIEF composite score or sub scale T-scores (BRI or MI) compared with subjects who received placebo. Although not statistically significant at Week 13, there was evidence of improvement from baseline in
the BRIEF composite, index, and domain scores. This suggests clinically meaningful improvement in executive dysfunction to endpoint, reflected in mean scores for both treatment groups that were no longer considered clinically significant (<65).

- A robust exposure response was developed that demonstrated that the decrease in ADHD-RS-IV score from the placebo response trajectory would be 37.1 % (95%CI: 32.2, 42.0%) per 0.1mg/kg of SPD503 exposure. The response was similar for all ADHD subtypes and for adolescent and child pediatric subjects with ADHD.

In summary, for subjects diagnosed with ADHD, overall efficacy of SPD503 was demonstrated for the primary objective and for 1 of the 2 key secondary objectives by demonstrating significant improvements in symptoms as measured by the ADHD-RS-IV and global functioning as measured by the CGI. The efficacy of SPD503 was supported by clinically meaningful improvement on the majority of secondary measures.

**Safety results:**

- The mean optimal dose in adolescents was 4.3mg. The mean weight adjusted optimal dose was 0.073mg/kg, with the majority of subjects (85.5%) optimized at doses between 0.05mg/kg and 0.12 mg/kg. This range of optimal doses was consistent with the range found to be efficacious in previous placebo controlled studies.

- The most frequently reported TEAEs were somnolence, headache, fatigue, dizziness, decreased appetite, nausea, nasopharyngitis, and sedation.

- One subject in the SPD503 group experienced 2 SAEs that were judged by the investigator as related: vomiting and withdrawal hypertension.

- Treatment-emergent AEs leading to discontinuation were reported by 3 (1.9%) placebo and 9 (5.7%) SPD503 subjects. Among the 9 SPD503 subjects who had AEs leading to discontinuation, events included: homicidal ideation, irritability, fatigue, orthostatic hypotension, somnolence, Wolff-Parkinson-White syndrome, diarrhea, headache, nausea, bradycardia, hypotension and dizziness, constipation, and dizziness postural.

- The SSEQ was also used in this study. As expected, due to the application of a targeted method to solicit effects, the SSEQ generally recorded a higher percentage of side effects in both the placebo and SPD503 groups. However, the overall conclusions regarding the side effect profile of SPD503 did not change.

- The mean (SD) number of treatment-emergent sedative events per subject was 1.2 (0.53) and 1.4 (0.81) among placebo and SPD503 subjects, respectively. The mean (SD) day of onset was 10.0 (10.25) and 14.1 (11.94) days for placebo and SPD503 respectively. No clinically meaningful differences were observed in the mean (SD) duration of individual events between subjects receiving placebo or SPD503 (43.3 [37.52] and 27.4 [26.94] days, respectively). In general, the incidence of sedative events decreased over time.

- The impact on blood pressure and pulse in this study was consistent with the known profile on SPD503.

- There were no clinically meaningful changes on mean ECG and QTc-related parameters and no ECG abnormality was reported as an SAE. No subjects in the SPD503 group had a QTcB or QTcF interval ≥500msec. One subject receiving SPD503 had a QTcF change from baseline of >60 msec. No TEAEs
were associated with the finding. There were no clinically meaningful changes on ECG-related parameters and no ECG abnormality was reported as an SAE. There were no ECG findings that could be attributed to treatment with SPD503.

- The PDSS Total Score showed no difference from placebo at Week 13.
- Overall, mean decreases in BPRS-C Total Scores were of numerically greater magnitude for the SPD503 group compared to placebo at Visit 13 (Week 13) and at LOTA; similar results were noted for the psychomotor excitation subscores. However, mean changes from baseline were similar between treatment groups at Visits 13 and LOTA for the behavior disorders, depression, thinking disturbance, withdrawal retardation, anxiety, and organicity subscores.

**Conclusions:**

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

**Date of report:** 03 Oct 2013, Version 1.0